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REVIEW

Phytoneering: a new way of therapy for rhinosinusitis

Fitoingegneria: una nuova terapia per le rinosinusiti

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SUMMARY

A growing amount of scientific evidence suggests that herbal medicine may be helpful as an adjuvant treatment in rhinosinusitis. Herein, we systematically review and determine the role, efficacy and safety of phytotherapy in the treatment of acute and chronic rhinosinusitis and establish the qualities of herbal drugs as demonstrated by in vitro and in vivo experiments. Eligible studies published in English or German from January 1990 until June 2014 were identified via electronic database searches. Keywords were: sinusitis, phytotherapy, phytomedicine and herbal drugs. Additional studies were obtained through the references of selected articles. Twenty-two articles met inclusion criteria. Overall, the publications indicated that herbal medicines can have mucolytic, antiviral, antimicrobial, anti-inflammatory and secretolytic effects in experimental animals. Phytotherapy has also been found to be efficacious in reducing the symptoms of acute and chronic rhinosinusitis in children and the adult population in vivo, demonstrating a high level of tolerability and safety. Herbal products developed using phytotherapy techniques have shown improvements in performance compared with previous formulations. The current literature suggests that phytotherapy is an effective and safe form of ancillary treatment for rhinosinusitis. In particular, herbal drugs made with the technique of phytoneering have proven effective in acute rhinosinusitis.

KEY WORDS: Phytoneering • Phytotherapy • Rhinosinusitis

RIASSUNTO

Evidenze scientifiche, sempre più presenti in letterature, suggeriscono che la fitoterapia è utile come trattamento adiuvante della rinosinusite. Lo scopo principale del nostro lavoro è esaminare sistematicamente e determinare il ruolo, l'efficacia e la sicurezza della fitoterapia nel trattamento della rinosinusite acuta e cronica e stabilire le qualità farmacologiche dei fitofarmaci in vitro e in vivo. Sono stati identificati attraverso ricerche nelle banche dati elettroniche studi pubblicati in inglese o in tedesco da 1 gennaio 1990 al giugno 2014. Le parole chiave usate erano: sinusite, fitoterapia, fitomedicina e farmaci a base di erbe. Ulteriori studi sono stati ottenuti attraverso i riferimenti negli articoli selezionati. Ventidue articoli hanno incontrato i criteri di inclusione. Nel complesso, gli articoli analizzati indicano che i farmaci a base di erbe possono avere effetti mucolitici, antimicrobici, antivirali, proprietà anti-infiammatorie e secretolitiche in animali da esperimento. La fitoterapia risulta efficace nel ridurre i sintomi di rinosinusite acuta e cronica nei bambini e nella popolazione adulta in vivo, dimostrando un elevato livello di tollerabilità e sicurezza. Prodotti a base di erbe sviluppati con tecniche di "fitoingegneria" hanno mostrato miglioramenti in termini di prestazioni rispetto alle formulazioni precedenti. La letteratura corrente suggerisce che la fitoterapia è una forma efficace e sicura per il trattamento ancillare nella rinosinusite. In particolare i fitofarmaci realizzati con la tecnica di "fitoingegneria" si sono dimostrati efficaci nella rinosinusite acuta.

PAROLE CHIAVE: Fitoingegneria • Fitoterapia • Rinosinusite

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Introduction

Acute rhinosinusitis (ARS) is one of the most common infections of the upper respiratory tract and affects a significant proportion of the population. In the US alone, people with sinus disorders spend more than \$2 billion annually, and make 1 million physician visits each year in pursuit of symptomatic relief. For adults seeking care in ambulatory medical practices, sinusitis is the most common diagnosis and is treated with antibiotics.

The clinical diagnosis of acute rhinosinusitis (ARS) in children is challenging, due to the overlapping of symptoms with other ordinary childhood nasal diseases, such as viral upper respiratory tract infections and allergic rhinitis, not to mention the difficulties related to physical assessment. ARS in children is defined as the sudden onset of two or more of the following symptoms, lasting less than 12 weeks: discoloured nasal discharge, nasal blockage/obstruction/congestion, cough in the day and night-time. Rhinosinusitis is an inflammatory process involving

the mucosa of the nose and sinuses. It is a multifactorial disease, in which factors such as mucociliary impairment, infection, allergy and swelling of the nasal mucosa can contribute to its genesis, maintenance and recurrence. Antibiotics are the most frequently used therapeutic agents in ARS, while there is reasonable evidence to support the addition of intranasal steroids¹.

Phytotherapy is the use of extracts of natural origin as medicines or health-promoting agents. Phytotherapeutic medicines differ from plant-derived medicines in their standard pharmacology. Whereas standard pharmacology isolates an active compound from a given plant, phytotherapy aims to preserve the complexity of substances from a given plant, with relatively less processing. In herbal medicine, plant material that has been processed in a repeatable operation, so that a discrete marker constituent is at a verified concentration, is then considered standardised.

The quality of crude drugs or plant medicines depends upon a variety of factors, including the variability in the species of plant being used, the plant's growing conditions, timing of harvest, post-harvest processing and storage conditions. Modern phytotherapy may use traditional methods of assessment of herbal drug quality, but more typically relies on modern processes, such as HPLC (high performance liquid chromatography), GC (gas chromatography), UV/Vis (ultraviolet-visible spectrophotometry) or AA (atomic absorption spectroscopy).

Complementary/alternative medicines are extensively used in the treatment of both ARS and chronic RS, but evidence-based recommendations are difficult to propose due to the lack of randomised controlled trials and methodological problems in many clinical studies and trials. To date, there are only a few double-blind, placebo-controlled, randomised studies that have assessed the efficacy of herbal compounds in treatment of ARS, which is not representative of the full spectrum of herbal remedies used in the treatment of ARS. Different herbal drugs have been proposed for the treatment of ARS.

Cyclamen europaeum extract (Nasodren®) is rich in saponins, which acts as a local surfactant on the mucous membranes to promote the intranasal drainage of fluid from the sinuses through a physical mechanism. Cyclamen is a member of the primrose family (Primulaceae) and has been used medicinally since ancient times. For example, Theophrastus in ancient Greece (4th–3rd centuries BC) recommended inserting a mixture of cyclamen extract and honey into the nose to treat nasal catarrh and headaches (“to clear the head”).

Cineole is a terpenoid oxide present in eucalyptus oils, amongst others. Eucalyptus has been shown to have anti-inflammatory, antiseptic and decongestant properties, and is traditionally used to treat asthma, nasal congestion, runny nose, cough, sore throat and sinusitis.

Bromelain is a proteolytic enzyme obtained from pineapple. Its physiological effects appear to include interactions with inflammatory, immune, cell signalling, coagulation molecules and related pathways. The enzyme's anti-inflammatory action is due to its inhibition of bradykinin production at the inflammatory site.

Andrographis paniculata is an annual herbaceous plant of the family Acanthaceae, native of India and Sri Lanka. The herb has a number of purported medicinal uses, although research has found that evidence of its effectiveness is limited to the treatment of upper respiratory tract infections, ulcerative colitis and rheumatic symptoms. Kan Jang® contains *Andrographis paniculata* and *Eleutherococcus senticosus* and may shorten the duration and lessen the symptoms of common cold.

Angocin® Anti-Infekt N contains mustard oils (isothiocyanates) that inhibit the growth of bacteria and viruses. It also contains natural antibiotics from nasturtium and horseradish, which make it effective in the treatment of respiratory and urinary tract infections.

A new method for the extraction of the phytopharmaceuticals contained in herbs has recently been developed. This so-called “phytoneering” from “phyto-engineering” consists of three phases: initially, the extracts are analysed by mass spectrometry to determine the component ingredients and their relative quantities; next the extracts collected are examined to find especially promising candidates, by systematically and automatically testing all extracts for their impact on cell culture systems with relevance to the disease. Finally, these findings allow for optimisation of extracts to enhance their effects. Using sophisticated separation technologies, partial extracts are produced that contain the particularly effective ingredients in higher concentrations compared with the original extract.

Sinupret® has been developed using phytoneering processes and contains extracts of five herbs: elder (*Sambucus nigra*, Caprifoliaceae) flowers, primrose (*Primula veris*, Primulaceae) flowers with calyx, common sorrel (*Rumex acetosa*, Polygonaceae), European vervain (*Verbena officinalis*, Verbenaceae) and gentian (*Gentiana lutea*, Gentianaceae) root. The flowers of the black elder act as a mucolytic. The active substances of the cowslip flowers and calyx act as mucolytic agents, have anti-inflammatory activity and combat the causes of disease: namely, viruses and bacteria. The leaves and stems of common sorrel act as mucolytic agents and have an anti-inflammatory effect. The leaves and stems of verbena also act as mucolytic agents and have antiviral activity. Gentian root contains substances with mucolytic action.

The primary outcome of our manuscript was to evaluate the efficacy and safety of this new way of extraction in the treatment of acute and chronic rhinosinusitis in children. The secondary outcome was assessment of pharmacological effects, such as anti-inflammatory or mucolytic activities, in vitro and in experimental animals.

Materials and methods

A PubMed literature search was performed in June 2014 using the following key words: “sinusitis”, “phytotherapy”, “phytomedicine” and “herbal drugs”. The additional filter selected was “Text Availability: Abstract”. The abstracts and titles obtained were screened independently by two of the authors (DP and JC) who subsequently met and discussed any divergences regarding citation insertion. The exclusion criteria were absence of the full text and the main text not being available in English or German. We also excluded reviews and articles on otitis media and bronchitis, which are beyond the scope of our review. We considered separately manuscripts that did not use the technique of extraction and processing of phytoneering, but reported data on phytotherapy and rhinosinusitis in children. All the main texts were retrieved and read by both reviewers.

Results

The initial search produced a total of 50 results using the abovementioned criteria. Twenty-two articles were eligible for inclusion. With regard to the articles on ARS, 6 articles were identified, in 4 of which patients were treated with phytoneering herbal drugs (Table I).

The studies analysed indicated that herbal drugs have mucolytic, antiviral, antimicrobial, anti-inflammatory and secretolytic activity in experimental animals. Phytotherapy in vivo has also been demonstrated to be efficacious in reducing the symptoms of acute and chronic rhinosinusitis in children and the adult population, showing a high level of tolerability and safety. Herbal products developed

using phytoneering techniques have shown improvements in performance compared with previous phytotherapeutic preparations, probably because the method allows for the duplication of the individual active components contained in plant extracts, thus enhancing the final pharmacological effects.

Antimicrobial and antiviral effects

The antimicrobial effects of phytoneering herbal drugs in vitro were assessed on *Staphylococcus aureus*, methicillin resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Escherichia coli* and *Haemophilus influenzae*. A phytoneering product (Sinupret-Bionorica) has bactericidal effects on Gram positive and negative bacteria, but was not effective against *E. coli* ².

In fact, experiments performed in New Zealand on white rabbits with experimentally-induced maxillary sinusitis by *Streptococcus pneumoniae* showed that phytoneering herbal extract (300 mg/kg b.w./day) reduced bacterial counts in sinuses, as well as the obstruction, opacification and inflammation of the sinus mucosa.

The phytoneering product has antiviral effects against adenovirus C subtype 5 (Adeno 5), human rhinovirus B subtype 14 (HRV 14) and the long strain of respiratory syncytial virus (RSV), in all of which the dry extract was significantly superior to oral drops (Fig. 1) ³.

In an animal study, rats and rabbits were inoculated with *Strep. pneumoniae* to provoke bacterial rhinosinusitis and then treated with the phytoneering product, which brought about a statistically significant reduction in bacterial growth after 8 days ⁴.

Table I. Literature reports on herbal therapy in children with ARS.

First author	Year	Study design	N	Days	Dosage	Preparation	Significant findings	Complications
Braum ¹⁸	1990	Randomised, open-label, comparative	114	21	2 tablets 3x/d or N-acetylcysteine: 200 mg 3x/d	Sinupret® Tablets	12.3% improved, 56.1% were w/out pathologic findings	None
Kraus ¹⁷	1992	Randomised, open-label, comparative	134	28	N/A	Sinupret® Tablets	49% classified as “nothing abnormal detected” or “improved”	None
Neubauer ¹⁵	1994	Randomised, placebo-controlled, double-blind	160	14	2 tablets 3x/d or placebo	Sinupret® Tablets	Improvements from baseline on radiograms	None
Biebach ¹⁶	2004	Open-label, multicentre	3109	N/A	20 drops 3x/d or 1 tablet 3x/d	Sinupret® Drops & Sinupret® Tablets	93% reported “little” nasal discharge or no discharge & 90% reported discharge as “thin” & “clear”	None
Braun ²⁰	2005	Comparative, multicentre	116	N/A	N/A	Bromelain-POS® Tablets	The duration of symptoms was lower	One case of pineapple allergy
Goos ²¹	2007	Prospective, multicentre	297	N/A	N/A	Angocin® Anti-Infekt N vs. antibiotic	Reduction of complaint score in 84.8% vs. 85.5%	< 1% of adverse events

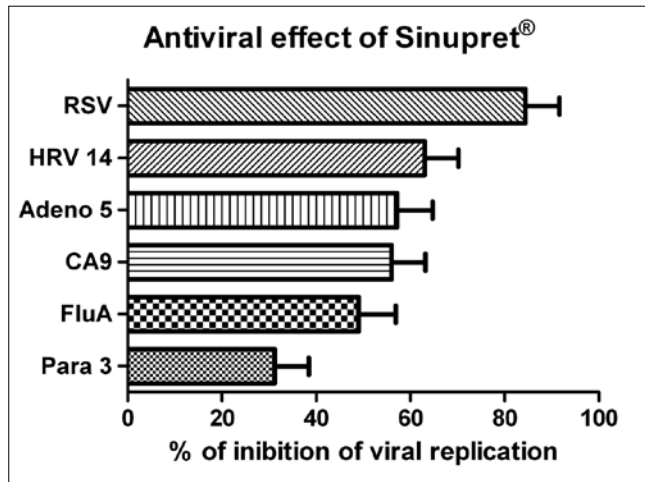


Fig. 1. Percentage of inhibition of viral replication with a 120 $\mu\text{m}/\text{ml}$ of Sinupret® for parainfluenza viruses (Para 3), influenza viruses (FluA), coxsackie viruses (CA9), adenoviruses (Adeno 5), human rhinoviruses (HRV 14) and respiratory syncytial viruses (RSV) (from Glatthaar-Saalmüller et al., 2011³, mod.).

A study on mice inoculated with Sendai virus (*Parainfluenza viridae*) showed that preventive treatment with the phytonering herbal drug determined a significantly longer survival time compared with placebo ($p < 0.05$)⁵. Eucalyptus oil and its main product 1,8-cineole demonstrated antimicrobial activity against microorganisms grown in planktonic cells and biofilm. Crude eucalyptus oil was significantly more efficacious than 1,8-cineole ($p < 0.05$) against microorganisms grown in suspensions of *Staphylococcus aureus*, MRSA, *Escherichia coli* and *Candida albicans*, and in biofilm cultures of MRSA and *Pseudomonas aeruginosa*⁶.

Secretolytic activity

The secretolytic activity of the phytonering herbal drug was assessed in rabbits by administering the individual herbs contained and then analysing the tracheal mucus. The phytonering product and all the individual herbs (especially European vervain and gentian root extracts) produced a statistically significant increase in the fluidity of secretions compared with baseline ($p < 0.05$ in all cases)⁷. Another study evaluated the effects of the phytonering herbal drug and its individual components on the secretion activity of rat respiratory epithelium using phenol red, demonstrating a dose-dependent effect on tracheo-bronchial secretion⁸.

The phytonering product extract stimulates the ciliary beat frequency of human bronchial epithelial cells, with a significant increase only 10 min post-application and dose-dependent effects lasting up to 1 hour (Fig. 2). The extract has also been shown to stimulate transepithelial Cl^- transport⁹.

Anti-inflammatory activity

The immunological role of the Sinupret (the phytonering Herbal drug) has been examined in human leukocytes in

vitro. The gentian root extract and vervain extract increased the phagocytic activity of neutrophils, while sorrel inhibited phagocytosis at high concentrations. At low concentrations it augmented phagocytosis, but only marginally. High concentrations of phytonering product slightly stimulated the proliferation of lymphocytes in vitro¹⁰.

The phytonering herbal drug was evaluated in rats in which inflammation was provoked in the lower extremities. It reduced itchy red wheals and the highest dose tested was as successful as phenylbutazone⁷.

The efficacy against bacterial infections of the upper airways was tested in mice inoculated intranasally with *Strep. pneumoniae* to induce bacterial rhinosinusitis. It significantly reduced bacterial growth ($p < 0.01$) and the amount of goblet cells (cells that secrete mucous) ($p < 0.05$), and also improved the quality of secretions compared with controls ($p < 0.01$)¹¹.

Anti-inflammatory action has also been demonstrated in rats with induced pleural inflammation. The rats in which the phytonering product was administered orally one hour before treatment (which caused inflammation after 4 hours) showed a lower volume of pleural effusion, less infiltration of polymorphonuclear leukocytes and decreased formation of PGE_2 in the exudates, as well as lower quantities of cyclooxygenase (COX)-2 protein in the lungs (Fig. 3)¹².

The anti-inflammatory activity of 1,8-cineole was evaluated in rats with carrageenan-induced inflammation or a cotton pellet-induced granuloma, and an inhibitory effect was demonstrated against these two types of experimental inflammation. In mice, an oral dose of 400 mg/kg of 1,8-cineole has been shown to inhibit the acetic acid-induced increase in peritoneal capillary permeability and the chemical nociception induced by intraplantar formalin and intraperitoneal acetic acid¹³.

The anti-inflammatory activity of bromelain has recently been demonstrated through changes in circadian cytokine profiles. A significant shift in the circadian profiles of the

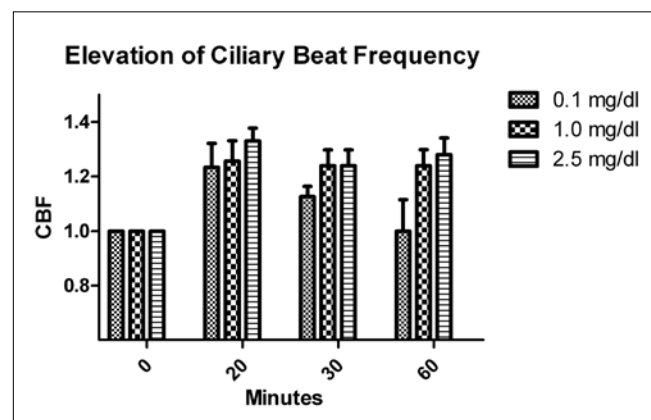


Fig. 2. Dose-dependent increase in of ciliary beat frequency with Sinupret® extract (from Kreindler et al., 2012⁹, mod.).

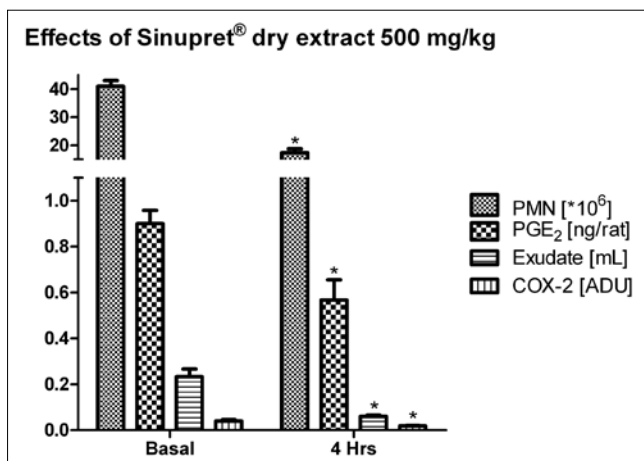


Fig. 3. Effects of Sinupret® dry extract in carrageenan-induced pleurisy in rats 1 h before intrapleural injection of carrageenan and after 4 h. Data are expressed as mean \pm SEM (from Rossi et al., 2012¹², mod.).

Th1 cell mediator interferon gamma ($p < 0.043$) was demonstrated after administration of 3000 units of bromelain, and similar trends were shown in the profiles of the Th2-type cytokine IL-5 as well as the immunosuppressive cytokine interleukin (IL)-10. This suggests a general effect on the antigen-specific (T cell) compartment of the human immune system¹⁴.

Acute rhinosinusitis (ARS)

A randomised, placebo-controlled, double-blind trial was conducted in 160 subjects (mean age 24.5 years) with acute bacterial sinusitis (opaque sinus radiographs at baseline) who were receiving antibiotic (vibramycin) and decongestant (otrivin) therapy, adding either Sinupret® or placebo tablets. Compared with placebo-treated patients, significantly more patients in the phytoneering product group showed improvements from baseline in radiographs ($p = 0.008$). These patients also reported improvements in mucosal swelling, nasal obstruction and headache. The authors concluded that the phytoneering herbal drug can improve basic (i.e. conventional drug) therapy¹⁵.

In children with ARS, phytoneering product in two formulations (drops and tablets) evaluated in 1638 girls and 1471 boys (mean age 6.9 years). The dosage varied according to the patients' age. Two-thirds (64%) of subjects took an average of 20 drops 3 times per day, while the others took tablets. At baseline, the most frequently found symptoms were "abundant" and "viscous" nasopharyngeal discharge, impaired nasal breathing and "moderately severe" cough.

At the final check-up (after an average of 12 days' treatment), 93% of children reported "little" nasal discharge or no discharge and 90% reported the discharge as "thin" and "clear." At the study end, only 0.3% of children reported severe impairment of nasal breathing and 75% had no cough. The symptoms "blocked nasal breathing",

"headache", "hoarseness" and "cough" clearly improved with the phytoneering product in both age groups and with both formulations. Nearly 90% of physicians involved assessed the efficacy of the phytoneering herbal drug as very good or good.

However, in 2-6-year-old children the sugar coated tablets were slightly superior to the drops in treating stuffy noses and coughs, while the drops were more effective at improving facial pain and headache (Fig. 4)¹⁶.

The major limitation of this study was that there was no placebo group or untreated control group. Acute rhinitis is often a self-limiting syndrome, so that a control group is necessary in such studies. Further limitations were the variable dosing, lack of information about the treatment period, and large percentage of the patients (74%) taking concomitant cold/flu medication, such as rhinological agents and/or antibiotics.

A randomised, open-label, comparative study was conducted in 134 patients with radiologically diagnosed ARS. All subjects were treated for 3 weeks with phytoneering sugar-coated tablets. After 3 weeks of treatment, 49% of patients were reported as having "nothing abnormal detected" or "improved"¹⁷. A limitation of the study was the lack of an untreated or placebo control group. It is unclear whether the 49% of patients showed improvements at 3 weeks due to the treatment or if rhinosinusitis resolved spontaneously.

A further randomised, open-label, comparative study was conducted in 114 patients with radiologically (X-ray) diagnosed ARS. All subjects were treated for 21 days with the phytoneering sugar-coated tablets. After 21 days of treatment, X-ray examination revealed that 12.3% (7/57) of phytoneering herbal drug-treated patients had improved and 56.1% (32/57) were without pathological findings. Approximately 85% of these subjects reported that they were "improved" or "cured"¹⁸. This study was also limited by the need for an untreated or placebo control group. Moreover, the researchers permitted the use of associated drugs, which could have affected the outcome.

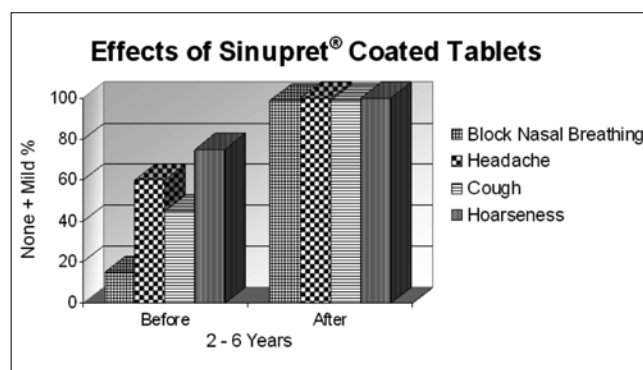


Fig. 4. Effects of Sinupret® coated tablets (three times a day) on disappearance of symptoms in 2-6-year-old children ($n = 293$) (from Biebach et al., 2004¹⁶, mod.).

A multicentre randomised, double-blind, placebo-controlled study was conducted in 386 adult patients with acute viral rhinosinusitis diagnosed radiologically (ultrasonography). One hundred and ninety subjects were treated with 160 mg phytonearing herbal product three times a day for 15 days with a mean follow-up of 14 days.

The major symptom score (rhinorrhoea, post nasal drip, nasal congestion, headache and facial pain) after 15 days was statistically significantly lower in the phytonearing herbal drug group, with 48.4% of patients considered cured. After treatment, ultrasonography showed 73.2% of patients treated with herbal drug were without pathological findings (vs. 61.6% in the placebo-treated group)¹⁹.

The activity of bromelain in children with ARS was evaluated in a trial involving 62 patients. The duration of symptoms was lower if patients were treated with only bromelain extract compared with standard therapy or combination therapy (6.66 vs. 7.95 vs. 9.06 days until resolution of symptoms, respectively)²⁰.

A prospective cohort study was performed involving 297 children with ARS treated with Angocin® Anti-Infekt N or with a standard antibiotic, according to the physician's decision. At the end of treatment, the reported symptoms were reduced by 84.8% vs. 85.5% in the antibiotic group. However, the study contained major limitations: prior to treatment symptoms in the Angocin® group were significantly less severe than those of the antibiotic group. Moreover, no standard protocol for treatment was used, being left to the judgment of the physician²¹.

Two randomised double-blind, placebo-controlled trials were conducted on populations of adults (n = 29 and n = 99) with ARS using *Cyclamen europaeum* extract. In the first study, after seven days of treatment, intranasal, lyophilised, reconstituted *Cyclamen europaeum* extract significantly reduced sinus opacification compared with placebo treatment on CT scans, and reduced the total symptom scores from baseline²². The second study, on the other hand, did not show significant differences in total symptom scores after 7 days, but only a reduction in facial pain and an improvement in endoscopically-assessed mucosal obstruction²³.

The activity of 1,8-cineole was demonstrated in a randomised, double-blinded controlled study on 75 patients with ARS. After a treatment period of 7 days, cineole brought about a statistically significant reduction in total symptom scores (11.0 ± 3.3 vs. 8.0 ± 3.0)²⁴.

A randomised double-blind, placebo-controlled trial was conducted on populations of 152 adults with acute non-purulent rhinosinusitis. A dose of 600 mg of cineole daily was administered. After 4 and 7 days, the symptoms-sum-score was significantly lower in treatment group²⁵.

Kan Jang® was evaluated in 95 patients with acute upper respiratory tract infections and showed significant improvements after 5 days in headache, nasal and throat symptoms, even in the sinusitis subgroup of this clinical study²⁶.

Roots of *Pelargonium sidoides* were compared to placebo in a randomised double-blind trial on 103 adults with acute rhinosinusitis. The sinusitis severity score after 7 days of treatment confirmed that the therapy was well tolerated with a decrease of 5.5 points²⁷.

Chronic rhinosinusitis (CRS)

A randomised, double-blind, placebo-controlled trial was conducted on 31 patients with CRS. Radiological results of the paranasal sinuses showed that 12/16 of the phytonearing herbal drug-treated patients experienced considerable improvements or total recovery compared with 6/15 placebo-treated patients (p value not reported). Treatment with phytonearing product showed a significant improvement in headache (p = 0.025) and in paranasal sinuses at X-ray (p = 0.001). The authors concluded that phytonearing components had a positive effect on subjective and objective findings in patients with chronic sinusitis²⁸. Although this study was limited by its small size, the objective measures provide credibility to support its conclusions.

A randomised, open-label, comparative study was conducted on 46 patients experiencing an exacerbation of CRS, as diagnosed radiologically. Seventeen subjects were treated for 21 days with phytonearing herbal tablets (2 tablets, 3 times per day). X-ray examination revealed that 23.5% (4/17) of the phytonearing product-treated patients improved and 41.7% (10/24) were without pathologic findings. The authors concluded that phytonearing drug was equivalent to N-acetylcysteine therapy¹⁸. This study was limited by the need for an untreated or placebo control group. In addition, the researchers permitted the use of associated drugs, which could have modified the outcome.

Discussion

The value of Sinupret® has been evaluated by many researchers. This preparation is the only one to use the phytonearing technique of production, which allows for greater concentration and purification of the herbal active ingredients.

This review of clinical findings has shown that Sinupret® is helpful in enhancing the results of pharmaceutical therapy. However, preliminary results evaluating the efficacy of Sinupret® in the treatment of chronic rhinosinusitis are ambiguous and larger prospective studies are needed.

Considering the primary outcome of efficacy and safety in the treatment of acute and chronic rhinosinusitis in children, herbal medicine can be considered as a viable ancillary therapy, as it is well tolerated by patients and not disdained by families or paediatricians. Various studies have reported improvements in subjective symptoms associated with ARS, such as nasal obstruction and head-

ache, as well better recovery by radiographic examination and in nasal mucosal swelling. Regarding the secondary outcome of safety, Sinupret® does have pharmacological effects, as demonstrated by research in vitro and in experimental animals. The effects that correlate with a potentially helpful role in the treatment of ARS in children are the antiviral and antimicrobial effects of Sinupret® and 1,8-cineole, and the anti-inflammatory and secretolytic effects of Sinupret® and bromelain.

Although until now herbal therapy was considered to be an ancillary therapy for adult population with viral and postviral ARS, it is useful in reducing the duration of symptoms and the use of standard therapies.

Herbal compounds have been commonly used in treatment of ARS, but only a few double-blind, placebo-controlled, randomised studies have shown their efficacy. However, the available data with herbal medicines prepared using the phytoneering technique of production encourage the use of this therapy in children with viral ARS as they are free of side effects and helpful in reducing the duration of symptoms and days of standard therapies. Hence, the benefit of herbal compounds in treatment of ARS need to be confirmed by more well designed and randomised clinical trials.

Conclusions

The current literature suggests that phytotherapy is an effective and safe ancillary treatment for RS in children. In particular, herbal medicines prepared with the technique of phytoneering (Sinupret®) have proven effective for acute rhinosinusitis treatment. This preparation technique proved to be superior compared with previous production methods for isolation, synthesis and duplication of the active components contained in herbs.

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References

- 1 Fokkens WJ, Lund VJ, Mullol J, et al. *European Position Paper on Rhinosinusitis and Nasal Polyps 2012*. Rhinol Suppl 2012;23:1-298.
- 2 Maune S, Schubert S, Schafer D. *Antimicrobial effects of a herbal medicinal product--a better understanding of host-defense mechanisms*. Paper presented at: World Allergy Congress; June 26-July 1, 2005; Munich, Germany.
- 3 Glatthaar-Saalmüller B, Rauchhaus U, Rode S, et al. *Antiviral activity in vitro of two preparations of the herbal medicinal product Sinupret® against viruses causing respiratory infections*. Phytomedicine 2011;19:1-7.
- 4 Ismail C. *Pharmacology of Sinupret. Recent results on the rationale for the Sinupret compound*. HNO 2005;53:S38-42.
- 5 Schmolz M, Ottendorfer D, Marz RW, et al. *Enhanced resistance to Sendai virus infection in DBA/2J mice with a botanical drug combination (Sinupret)*. Int Immunopharmacol 2001;1:1841-8.
- 6 Hendry ER, Worthington T, Conway BR, et al. *Antimicrobial efficacy of eucalyptus oil and 1,8-cineole alone and in combination with chlorhexidine digluconate against microorganisms grown in planktonic and biofilm cultures*. J Antimicrob Chemother 2009;64:1219-25.
- 7 Marz RW, Ismail C, Popp MA. *Action profile and efficacy of a herbal combination preparation for the treatment of sinusitis*. Phytotherapy 1999;149:202-8.
- 8 Curle P, Fraimbault V. *The secretolytic action of herbal drugs assessed by the phenol red secretion test new data for old herbal drugs and a combination*. Paper presented at: 4th and International Congress on Phytotherapy. 1992; Munich, Germany.
- 9 Kreindler JL, Chen B, Kreitman Y, et al. *The novel dry extract BNO 1011 stimulates chloride transport and ciliary beat frequency in human respiratory epithelial cultures*. Am J Rhinol Allergy 2012;26:439-43.
- 10 Schmolz M. *Immunological features of extracts from Radix Gentianae, Flores Primulae, Flores Sambuci, Herba Verbenae, and Herba Rumicis as well as from a combination hereof (Sinupret)*. Paper presented at: 4th and International Congress on Phytotherapy. 1992; Munich, Germany.
- 11 Tcacencu I, Sanstedt K, Ismail C, et al. *Anti-inflammatory effect of an herbal combination preparation in a murine model of bacterial rhinosinusitis*. Paper presented at: Phytopharmaka und Phytotherapie-Forschung und Praxis. 2002; Berlin, Germany.
- 12 Rossi A, Dehm F, Kiesselbach C, et al. *The novel Sinupret® dry extract exhibits anti-inflammatory effectiveness in vivo*. Fitoterapia 2012;83:715-20.
- 13 Santos FA, Rao VS. *Antiinflammatory and antinociceptive effects of 1,8-cineole a terpenoid oxide present in many plant essential oils*. Phytother Res 2000;14:240-4.
- 14 Müller S, März R, Schmolz M, et al. *Placebo-controlled randomized clinical trial on the immunomodulating activities of low- and high-dose bromelain after oral administration - new evidence on the antiinflammatory mode of action of bromelain*. Phytother Res 2013;27:199-204.
- 15 Neubauer N, Marz RW. *Placebo-controlled, randomized double-blind clinical trial with Sinupret sugar-coated tablets on the basis of a therapy with antibiotics and decongestant nasal drops in acute sinusitis*. Phytomed 1994;1:177-81.
- 16 Biebach K, Kramer A. *Effective treatment of rhinosinusitis in children*. Pad 2004;10.
- 17 Kraus P, Schwender W. *Randomized, open comparative study with Sinupret sugar-coated tablets vs. Gelomyrtol F. conducted at the Germany army hospital in Amberg*. Paper presented at: 4th and International Congress on Phytotherapy. 1992; Munich, Germany.
- 18 Braum D, Marz RW. *Randomised, open comparative study of Sinupret versus N-acetylcysteine in cases of sinusitis*. Neu-markt, Germany: Bionorica; 1990.
- 19 Jund R, Mondigler M, Steindl H, et al. *Clinical efficacy of a dry extract of five herbal drugs in acute viral rhinosinusitis*. Rhinology 2012;50:417-26.

- ²⁰ Braun JM, Schneider B, Beuth HJ. *Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany*. In Vivo 2005;19:417-21.
- ²¹ Goos KH, Albrecht U, Schneider B. *On-going investigations on efficacy and safety profile of a herbal drug containing nasturtium herb and horseradish root in acute sinusitis, acute bronchitis and acute urinary tract infection in children in comparison with other antibiotic treatments*. Arzneimittelforschung 2007;57:238-46.
- ²² Ponikau JU, Hamilos DL, Barreto A, et al. *An exploratory trial of Cyclamen europaeum extract for acute rhinosinusitis*. Laryngoscope 2012;122:1887-92.
- ²³ Pfaar O, Mullol J, Anders C, et al. *Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial*. Rhinology 2012;50:37-44.
- ²⁴ Tesche S, Metternich F, Sonnemann U, et al. *The value of herbal medicines in the treatment of acute non-purulent rhinosinusitis. Results of a double-blind, randomised, controlled trial*. Eur Arch Otorhinolaryngol 2008;265:1355-9.
- ²⁵ Kehrl W, Sonnemann U, Dethlefsen U. *Therapy for acute nonpurulent rhinosinusitis with cineole: results of a double-blind, randomized, placebo-controlled trial*. Laryngoscope 2004;114:738-42.
- ²⁶ Gabrielian ES, Shukarian AK, Goukasova GI, et al. *A double blind, placebo-controlled study of Andrographis paniculata fixed combination Kan Jang in the treatment of acute upper respiratory tract infections including sinusitis*. Phytomedicine 2002;9:589-97.
- ²⁷ Bachert C, Schapowal A, Funk P, et al. *Treatment of acute rhinosinusitis with the preparation from pelargonium sidoides eps 7630: A randomized, double-blind, placebo-controlled trial*. Rhinology 2009;47:51-8.
- ²⁸ Richstein A, Mann W. *Treatment of chronic rhino-sinusitis with Sinupret*. Schewiz Zschr GanzheitsMedizin 1999;11:280-3.

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HEAD AND NECK

Tracheocutaneous fistula in patients undergoing supracricoid partial laryngectomy: the role of chronic aspiration

Fistola tracheocutanea in pazienti sottoposti a laringectomia sovracricoidea: il ruolo dell'aspirazione cronica

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SUMMARY

The aim of the present retrospective controlled study was to analyse and compare risk factors for tracheocutaneous fistula in patients who received tracheostomy after supracricoid partial laryngectomy with those who received tracheostomy for other causes. We enrolled 39 patients with tracheocutaneous fistulas who were divided into two groups. The first received temporary tracheostomy for supracricoid partial laryngectomies (n = 21), while the control group consisted of patients who received temporary tracheostomy for other causes (n = 18). Risk factors believed to play a role in the pathogenesis of tracheocutaneous fistula were examined including advanced age, cardiopathy, local infections, radiotherapy, elevated body mass index, malnutrition, decannulation time and aspiration grade. The Leipzig and Pearson scale score was significantly higher in the supracricoid partial laryngectomy group (p = 0.006 and 0.031 for univariate and multivariate analyses, respectively). The penetration/aspiration score was significantly higher in the supracricoid partial laryngectomy group as determined by univariate analysis (p = 0.014). The decannulation time was significantly lower in the supracricoid partial laryngectomy group (p = 0.004 and 0.0004 for univariate and multivariate analyses, respectively). The number of surgical closures for tracheocutaneous fistula was significantly higher in the supracricoid partial laryngectomy group by univariate analysis (p = 0.027). These results suggest that chronic aspiration and related cough may be important pathogenic factors for tracheocutaneous fistula and could be responsible for the significantly higher rates of closure failure in patients after supracricoid partial laryngectomy.

KEY WORDS: Aspiration • Risk factors • Supracricoid partial laryngectomy • Tracheocutaneous fistula • Tracheostomy

RIASSUNTO

Lo scopo del presente studio retrospettivo controllato è quello di analizzare e confrontare i potenziali fattori di rischio per fistola tracheocutanea tra i pazienti sottoposti a tracheostomia dopo laringectomia sovracricoidea e pazienti che hanno ricevuto tracheostomia per altre cause. Abbiamo arruolato 39 pazienti con fistola tracheocutanea e li abbiamo suddivisi in due gruppi. Il primo gruppo era costituito da pazienti che hanno ricevuto tracheostomia temporanea dopo laringectomia sovracricoidea (21 pazienti) mentre il gruppo di controllo era costituito da pazienti che hanno ricevuto tracheostomia temporanea per altre cause (18 pazienti). I seguenti fattori di rischio ritenuti svolgere un ruolo nella patogenesi della fistola tracheocutanea sono stati esaminati: età avanzata, cardiopatie, infezioni locali, radioterapia adiuvante, elevato indice di massa corporea, malnutrizione, tempo di decannulazione e grado di aspirazione. Il punteggio della scala di Leipzig e Pearson era significativamente più alto nel gruppo sottoposto a laringectomia sovracricoidea (p = 0,006 e 0,031 rispettivamente all'analisi univariata e multivariata). Il punteggio della scala penetrazione/aspirazione era significativamente più alto nel gruppo sottoposto a laringectomia sovracricoidea, come determinato dall'analisi univariata (p = 0.014). Il tempo di decannulazione era significativamente più basso nel gruppo sottoposto a laringectomia sovracricoidea (p = 0,004 e 0,0004 rispettivamente all'analisi univariata e multivariata). Il numero di procedure chirurgiche richieste per la chiusura della fistola tracheocutanea era significativamente più alto nel gruppo sottoposto a laringectomia sovracricoidea, come determinato dall'analisi univariata (p = 0,027). Questi risultati suggeriscono che l'aspirazione cronica e la tosse correlata potrebbero essere importanti fattori di rischio per fistola tracheocutanea e potrebbero essere responsabili del significativamente più alto tasso di fallimento di chiusura della fistola in pazienti sottoposti a laringectomia sovracricoidea.

PAROLE CHIAVE: Aspirazione • Penetrazione • Laringectomia sovracricoidea • Deglutizione • Fistola tracheocutanea

Introduction

Tracheocutaneous fistula (TCF) is commonly regarded as a pathological complication of temporary tracheostomy that results from the failure of spontaneous tracheostomy closure after decannulation. Chronic TCF can significantly impair quality of life, vocalisation and local hygiene¹. Although many of these fistulas close spontaneously after decannulation or after local debridement, a significant percentage do not and require surgical closure². The incidence of fistula formation is known to be related to cannulation time. Kulber et al. reported that fistulas do not develop if the cannulation time is less than 16 weeks, but that the incidence increases to 70% when the cannulation period is greater than 16 weeks³. Furthermore, other factors such as previous irradiation of the neck, previous tracheostomy and obesity have been suggested to be risk factors for TCF⁴.

Despite the fact that TCF is a common complication of supracricoid partial laryngectomy (SPL) and that SPL has been used for a number of decades⁵⁻⁷, there is a paucity of studies in the English language literature on its incidence, risk factors and pathogenesis in patients undergoing SPL. In our experience with SPL, tracheostomy closure after decannulation occurs spontaneously or after local debridement in about 70% of cases, while in about 30% of cases surgery is required. After SPL, TCF surgical closure is challenging since the laryngeal airway can be suboptimal and abnormal increases in subglottic pressure during the expiration phase can be present⁵⁻⁷. Nonetheless, patients who have undergone SPL are often chronic inhalers with different degrees of cough⁸, which could represent a further obstacle characterised by a sudden and strong increase in subglottic pressure.

The aim of the present retrospective controlled study was to analyse and compare the incidence of potential risk factors for TCF between patients who underwent SPL and those who received tracheostomy for other causes.

Materials and methods

This study was designed as a retrospective controlled evaluation of patients who underwent surgical TCF closure at the Sensory Organs Department of Policlinico "Umberto I", Sapienza Università di Roma between September 2007 and May 2013. Approval for this study was obtained from the local Institutional Review Board.

Patients

Inclusion criteria were as follows: 1) adequate clinical documentation; 2) adequate respiratory space before decannulation (i.e. the ability to maintain a closed tracheal cannula for at least 7 days before decannulation); 3) absence of steroid therapy for at least 1 month before decannulation; 4) adequate swallowing and/or adequate swallowing rehabilitation therapy; 5) adequate follow-up (at

least 6 months after surgical TCF closure); and 6) TCF persistence for at least 2 weeks post-decannulation. Tracheostomies were performed by the same surgical team using the Bjork flap technique⁹. Patients with previous histories of decannulation were excluded from the study. A total of 39 patients were enrolled.

Risk factors and comorbidities

The medical records of identified patients were examined for the following risk factors that are believed to play roles in the wound healing process: advanced age, cardiopathy, local infections, neck radiotherapy, body mass index (BMI) and malnutrition. Advanced age was defined as greater than 65 years. Cardiopathies were considered in cases of diagnosed diseases that had been treated with medications or lifestyle changes. Local infections were defined as tracheostomal infections with or without fistulae that required systemic antibiotic treatment and/or advanced local dressings. Neck radiotherapy included primary and adjuvant treatments. Overweight patients were defined as those with a BMI > 25. Malnutrition was defined as > 10% weight loss in the 20 days before surgery due to reduction in oral food intake.

Furthermore, we evaluated other clinical factors that are possibly implicated in the pathogenesis of TCF such as delayed decannulation (> 16 weeks), chronic inhalation and related cough. Assessments of inhalation were obtained for each patient using the Leipzig and Pearson scale^{10 11} (LPS) and the Penetration Aspiration Scale¹² (PAS); these scales evaluate the degree of penetration/aspiration. The LPS is scored as follows: 0, no problems; 1, occasional cough but no clinical problems; 2, constant cough worsening with meals or swallowing; and 3, pulmonary complications. The PAS is scored as follows: a, contrast does not enter the airway; b, contrast enters the airway and remains above the vocal folds with no residue; c, contrast remains above the vocal folds, and visible residue remains; d, contrast contacts the vocal folds, and no residue is present; e, contrast contacts the vocal folds, and visible residue remains; f, contrast passes the glottis, and no subglottic residue is visible; g, contrast passes the glottis, and visible subglottic residue is present despite the patient's response; and 8, contrast passes the glottis, and visible subglottic residue is present in the absence of a patient response.

Patients were divided into 2 groups. The first consisted of patients with TCF after SPL (SPL group), while the control group included patients with TCF after bilateral vocal cord palsy, transoral laser surgery for malignancy, open oral/oropharyngeal carcinoma surgery, or prolonged intubation (OC group). Even if the control group was composed of patients who had undergone tracheostomy for different causes, in all cases main laryngeal architecture was preserved and no upper airway strictures responsible for increased upper airway resistance were present.

TCF surgical closure

TCF closure was performed for all patients using the same surgical technique under local anaesthesia. A horizontal skin incision passing through the lower border of the TCF was made followed by a second incision circling the TCF border. When possible we repositioned the cartilage flap obtained after Bjork flap technique tracheostomy. The tracheocutaneous fistula was isolated and vertically closed using 3/0 vicryl suture. Skin flap was reapproximated using 3/0 subcutaneous vicryl suture. The redundant skin was trimmed to obtain a horizontal cosmetic suture, and closure of the skin was completed using 4/0 silk suture. Oral antibiotic therapy was administered for 9 days.

Statistical analyses

Statistical analyses were performed using SPSS 15.0 for Windows. Comparisons of qualitative variables were performed with the chi-square test. Multivariate analysis was performed with multiple logistic regression. P values < 0.05 were considered statistically significant.

Results

Within the study period, 83 patients underwent SPL in our department. Twenty-seven (32%) developed TCF, and 6 (7%) patients were excluded because they did not meet inclusion criteria. In the same period, 127 tracheostomies were performed for other reasons. Twenty (16%) developed TCF, and 2 (1.5%) cases were excluded because they did not meet inclusion criteria. The incidence of TCF between SPL patients and those who received tracheostomy for other reasons was statistically significant ($p = 0.007$). All TCF derived from the failure of conservative TCF closure strategies after decannulation such as fistula debridement with compressive dressings. Relevant demographics and patient characteristics, including primary pathologies for the OC group, are reported in Table I. Given our inclusion and exclusion criteria, we enrolled a total of 39 patients with TCF, and of these 21 (54%) patients were

enrolled after SPL (SPL group), while 18 (46%) received tracheostomy for other reasons (OC group).

TCF closure was accomplished successfully in all cases. All patients experienced regular postoperative courses during the first week without complications in terms of bleeding and airway compromise. Four patients (10%) experienced foreign body reactions to the absorbable sutures that required small incisions for their removal. Among the SPL group, 9 patients (43%) required more than 1 surgical treatment: 7 (33%) required 2 treatments, and 2 (10%) required 3 treatments. In the OC group, only 1 patient (6%) required more than 1 surgical treatment (2 treatments). When the residual fistula was less than 2 mm in diameter, the surgical technique consisted of debriding of margins and closure with simple suture; otherwise, the technique described above was utilised.

The risk factor data are summarised in Table II. When comparing the two groups, the overall multivariate model revealed a statistically significant difference ($p = 0.003$). However, there were no significant differences between the SPL and OC groups in terms of advanced age, cardiopathies, local infection, neck radiotherapy, BMI, or malnutrition ($p > 0.05$). LPS scores were significantly higher in the SPL group according to univariate and multivariate analyses ($p = 0.006$ and 0.031 , respectively), with $t = 2.25$ and standard error = 0.11. The PAS scores revealed penetration/aspiration in 39% of cases in the SPL group and in 17% in the OC group. This difference was statistically significant in univariate analysis ($p = 0.014$), but not in multivariate analysis ($p = 0.561$, $t = 0.58$, standard error = 0.08). Decannulation times were significantly lower in the SPL group according to univariate and multivariate analyses ($p = 0.004$ and 0.0004 , respectively), with $t = -3.99$ and standard error = 0.15. The numbers of surgical procedures were significantly higher in the SPL group according to univariate analysis ($p = 0.027$, Table III).

Discussion

TCF is a complication of temporary tracheostomy that results from the failure of spontaneous tracheostomy closure after decannulation that can significantly impair quality of life, vocalisation and local hygiene^{12 13 14}. Despite its clinical impact, there are few studies in the English literature on its risk factors and pathogenesis. Although decannulation time seems to be the only universally accepted risk factor for TCF, previous irradiation of the neck, previous tracheostomy and obesity have been suggested to be risk factors for TCF. Incidences of TCF up to 70% have been reported when tracheostomies are maintained for more than 16 weeks³. However, further investigations are needed to confirm the roles of the currently suspected risk factors and to identify new ones. Agents affecting wound healing could potentially represent risk factors for TCF, and for this reason we included data on age, cardiopa-

Table I. Demographics and comorbidities.

Characteristics	
Mean age (years)	59.3
Age range (years)	32-80
Gender, N (%)	
Male	27 (69)
Female	12 (31)
Tracheostomy for (N, %):	
Supracricoid laryngectomy	21 (53)
Bilateral vocal cord palsy	7 (18)
Transoral laser surgery for malignancy	5 (13)
Open oral/oropharyngeal carcinoma surgery	3 (8)
Prolonged intubation	3 (8)

Table II. Univariate and multivariate analysis of risk factors.

Characteristic	SPL (21)	OC (18)	p univariate	p multivariate
Age, N (%)				
≥ 65 years	8 (38)	5 (28)		
< 65 years	13 (62)	13 (72)	0.733	0.153
Cardiopathy, N (%)				
present	5 (24)	3 (17)		
absent	16 (76)	15 (83)	0.878	0.168
Local infection, N (%)				
present	2 (10)	2 (11)		
absent	19 (90)	16 (89)	0.714	0.788
Radiotherapy, N (%)				
yes	6 (29)	3 (17)		
no	15 (71)	15 (83)	0.618	0.666
BMI				
≥ 25	3 (14)	5 (28)		
< 25	18 (86)	13 (72)	0.520	0.192
Malnutrition, N (%)				
present	3 (14)	1 (6)		
absent	18 (86)	17 (94)	0.714	0.711
Leipzig and Pearson Scale, N (%)				
0	5 (24)	13 (72)		
1	8 (38)	4 (22)		
2	8 (38)	1 (6)	0.006	0.031
Penetration-Aspiration Scale, N (%)				
1	13 (62)	17 (94)		
2	3 (14)	1 (6)		
3	3 (14)	-		
4	2 (10)	-	0.014	0.561
Decannulation time, N (%)				
≤ 16 weeks	14 (67)	3 (17)		
> 16 weeks	7 (33)	15 (83)	0.004	0.0004

BMI: body mass index; Bolded values: statistically significant.

thies, local infections, neck radiotherapy, BMI and malnutrition¹⁵⁻¹⁸.

In the light of our long-term experience with SPL, we were interested in investigating the role of chronic cough and aspiration in the pathogenesis of TCF. SPL causes important alterations to the normal anatomy of the upper digestive tract, particularly in its intersection with the airways⁵⁻⁷. Postoperative sequelae affecting swallowing and phonation are always present, and postoperative rehabilitation is required. Although functional deglutition is usually recovered and allows the patient to be decannulated, sporadic episodes of aspiration can occasionally occur. In a previously published series of 116 patients, our group reported that chronic aspiration was suspected in 68% of patients, based on fibre optic endoscopic evaluation of swallowing and radiologically documented with videofluoroscopy in 39% of cases. On these bases, at least three mechanisms that could delay the tracheos-

tomy closure in SPL patients can be hypothesised: 1) aspiration with chronic coughing that is related to sudden and important increases in subglottic pressure; 2) inhaled saliva that, due to proteolytic activity, may be responsible for fibrin digestion and delays in wound healing; and 3) stenotic neoglottal space with abnormal increases in subglottic pressure during the expiration phase. In the current study, we quantified chronic cough and inhalation using the LPS^{10,11} (cough grade) and the PAS¹² (inhalation grade). We also collected data on the surgical success of TCF, quantifying and comparing the number of surgical procedures between the SPL and OC groups.

Our results showed that advanced age, cardiopathies, local infections, neck radiotherapy, BMI and malnutrition were not significantly different between the SPL and OC groups (Table II). Thus, these variables had the same potential impact in the SPL group as in the OC group. Interestingly, decannulation times were significantly low-

Table III. Surgical procedures.

Surgical Procedures, N (%)	SPL (21)	OC (18)	p
1	12 (57)	17 (94)	
2	7 (33)	1 (6)	
3	2 (10)	-	0.027

er in the SPL group by both univariate and multivariate analyses ($p = 0.004$ and 0.0004 , respectively). TCF occurred after 16 weeks in 33% of cases in the SPL group compared with 83% in the OC group. While the data on the OC group conform with the previous literature, the results in the SPL group show that the incidence of TCF was not influenced by delayed decannulation^{19,20}. The prevalence of penetration/aspiration was higher in the SPL group (38% SPL group, 6% of OC group), with a difference that was statistically significant in univariate analysis ($p = 0.014$). Furthermore, LPS scores were significantly higher in the SPL group in both univariate and multivariate analyses ($p = 0.006$ and 0.031 , respectively). Finally, the numbers of surgical procedures were significantly higher in the SPL group by univariate analysis ($p = 0.027$, Table III). In cases in which the TCF failed to close, patients complained of saliva leakage through the surgical wound. These findings were consistent with our hypothesis and were strengthened by the results of PAS and LPS scores.

To our knowledge this is the first study to investigate the risk factors and pathogenesis of TCF in SPL patients. We showed that the incidence of TCF was significantly higher in SPL patients. The incidence/prevalence of commonly recognised risk factors and factors affecting wound healing were not statistically different between the SPL and OC groups, while chronic aspiration and related cough were significantly higher in the SPL group. Based on these results, we hypothesise that TCF in SPL patients has a different pathogenesis compared to that in patients who received tracheostomy for other pathologies. Chronic cough and aspiration could play an important role favouring the onset of TCF, independent of decannulation timing, and may also influence the surgical failure and relapse rate.

On this basis, as recently advocated by Schindler et al.²¹, patients should be prepared for subsequent endoscopic surgery, laser surgery, or injective laryngoplasty in order to correct the anatomic and functional results of SPL, to achieve the best laryngeal function possible and to minimise complications such as TCF.

Finally, in order to better clarify the role of chronic cough and aspiration further studies are needed. It would be particularly desirable to conduct a prospective study investigating possible correlations between the degree of chronic cough and aspiration with the incidence and relapse rate of TCF using spirometric data (in particular FEV1).

Conclusions

The results of our experience suggest that chronic aspiration and related cough with saliva leakage should be investigated as pathogenetic factors in TCF formation and closure failure in patients who have undergone SPL.

References

- Bertholz L, Vail S, Berlet A. *Management of tracheocutaneous fistula*. Arch Otolaryngol Head Neck Surg 1992;118:869-71.
- Eliashar R, Sichel JY, Eliachar I. *A new surgical technique for primary closure of long-term tracheostomy*. Otolaryngol Head Neck Surg 2005;132:15.
- Kulber H, Passy V. *Tracheostomy closure and scar revisions*. Arch Otolaryngol 1972;96:22-6.
- Khaja SF, Fletcher AM, Hoffman HT. *Local repair of persistent tracheocutaneous fistulas*. Ann Otol Rhinol Laryngol 2011;120:622-6.
- De Virgilio A, Fusconi M, Gallo A, et al. *The oncologic radicality of supracricoid partial laryngectomy with cricothyroidopexy in the treatment of advanced N0-N1 laryngeal squamous cell carcinoma*. Laryngoscope 2012;122:826-33.
- Bussu F, Paludetti G, Almadori G, et al. *Comparison of total laryngectomy with surgical (cricothyroidopexy) and nonsurgical organ preservation modalities in advanced laryngeal squamous cell carcinomas: a multicenter retrospective analysis*. Head Neck 2013;35:554-61.
- de Vincentiis M, De Virgilio A, Bussu F, et al. *Oncological results of the surgical salvage of recurrent laryngeal SCC in a multicentric retrospective series. The emerging role of supracricoid partial laryngectomy*. Head Neck 2015;37:84-91.
- Simonelli M, Ruoppolo G, de Vincentiis M, et al. *Swallowing ability and chronic aspiration after supracricoid partial laryngectomy*. Otolaryngol Head Neck Surg 2010;142:873-8.
- Bjork VO, Engstrom CG. *The treatment of ventilatory insufficiency by tracheostomy and artificial ventilation; a study of 61 thoracic surgical cases*. J Thorac Surg 1957;34:228-41.
- Leipzig B. *Neoglottic reconstruction following total laryngectomy: a reappraisal*. Ann Otol Rhinol Laryngol 1980;89:534-7.
- Pearson BW. *Subtotal laryngectomy*. Laryngoscope 1981;91:1904-12.
- Rosenbek JC, Robbins J, Roecker EV, et al. *A Penetration-Aspiration Scale*. Dysphagia 1996;11:93-8.
- Kouloulis V, Triantopoulou S, Vrouvas J, et al. *Combined chemoradiotherapy with local microwave hyperthermia for treatment of T3N0 laryngeal carcinoma: a retrospective study with long-term follow-up*. Acta Otorhinolaryngol Ital 2014;34:167-73.

- ¹⁴ Dedivitis RA, Aires FT, Pfuetszenreiter EG Jr, et al. *Stapler suture of the pharynx after total laryngectomy*. Acta Otorhinolaryngol Ital 2014;34:94-8.
- ¹⁵ Crosetti E, Garofalo P, Bosio C, et al. *How the operated larynx ages*. Acta Otorhinolaryngol Ital 2014;34:19-28.
- ¹⁶ Russi EG, Sanguineti G, Chiesa F, et al. *Is there a role for postoperative radiotherapy following open partial laryngectomy when prognostic factors on the pathological specimen are unfavourable? A survey of head and neck surgical/radiation oncologists*. Acta Otorhinolaryngol Ital 2013;33:311-9.
- ¹⁷ Guo S, Di Pietro LA. *Factors affecting wound healing*. J Dent Res 2010;89:219-29.
- ¹⁸ Arnold M, Barbul A. *Nutrition and wound healing*. Plast Recon Surg 2006;117:42S-58.
- ¹⁹ Ganly I, Patel SG, Matsuo J, et al. *Analysis of postoperative complications of open partial laryngectomy*. Head Neck 2009;31:338-45.
- ²⁰ De Virgilio A, Greco A, Gallo A, et al. *Tracheostomal stenosis clinical risk factors in patients who have undergone total laryngectomy and adjuvant radiotherapy*. Eur Arch Otorhinolaryngol 2013;270:3187-9.
- ²¹ Schindler A, Fantini M, Pizzorni N, et al. *Swallowing, voice, and quality of life after supratracheal laryngectomy: preliminary long-term results*. Head Neck 2014 Feb 20. doi: 10.1002/hed.23636 [Epub ahead of print].

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HEAD AND NECK

The immunohistochemical peptidergic expression of leptin is associated with recurrence of malignancy in laryngeal squamous cell carcinoma

L'espressione peptidergica immunoistochimica della leptina è associata con la recidiva del carcinoma squamoso laringeo

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SUMMARY

Leptin is a peptide that plays a key role in the control of satiety, energy expenditure, food intake and various reproductive processes. In the last years, the expression of leptin had been found in malignant cells of various origins. The aim of this study is to evaluate leptin expression in human laryngeal squamous cell carcinoma (SCC) and to investigate its possible role in predicting prognosis. Leptin expression was determined by immunohistochemistry in pathological and healthy tissue specimens from 24 patients with laryngeal SCC. Specimens were stained with an anti-leptin antibody. All measurements were performed using a computer-based image analysis system and scale of staining intensity was determined. All tumoural specimens showed significant immunoreactivity for leptin compared to healthy tissues ($p \leq 0.05$), but showed different immunoreactivity that was related to clinicopathological features. High leptin expression was not significantly related with TNM, histological grading (HG) or advanced (III and IV) clinical stage ($p > 0.05$). Recurrence of malignancy was found to be significantly related with high expression of leptin by Spearman's rank correlation test ($\rho = 0.59$; $p = 0.002$), Fisher's test ($p = 0.017$) and Kaplan-Meier product-limit estimate (Log-rank test, $p \leq 0.05$). In particular, multivariate logistic regression analysis showed that recurrences were significantly related with nodal involvement, HG and leptin expression ($p \leq 0.05$). These preliminary results suggest that leptin may be a valuable parameter for predicting prognosis in laryngeal SCC.

KEY WORDS: Leptin • Laryngeal carcinoma • Malignancy recurrence

RIASSUNTO

La leptina è un peptide che svolge un ruolo chiave nel controllo della sazietà, del dispendio energetico, dell'assunzione di cibo, e in vari processi riproduttivi. Negli ultimi anni, la leptina è stata trovata espressa nelle cellule maligne di varia origine. Lo scopo di questo studio è quello di valutare l'espressione di leptina nel carcinoma a cellule squamose della laringe umana (SCC) e di ricercare un suo possibile ruolo prognostico. L'espressione di leptina è stata determinata mediante immunoistochimica in campioni di tessuto patologico e sano di 24 pazienti con SCC laringea. I campioni sono stati colorati con anticorpo monoclonale anti-leptina. La valutazione dell'espressione immunoistochimica è stata eseguita da un sistema computerizzato che analizzava le immagini e stabiliva una scala di intensità di colorazione. Tutti i campioni tumorali esaminati hanno mostrato immunoreattività significativa per la leptina rispetto ai tessuti sani ($p \leq 0,05$), ma è stata mostrata una diversa correlazione tra immunoreattività e caratteristiche clinico-patologiche. L'alta espressione della leptina non è correlata in modo statisticamente significativo con stadiazione TNM, grading istologico (HG) e stadio clinico avanzato ($p > 0,05$). L'insorgenza di recidive è risultata significativamente correlata con alta espressione di leptina tramite il test di correlazione di Spearman ($\rho = 0,59$, $p = 0,002$), test di Fisher ($p = 0,017$) e analisi di Kaplan-Meier (log-rank test, $p \leq 0,05$). In particolare, l'analisi di regressione logistica multivariata ha dimostrato che le recidive erano significativamente correlate con il coinvolgimento linfonodale (N), HG e l'espressione di leptina ($p \leq 0,05$). I nostri risultati preliminari suggeriscono che la leptina può essere un utile parametro prognostico.

PAROLE CHIAVE: Leptina • Carcinoma della laringe • Recidiva

Introduction

Leptin is a peptide produced by peptidergic cells or those able to process and secrete peptides. Originally, this function was considered proper and exclusive of certain neurons of the magnocellular and parvocellular hypothalamus¹⁻³. For the first time, Pearse found cells with monoaminergic function (amine precursor uptake and decarboxylation system, APUD) in the gastro-entero-pancreatic system (GEP)^{4,5}. Later, it was demonstrated that these cells originated from a common precursor, namely neural crest cells, which have the ability to produce hormonal neuropeptides⁶. From this primitive neuroectodermal site, cells migrate to other organs: GEP, lung, heart, reproductive and urinary system^{7,8}. Therefore, the APUD system was renamed as the Diffuse Neuro-Endocrine System (DNES)⁹.

Leptin (167 amino acids with a molecular mass of 16 kDa) is considered the typical neuropeptide with anorexic function, and is also called the “satiety hormone” because it plays a key role in control of energy expenditure and food intake. Leptin was identified for the first time in white and brown adipocytes¹⁰. The plasmatic levels of leptin are representative of adipose tissue and increases are related in a logarithmic fashion with an increase in body mass in mice^{11,12}. Leptin acts on the hypothalamic receptor (OBR) where it exerts the control of food intake and body weight through a negative feedback mechanism (anorexigenic function)¹³. Although initially thought to be exclusively expressed and secreted by adipocytes, leptin has been identified in other tissues related with nutritional homeostasis, such as gastric¹⁴ and salivary glands¹⁵⁻¹⁹. Leptin was later identified in organs unrelated with nutritional balance such as the placenta²⁰, mammary epithelial cells²¹ and lung²², where it performs a different functional role.

In addition, leptin or its receptors have been observed in gastric, colorectal and breast cancers. It is believed to have a role in stimulating cell proliferation, and is associated with a risk of developing cancer as well as progression and invasiveness²³⁻²⁵.

To date, the role of leptin in the development of the carcinoma of the larynx has not been investigated. Laryngeal cancer represents 20.8% of head and neck squamous cell carcinoma (HNSCC)²⁶, and although a large variety of malignancies may occur in the larynx, 85-95% of laryngeal malignancies are squamous cell carcinoma (SCC), arising from the epithelial lining of the larynx²⁷.

Patients with HNSCC have greatly benefited from the recent advances in surgical techniques, radiation therapy and chemotherapy. However, the survival rates for SCC have not improved significantly over the past two decades²⁸.

The principal endpoint of this study was to evaluate peptidergic immunohistochemical expression of leptin in la-

ryngeal SCCs and secondly to investigate its possible role in predicting prognosis and loco-regional recurrences.

Materials and methods

Patients

A consecutive series of 24 patients affected by laryngeal SCC were identified at the Section of Otolaryngology of Palermo University between 2010 and 2012. Selected patients had an age between 43 and 85 years, with mean age 62.3 years (SD 13.53). Informed consent was obtained from each patient. All patients were male and heavy smokers (> 20 cigarettes/day). All patients were examined with a flexible fiberoptic laryngoscopy. Subsequently, all patients underwent head and neck computerised tomography (CT) to highlight extension of the tumour and nodal involvement. Patients were biopsied by suspension microlaryngoscopy (DML). The Department of Human Pathology concluded that biopsy specimens were compatible with laryngeal SCC.

All patients underwent partial or total laryngectomy. In 22 (91.6%) cases, neck dissection was also performed. Ten (41.6%) patients underwent also post-operative radiotherapy. All specimens were sent to the Histology and Embryology Section of the University of Palermo. For each patient, two samples were collected from different locations: tumour (central portion of lesion without necrosis signs) and healthy epithelium (> 1 cm distance to the tumour margin resulting negative for malignancy at histological examination). Healthy laryngeal tissues were used as controls. All patients were subjected to follow-up. Mean follow-up time (calculated in months from treatment completion to the last otolaryngological control) was 32.25 months (range 13-39 months). Pathological staging according to the Tumor, Lymph Node, Metastases TNM system of the Union for International Cancer Control (7th edition) and histological grade was determined according to the degree of differentiation of the tumour. The characteristics of the patients studied and clinic-pathological features are shown in Table I.

Tissue preparation

All tissues were fixed in 10% buffered formalin and after 12-24 hours depending on the size of the sample were subjected to a wash cycle in H₂O and then dehydrated with increasing grade alcohol solutions (70%, 95%, 100%) and cleared in xylene before inclusion in paraffin. Samples were cut and processed for immunohistochemistry using monoclonal antibodies against leptin and revealed using an En Vision + System-HRP detection kit with AEC as the substrate (Dako).

Immunohistochemistry

Serial sections 8 m thick were cut with a Leica microtome RM2145, dried overnight at 37°C and then stored at room

Table I. Clinicopathologic characteristics of 24 patients with laryngeal squamous cell carcinoma and correlation with expression of leptin.

Parameter	N (%)	Leptin		p value
		Low	High	
Cases	24	8 (33.3)	16 (66.6)	
Age (years)	≤ 59	8 (33.3)	4 (50)	0.17
	> 59	16 (66.6)	4 (25)	
pT1	-	-	-	
pT2	6 (25)	4 (66.6)	2 (33.3)	
pT3	12 (50)	4 (33.3)	8 (66.6)	
PT4	6 (25)	-	6 (100)	
T stage (early/advanced)				
	T1-T2 (early)	6 (25)	4 (66.6)	0.062
	T3-T4 (advanced)	18 (75)	4 (22.2)	
pN0	14 (58.3)	4 (28.6)	10 (71.4)	
pN1	2 (8.3)	-	2 (100)	
pN2	6 (25)	4 (66.6)	2 (33.3)	
pN3	2 (8.3)	-	2 (100)	
Tot		8 (33.3)	16 (66.6)	
N0 and N+ category				
	N0	14 (58.3)	4 (28.6)	0.43
	N+	10 (41.6)	4 (40)	
Stage I	-	-	-	
Stage II	4 (16.6)	2 (50)	2 (50)	
Stage III	8 (33.3)	2 (25)	6 (75)	
Stage IV	12 (50)	4 (33.3)	8 (66.6)	
Stage (early/advanced)				
	Early (I-II)	4 (16.6)	2 (50)	0.47
	Advanced (III-IV)	20 (83.3)	6 (30)	
Grading (early and advanced)				
G1	4 (16.6)	-	4 (100)	0.17
G2	10 (41.6)	4 (40)	6 (60)	
G3	10 (41.6)	4 (40)	6 (60)	
	Early (G1)	4	4	
	Advanced (G2-G3)	20	12	
Loco-regional recurrence				
	No	16 (66.6)	8 (50)	0.017
	Yes	8(33.3)	-	

temperature. The day after, slides were dewaxed and re-hydrated by sequential immersion in a graded series of alcohols and transferred into water for 5 min; to inhibit any endogenous peroxidase activity slides were treated for 5 min with Peroxidase Block in hydrated incubation enclosure at room temperature. Subsequently, sections were transferred in PBS (Na_2HPO_4 , KH_2PO_4 , KCl, NaCl pH 7.4-7.6) at room temperature. The protocol was performed using the kit En-Vision + System HRP with AEC as the substrate (Dako). After rinsing with PBS for 4 min, sections were incubated overnight at 4°C with polyclonal anti-leptin (Ob A-20) (Santa Cruz Biotechnology, Inc)

diluted 1:100. After the incubation, any excess antibody was removed by washing with PBS for 5 min. Sections were incubated with peroxidase-labelled polymer conjugated to goat anti-rabbit immunoglobulin in Tris-HCl buffer containing stabilising protein and an antimicrobial agent. Unbound polymer was removed by washing (2x with PBS, 5 min each) and subsequently AEC chromogen in substrate buffer was then added for 5 min and the reaction was stopped in distilled water. Slides were removed from water and one drop of aqueous mounting medium (DAKO Faramount) and a coverslip, were applied to tissue sections.

Negative controls were performed by omission of primary antibody, and by incubating sections with antiserum saturated with homologous antigen.

Image analysis

Immunohistochemical specimens were examined using a Leica Laborlux S Microscope (Leica Microsystem GmbH Wetzlar, Germany) with a Nikon DSL2 photo digital system (Nikon Corp, Tokyo, Japan). Each sample was analysed with a double-blind system with two different operators. Moreover, the results were compared to an image analysis obtained from digital TIF files. Adobe Photoshop CS6 extended (Adobe Systems Inc., San Jose, CA) was used to elaborate images. Choosing the image in a field of $\times 40$, we converted the image colour profile from RGB to CMYK. Next, we chose the yellow channel because the literature indicates that it has the best linear response to colour intensity and thus to the presence of protein.

The images were processed and coded by the software in a grey intensity scale according to colour luminance (from 0 to 256 grey values in our measurements). In particular, 0 is white colour and corresponds to lowest value of intensity, while 256 is black colour and corresponds to highest value of intensity. The staining was scored as 0 (0-50 grey value) if there was no immunoreactivity, 1 (51-100 grey value) if staining was slight, 2 (101-150 grey value) if staining was moderate, 3 (151-200 grey value) if staining was high and 4 (201-256 grey value) if staining was maximum.

Statistical analysis

All statistical analyses were performed using the R statistical software package version 2.2.0. Fisher's exact test was used for comparison between categorical variables and correlation with clinical data was evaluated by Spearman correlation coefficient. Time-to-event analyses were calculated using the Kaplan-Meier product-limit estimate. Multivariate logistic regression analysis was also applied to evaluate the association between malignancy recurrence after treatment, leptin expression and other pathological features. We considered a $p \leq 0.05$ to be significant; values in the following range $0.10 > p > 0.05$ were considered to indicate a statistical trend.

Results

Clinicopathologic and histological characteristics of patients

All 24 patients included in this study were affected by SCC and were male, with a mean age of 62.3 years (SD 13.5; range 43-85 years) (Table I). Following guidelines of laryngeal cancer treatment proposed by the Italian Society of Otorhinolaryngology and Cervicofacial Surgery²⁹, total laryngectomy was performed in 10 (41.6%) cases and partial laryngectomy in 14 (58.3%), of which 10 pa-

tients with horizontal supraglottic laryngectomy (HSL), two with frontal-lateral laryngectomy (FLL) and two with cricothyroidopexy (CHP). Six patients had a T2 pathological tumour stage, 12 had T3 and six had T4. Twenty-two (91.6%) patients received selective neck dissection simultaneously to removal of the primary tumour and lymph node metastasis were present in 10 (41.6%) cases (pN+). There were no distant metastases.

Six (25%) patients had early cancer (Stage I or II) and 18 (75%) had advanced cancer (Stage III or IV). Four patients had a well differentiated tumour (G1), 10 had a moderately differentiated tumour (G2) and 10 a poorly differentiated tumour (G3).

Ten (41.6%) patients underwent postoperative radiotherapy. Mean follow-up time (calculated in months from treatment completion to the last otolaryngological control) was 32.25 months (range 13-39 months). During follow-up, 8 (33.3%) patients developed a malignancy recurrence (4 local recurrences, 4 recurrences to neck lymph nodes) after a mean period of 14.25 months (SD 7.10 months).

All tumour tissues showed significant expression of leptin ($p \leq 0.05$) compared with healthy control tissues (Table II). In particular, 8 cases showed low immunoreactivity (33%) and 16 cases showed high immunoreactivity (66.6%). High expression was seen in the neoplastic mucosal epithelium and in solid nests of tumour cells infiltrating connective underlying structures (Fig. 5a). The glandular epithelium showed negative immunohistochemistry (Fig. 5b). Cytoplasmic staining was predominant in all tissues. Among the healthy control tissues, only 6 cases (25%) showed a low immunoreactivity (1 according to our score) (Fig. 5c).

Comparing the immunohistochemical features of each case, we found a different expression of leptin in relation to different clinicopathological features.

Leptin and TNM staging

18 (75%) patients with advanced stage (T3-T4) showed immunoreactivity for leptin. In particular, 14 (77%) of these had high expression of leptin, showing a statistical trend, but without a significant difference compared with patients with early stage tumours ($p = 0.062$). In the 10 cases that were pN+, Fisher's test did not reveal any significant difference ($p = 0.43$) between patients with high expression of leptin (60%) compared with pN+ cases with low expression (40%). Spearman's rank correlation test showed a statistical trend between leptin and T isolated

Table II. Expression of leptin in laryngeal squamous cell carcinoma and normal laryngeal tissues.

	Cases	Controls	p value
Leptin			
Yes	24	6	0.001
No	0	18	

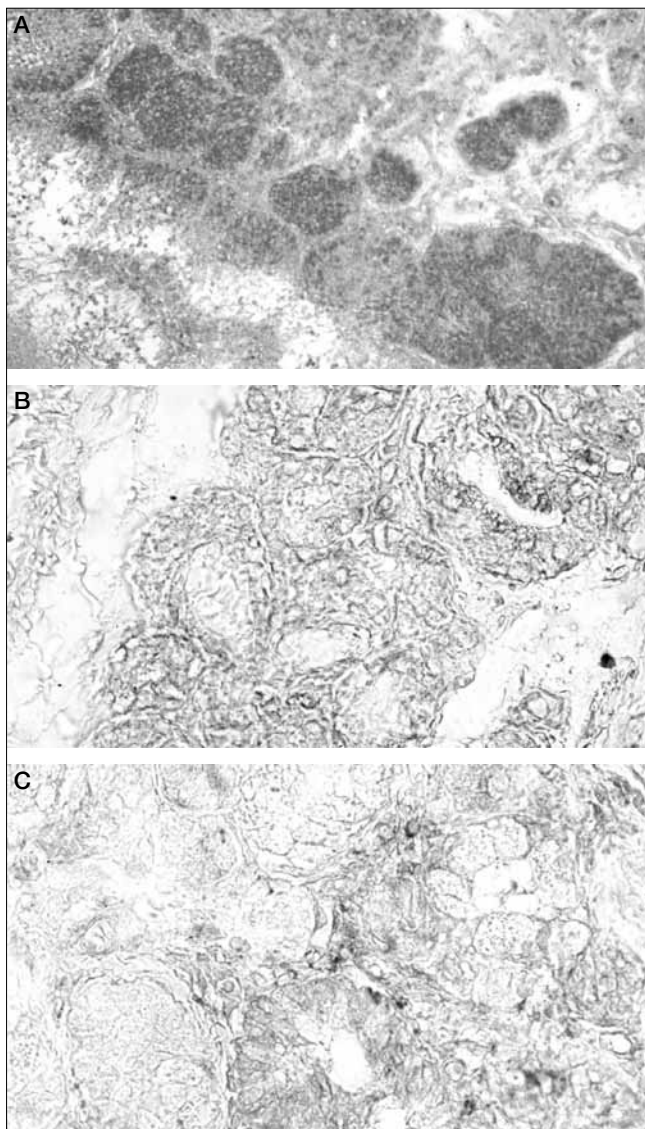


Fig. 1. **A:** High leptin immunoreactivity in solid nests of tumour cells infiltrating underlying connective structures (x10); **B:** lack of leptin immunoreactivity in glandular epithelium (x40); **C:** low leptin expression in normal laryngeal mucosa (x40).

stage ($\rho = 0.39$; $p = 0.055$), while no significant correlation with N isolated stage was seen ($\rho = 0.19$; $p = 0.35$).

Analysing the complete disease stage, there were no statistical differences between patients with high expression of leptin in advanced stage (70%) and those with high expression in early stage (50%) ($p = 0.47$). Spearman's rank correlation test did not show any significant correlation between leptin and stage ($\rho = 0$; $p = 1$).

Leptin and grading

In the advanced grade group (G2-G3), 14 (70%) patients shown high expression of leptin without significant relation with grading ($p = 0.47$). Spearman's rank correlation test showed a statistical trend between leptin expression and grading ($\rho = 0.4$; $p = 0.055$).

Leptin and tumour recurrence

The eight cases that developed recurrence were all associated with high immunoreactivity for leptin ($p = 0.017$). In particular, the Log-rank test showed a significant relation between high levels of leptin and risk of recurrence ($p = 0.0322$) (Fig. 2).

Spearman's rank correlation test showed significant correlation between leptin expression and recurrence ($\rho = 0.59$; $p = 0.002$).

Multivariate logistic regression analysis showed the following results (Table III): recurrence of malignancy was significantly related to leptin expression (odds ratio [OR] = 4.41; $p = 0.0003$; 95% confidence interval [CI] 1.68-4.75), to pN+ (OR = 3.73; $p = 0.001$; 95%CI 0.58 - 4.09) and to HG (OR = 2.95; $p = 0.008$; 95% CI 0.56-3.33).

Discussion

To the best of our knowledge, leptin expression in the head and neck cancers has been poorly investigated and there are no studies with which to compare our results. The few references concern salivary gland tumours. In particular, Schapher et al.³⁰ found that leptin was expressed in much higher amounts in human salivary gland tumours than in healthy tissues and hypothesised that the analysis of leptin concentrations in saliva samples might be used as a diagnostic marker to identify these tumours.

For the first time, we demonstrated the immunohistochemical expression of leptin in laryngeal SCC and its possible role in malignant recurrence.

Our results highlighted the expression of leptin and showed a statistically significant difference with control tissues (Table II). In consideration of this result, we focused on the relation between leptin expression and laryngeal SCC (TNM and grading).

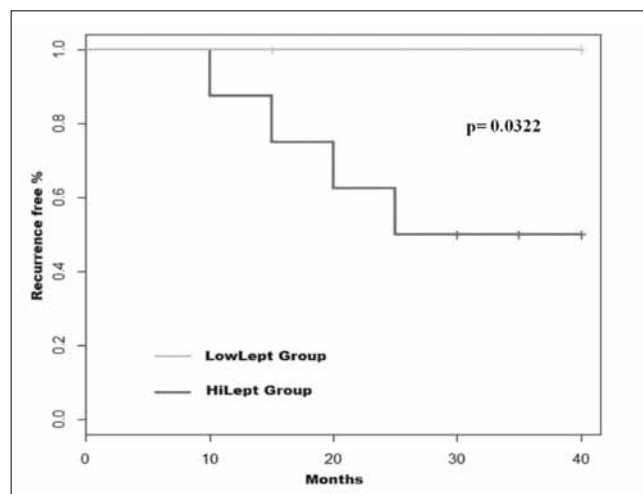


Fig. 2. Kaplan-Meier recurrence-free curves categorised by leptin expression (high versus low intensity). P values were estimated using the log-rank test.

Table III. Multivariate logistic regression analysis for loco-regional recurrences.

Parameter	Odds ratio	p value	95% Confidence interval
T	0.53	0.59	0.20-2.02
N	3.73	0.001	0.58-4.09
Stage	0.98	0.33	0.86-2.37
Histological grade	2.95	0.008	0.56-3.33
Leptin	4.41	0.0003	1.68-4.75

We first analysed variations in leptin as related to TNM and found no correlation considering the complete TNM staging. However, by studying individual clinicopathological features we obtained interesting results. Concerning T stage, we observed higher expression in cases of advanced tumour, although this did not reach statistical significance compared with early T stages. In our opinion, the lack of statistical significance could be explained by the small size of our sample. Considering categories N0 and N+, no significant differences in leptin expression were seen. Indeed, there appears to be slightly higher leptin expression in N0 tumours. These results on TNM and leptin expression could indicate a presence of leptin in primary tumours, not as a factor promoting lymph node metastasis, but as a growth factor mainly related to size and malignant degeneration of the tumour.

A similar result was also obtained investigating grading, where leptin expression, although not statistically significant, was increased in cases of advanced grade. Again, this statistical trend leads us to consider leptin as a growth factor involved in tumour growth.

In this regard, many authors have demonstrated a possible role for leptin. In particular, in physiological conditions it has been reported that proliferation of cells in salivary glands is reduced in the presence of leptin³¹. Goren et al.³² noted that *in vivo* leptin stimulates the proliferation of murine and human oral keratinocytes. It has also been proposed that leptin acts as a growth factor in epithelial cells colonic mucosa³³, in human and murine thacheo-bronchial cells³⁴ and in cultured preadipocyte cells³⁵. Martin-Romero et al. showed that human leptin stimulates the production of IL-2 and IFN-gamma, stimulating murine peritoneal macrophages and human monocytes as well as T lymphocytes³⁶. Finally, Wolf et al. reported that the infusion of recombinant leptin stimulates the expression of TGF-beta 1 in cultures of glomerular endothelial cells, and therefore leptin could be a growth factor for renal endothelial cells³⁷.

In pathological conditions, leptin and its receptor have been identified in malignant cells of diverse origins, including lung and gastric carcinomas and leukaemic cells, and the expression of leptin in pituitary adenomas has been correlated to greater tumour invasiveness^{38,39}.

In addition, an autocrine function of leptin has been hypothesised because it promotes the increase of its expres-

sion through self-stimulation and increases the expression of its own receptor⁴⁰. Unfortunately, this autocrine pathway has not been demonstrated in laryngeal SSC, but our study suggests that this is likely, also because Kowalczyk et al. have shown that expression of leptin in samples of laryngeal SCC is not related to serum leptin concentrations, and for this reason it is considered a possible paracrine product of the cancer, and not a product of other tissues⁴¹.

During follow-up, 8 patients developed loco-regional recurrence, which was significantly associated with high expression of leptin ($p = 0.017$) compared to tumours with low expression (Log-rank test, $p < 0.05$). Moreover, Spearman's rank correlation test also showed a statistically significant result ($r = 0.59$; $p = 0.002$) demonstrating that, in all cases of recurrence, the primary tumour had high expression of leptin.

In fact, Kaplan-Meier curves have shown a significant presence of recurrences in cases with high expression of leptin. This could be explained by the fact that leptin is probably expressed in advanced stages of cancer, where we found a statistical trend, playing a key role in spreading and survival of tumour cells. We also observed high focal expression of leptin in solid nests of tumour cells infiltrating the underlying connective.

For this reason, we believe that leptin may be a useful histological marker for predicting recurrence of malignancy. The results of our immunohistochemical study and literature data, supporting the involvement of leptin in other neoplastic diseases, lead us to believe that this neuropeptide may play a role in tumorigenesis and increase the risk of recurrence, and therefore could become an important cancer biomarker in the larynx.

Conclusions

Although this study has several weaknesses such as different treatments in a small cohort inhomogeneous for stage, our preliminary results suggest that leptin in primary laryngeal SCCs may be a valuable parameter for predicting patients at increased risk of recurrence after treatment. This evidence may be potentially relevant for implementation of closer follow-up protocols, to establish alternative therapeutic regimens in patients with high expression of leptin in laryngeal SCC and to use this peptide as a cancer marker.

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References

- 1 Scharrer E, Scharrer B. *Hormones produced by neurosecretory cells*. Recent Prog Horm Res 1954;10:193-240.
- 2 Martini L. *Recent advances in the study of the Hypothalamic Releasing Factors*. In: Knowels F, Vollrath L, editors. *Neurosecretion The Final Neuroendocrine Pathway*. Berlin: Springer-Verlag; 1974. p. 135-47.
- 3 Tessitore V. *Il neurone monoaminergico e il neurone peptidergico*. Ital J Anat Embryol 1978;83:25-101.
- 4 Pearse AG. *Common cytochemical properties of cells producing polypeptide hormones, with particular reference to calcitonin and the thyroid C cells*. Vet Rec 1966;79:587-90.
- 5 Bloom SR, Polak JM. *Gut hormone overview*. In: Bloom SR, editor. *Gut Hormones*. London: Churchill and Livingstone; 1978. p. 3-18.
- 6 Le Douarin NM. *The embryological origin of the endocrine cells associated with the digestive tract*. In: Bloom SR, editor. *Gut Hormones*. London: Churchill and Livingstone; 1978. p. 49-56.
- 7 Evsukova EV. *APUD cells. The human pulmonary neuroendocrine system*. Fiziol Cheloveka 2006;32:121-30.
- 8 Lindheim SR, Sauer MV, Carmina E, et al. *Circulating leptin levels during ovulation induction: relation to adiposity and ovarian morphology*. Fertil Steril 2000;73:493-8.
- 9 Pearse AGE, Polak JM. *The diffuse neuroendocrine system and the APUD concept*. In: Bloom SR, editor. *Gut Hormones*. London: Churchill and Livingstone; 1978. p. 33-9.
- 10 Cinti S, Frederich RC, Zingaretti MC, et al. *Immunohistochemical localization of leptin and uncoupling protein in white and brown adipose tissue*. Endocrinology 1997;138:797-804.
- 11 Collins S, Kuhn C, Petro AE, et al. *Role of leptin in fat regulation*. Nature 1996;380:677.
- 12 Dagogo-Jack S, Fanelli C, Paramore D, et al. *Plasma leptin and insulin relationship in obese and nonobese humans*. Diabetes 1996;45:695-8.
- 13 Malik KF, Young WS 3rd. *Localization of binding sites in the central nervous system for leptin (OB protein) in normal, obese (ob/ob), and diabetic (db/db) C57BL/6J mice*. Endocrinology 1996;137:1497-500.
- 14 Cinti S, De Matteis R, Picó C, et al. *Secretory granules of endocrine and chief cells of human stomach mucosa contain leptin*. Int J Obes Relat Metab Disord 2000;24:789-93.
- 15 Bonaventura G, Cucco D, Leone A, et al. *The role of new neurocrine and neuroendocrine messengers on the regulation of the function of major salivary glands in some mammals. An immunohistochemical study*. Ital J Anat Embryol 2008;113:40.
- 16 Gröschl M, Topf HG, Kratzsch J, et al. *Salivary leptin induces increased expression of growth factors in oral keratinocytes*. J Mol Endocrinol 2005;34:353-66.
- 17 Bohlender J, Rauh M, Zenk J, et al. *Differential distribution and expression of leptin and the functional leptin receptor in major salivary glands of humans*. J Endocrinol 2003;178:217-23.
- 18 Leone A, Spatola GF, Cucco D, et al. *Immunohistochemical expression and distribution of orexin, orphanin and leptin in the major salivary glands of some mammals*. Folia Histochem Cytobiol 2012;50:504-12.
- 19 De Matteis R, Puxeddu R, Riva A, et al. *Intralobular ducts of human major salivary glands contain leptin and its receptor*. J Anat 2002;201:363-70.
- 20 Hoggard N, Hunter L, Duncan JS, et al. *Leptin and leptin receptor mRNA and protein expression in the murine fetus and placenta*. Proc Natl Acad Sci USA 1997;94:11073-8.
- 21 Smith-Kirwin SM, O'Connor DM, De Johnston J, et al. *Leptin expression in human mammary epithelial cells and breast milk*. J Clin Endocrinol Metab 1998;83:1810-3.
- 22 Bonaventura G, Cucco D, Spatola GF, et al. *Leptin immunohistochemical expression in rat respiratory system*. In: Gerbino A, Zummo G, Cresciamanno G, editors. *Experimental Medicine Reviews*. Vol. 2/3. Palermo: Plumelia; 2009. p. 57.
- 23 Frankenberry KA, Skinner H, Somasundar P, et al. *Leptin receptor expression and cell signaling in breast cancer*. Int J Oncol 2006;28:985-93.
- 24 Cascio S, Bartella V, Auriemma A, et al. *Mechanism of leptin expression in breast cancer cells: role of hypoxia inducible factor-1alpha*. Oncogene 2008;27:540-7.
- 25 Chia VM, Newcomb PA, Lampe JW, et al. *Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk*. Cancer Epidemiol Biomarkers Prev 2007;16:2697-703.
- 26 Cooper JS, Porter K, Mallin K, et al. *National Cancer Database report on cancer of the head and neck: 10-year update*. Head Neck;31:748-58.
- 27 Barnes L, Tse LY, Hunt JL, et al. *Tumours of the hypopharynx, larynx and trachea: introduction*. In: Barnes L, Eveson J, Reichart P, et al., editors. *World Health Organization Classification of Tumours. Pathology and Genetics of Head and Neck Tumours*. Lyon: IARC Press; 2005. p. 111-17.
- 28 Forastiere A, Koch W, Trotti A, et al. *Head-and-neck cancer*. N Engl J Med 2001;345:1890-900.
- 29 Società Italiana di Otorinolaringoiatria e Chirurgia Cervico-Facciale (SIOeChC-F). *Linee guida sul "Cancro della Laringe"*. Argomenti Acta Otorhinolaryngol Ital 2008;II:33-49.
- 30 Schapher M, Wendler O, Gröschl M, et al. *Salivary leptin as a candidate diagnostic marker in salivary gland tumors*. Clin Chem 2009;55:914-22.
- 31 Higa M, Shimabukuro M, Fukuchi M, et al. *Atrophic change of rat salivary gland during adenovirus-induced hyperleptinemia*. Biochem Biophys Res Commun 2002;291:675-9.
- 32 Goren I, Pfeilchifter J, Frank S. *Determination of leptin signalling pathways in human and murine keratinocytes*. Biochem Biophys Res Commun 2003;303:1080-5.
- 33 Hardwick JC, Van Den Brink GR, Offerhaus GJ, et al. *Leptin is a growth factor for colonic epithelial cells*. Gastroenterology 2001;121:79-90.
- 34 Tsuchiya T, Shimizu H, Hori T, et al. *Expression of leptin receptor in lung: leptin as a growth factor*. Eur J Pharmacol 1999;365:273-9.

- ³⁵ Zwirska-Korczala K, Adamczyk-Sowa M, Sowa P, et al. *Role of leptin, ghrelin, angiotensin II and orexins in 3T3 L1 preadipocyte cells proliferation and oxidative metabolism.* J Physiol Pharmacol 2007;58(Suppl 1):53-64.
- ³⁶ Martin-Romero C, Santos- Alvarez J, Goberna R, et al. *Human leptin enhances activation and proliferation of human circulating T lymphocytes.* Cell Immunol 2000;199:15-24.
- ³⁷ Wolf G, Hamann A, Han DC, et al. *Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis (secoments).* Kidney Int 1999;56:860-72.
- ³⁸ Mix H, Widjaja A, Jandl O, et al. *Expression of leptin receptor isoforms in the human stomach.* Gut 2000;47:481-6.
- ³⁹ Hino M, Nakano T, Yamane T, et al. *Leptin receptor and leukemia.* Leuk Lymphoma 2000;36:457-61.
- ⁴⁰ Chen C, Chang YC, Liu CL, et al. *Leptin-induced growth of human ZR-75-1 breast cancer cells is associated with up-regulation of cyclin D1 and c-Myc and down-regulation of tumor suppressor p53 and p21WAF1/CIP1.* Breast Cancer Res Treat 2006;98:121-32.
- ⁴¹ Kowalczyk A, Wiecek A, Franek E, et al. *[Plasma concentration of leptin, neuropeptide Y and tumor necrosis factor alpha in patients with cancers, before and after radio- and chemotherapy].* Pol Arch Med Wewn 2001;106:657-68.

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HEAD AND NECK

Doppler ultrasonography before thyroidectomy is not useful to prevent cerebrovascular accident

L'ecodoppler pre-operatorio non previene il rischio di eventi cerebrovascolari post-tiroidectomia

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SUMMARY

Surgical manipulation of the cervical vascular bundle during neck surgery may promote a thromboembolic event. We evaluated if thyroid surgery is associated with any alterations in the carotid artery wall that would imply an augmented risk of cerebrovascular accident (CVA). A prospective evaluation of a consecutive series of patients who underwent total thyroidectomy was performed. High resolution Doppler ultrasonography (HR-DU) was performed the day before and three days after surgery in asymptomatic consenting patients scheduled for total thyroidectomy. Two hundred patients were recruited. Preoperatively, no hemodynamically significant stenosis (> 70%) was observed. Surgery was delayed in one patient because of asymptomatic subclavian steal syndrome. The remaining 199 patients underwent total thyroidectomy. No modification of preoperative findings was observed at the postoperative HR-DU evaluation. No CVA was observed. In the absence of any significant stenosis, thyroid surgery does not affect the presence and extent of arterial wall disease and the consequent risk of CVA. Thus, screening with HR-DU does not seem beneficial in a generally asymptomatic population without significant risk factors.

KEY WORDS: Thyroidectomy • Thyroid surgery • Complications • Postoperative stroke • Doppler ultrasonography

RIASSUNTO

La manipolazione del fascio vascolo-nervoso in corso di interventi chirurgici del collo potrebbe facilitare l'instaurarsi di eventi tromboembolici. Abbiamo eseguito una valutazione prospettica di una serie consecutiva di pazienti sottoposti a tiroidectomia totale. Abbiamo valutato se l'intervento chirurgico di tiroidectomia può comportare alterazioni di parete dell'arteria carotide in grado di determinare un rischio aumentato di accidenti cerebro-vascolari. In tutti i pazienti asintomatici per eventi cerebro-vascolari sottoposti a tiroidectomia totale, è stato eseguito un ecodoppler ad alta risoluzione il giorno prima e tre giorni dopo l'intervento chirurgico programmato. Sono stati inclusi 200 pazienti. Alla valutazione preoperatoria non sono state evidenziate stenosi carotidiche emodinamicamente significative (> 70%). L'intervento chirurgico è stato rimandato in un paziente nel quale è stata posta diagnosi di sindrome del furto della succlavia. I rimanenti 199 pazienti sono stati sottoposti a tiroidectomia totale. La valutazione doppler post-operatoria è risultata invariata rispetto a quella pre-operatoria. Nella serie esaminata non sono stati osservati casi di accidenti cerebro-vascolari. In assenza di stenosi carotidiche emodinamicamente significative, l'intervento chirurgico di tiroidectomia non influisce sulla presenza ed estensione della patologia di parete carotidea e sul conseguente rischio di accidenti cerebro-vascolari. In assenza di significativi fattori di rischio, l'esecuzione dell'ecodoppler di screening non sembra indicato nella popolazione generale asintomatica per eventi cerebro-vascolari.

PAROLE CHIAVE: Tiroidectomia • Chirurgia del collo • Complicanze • Ictus post-operatorio • Ecodoppler

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Introduction

Carotid artery stenosis (CAS) is the single most important risk factor for cerebrovascular accident (CVA)¹. Surgery implies an increased risk of CVA in patients with CAS, perhaps because of the thromboembolic risk related to surgery, but also of the surgical and anaesthetic manoeuvres². It is well known that among general surgical patients, those who undergo neck surgeries are at increased risk of CVA compared with those who undergo non-neck

procedures¹⁻³. In addition to surgical manoeuvres, this increased risk could be simply related to the fact that neck hyperextension is often required during surgical procedures on the neck, which could lead to intimal tearing of the carotid artery and thrombus formation or plaque ulceration from turbulent blood flow¹⁻³.

Among neck surgical procedures, thyroidectomy is probably the most frequently performed⁴. At present, mortality for this procedure approaches 0% with an overall complication rate that is less than 3% (i.e. compressive

haematoma, recurrent laryngeal nerve palsy and hypoparathyroidism)⁵. Even if CVA following thyroid surgery has been anecdotally reported in the literature⁶⁻⁷, perioperative embolic stroke represents the source of malpractice litigation following thyroid surgery in 3% of cases⁴. At least from a theoretical point of view, this operation could imply an increased risk of such a feared complication because of surgical manipulation of the cervical vascular bundle during thyroidectomy. Indeed, retraction of the common carotid artery (CCA) is an important step to expose the trachea-oesophageal groove and safely trace the course of the inferior laryngeal nerve. The risk to reduce vascular flow, with potential ocular or central nervous system damage, is well known and described, as well as the potential to dislodge thrombus or plaque, especially in older patients with a large thyroid gland that requires important retraction and extensive dissection⁸.

However, if this is true for older patients with particular risk factor for CAS, it is not known if surgical manipulation of the cervical neurovascular bundle is a manoeuvre at risk for the general population. This for two main reasons. First, no exact and definitive data concerning the prevalence of the CAS in the general population are available. Secondly, no data concerning the impact of the surgical manipulation during thyroidectomy on the wall of the CCA are available.

We have recently observed a post-thyroidectomy CVA and death in a 45-year-old male patient with an asymptomatic and non-significant carotid stenosis (30-40%). For this reason, we designed this prospective study with the aim to evaluate in a large series of patients aged 40 years or more the prevalence of CAS and the eventual alteration of the carotid wall related to the surgical procedure, in order to define the utility of routine high resolution Doppler ultrasonography (HR-DU) examination to prevent CVA following thyroid surgery.

Materials and methods

All the patients scheduled for total thyroidectomy (TT) between 1 June 2009 to 30 March 2010 aged 40 years or more were considered eligible. Previous CVA accident, history of CAS or cerebrovascular disease were considered exclusion criteria. Eligible patients provided an informed consent for inclusion in the study. The study protocol was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore, Faculty of Medicine and Surgery in Rome, Italy.

Study protocol

All recruited patients underwent HR-DU the day before and three days after surgery using the iU22 2D ultrasound system (Philips Electronics, Amsterdam, The Netherlands) with a 7 MHz linear transducer. Patients were examined in the supine position with the neck ro-

tated 45° in the direction opposite the site being examined. To avoid interobserver variability, all measurements were performed by the same operator (A.S.), who was unaware of the subjects' clinical and laboratory findings. The common, internal and external carotid arteries and the vertebral arteries were examined on both sides to exclude stenosis. The intima-media thickness (IMT) of the CCA on each side was assessed. IMT was measured on the far wall at 5, 10 and 15 mm proximal to the carotid bifurcation over both right and left common carotid arteries⁹. The IMT was defined as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line (Fig. 1). Reproducibility of the IMT measurement was acceptable as demonstrated by coefficient of variation (CV) of 3% for the common carotid artery IMT. CV was calculated from two repeated measurements performed in 10 patients and five controls on two different occasions, according to the method described by Bland and Altman¹⁰. IMT was defined as the mean of the three measurements per side. For the purpose



Fig. 1. Left common carotid artery visualisation (1a) and intima-media thickness (IMT) evaluation (1b) (see text).

of the present study, HR-DU findings of IMT were classified in four different patterns (I to IV). Pattern I included normal wall intima-media thickness (IMT) (≤ 0.9 mm); pattern II wall thickening without plaque (IMT between 0.9 and 1.3 mm); pattern III wall thickening > 1.3 mm atherosclerotic plaque without stenosis ($< 35\%$); pattern IV: wall thickening > 1.3 mm with stenosing atherosclerotic plaque ($> 35\%$). The degree of stenosis was expressed as the percentage of luminal narrowing and the ipsilateral internal/common carotid artery flow velocity ratio was evaluated. Patients were considered to have clinically significant carotid disease if they had stenosis $\geq 70\%$ in at least one internal carotid artery¹¹.

Data were prospectively recorded in a specifically designed database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA). The following parameters were collected: age, sex, patient's history and risk factors for CAS if any (hypertension, peripheral vascular disease, diabetes mellitus, smoking habit, atherosclerotic heart disease), preoperative diagnosis, operative time, final histology, complications, and pre- and postoperative HR-DU findings.

Surgical technique

All procedures were performed by an experienced endocrine surgeon or by a resident operating under supervision. Total thyroidectomy was performed in all cases. The surgical technique has been described elsewhere^{12,13}. The neck of the patients is hyperextended on the operating table. During any procedure, minimal lateral retraction of the carotid artery is obtained by means of Farabeuf retractors, in order to expose the tracheo-oesophageal groove and to have a good exposition of the inferior laryngeal nerve, which is usually identified where it crosses the inferior thyroid artery and then followed until its entrance into the larynx.

Surgical outcomes

Laryngoscopy was performed postoperatively to check vocal cord motility in all patients. Postoperative PTH, calcium and phosphorus levels were measured in all cases. Hypocalcaemia was defined as a serum calcium level below 8.0 mg/dl, even if only in a single measurement. Hypocalcaemic patients received supplementation therapy even if asymptomatic. Supplementation therapy always included oral calcium and vitamin D (calcitriol). Recurrent laryngeal nerve palsy and hypoparathyroidism were considered definitive if they did not recover within 12 months after intervention.

Follow-up evaluation was obtained by outpatient consultations or telephone contacts with patients or their referring physicians. Patients with hypoparathyroidism were followed by periodical serum measurements of calcium, phosphorus and PTH, and on the basis of these findings supplementation therapy was subsequently tapered. Pa-

tients with vocal cord palsy were followed with periodical laryngoscopy and underwent speech therapy when necessary.

Results

Two hundred consecutive patients were recruited for this study. There were 155 females and 45 males with a mean age of 54.1 ± 10.5 years (range: 40-84). Demographic, clinical, surgical and pathological characteristics of patients are reported in Table I. Overall risk factors for carotid atherosclerotic disease were found in 93 patients (48.2%): smoking in 37, hypertension in 31, diabetes in 9 and combined risk factors in 16 patients.

One hundred and ninety-nine patients underwent total thyroidectomy. In the remaining patient, surgery was delayed because of HR-DU evidence of asymptomatic subclavian steal syndrome, that was referred to vascular surgeons.

Postoperative complications included: 3 transient recurrent laryngeal nerve palsy (1.5%), 54 transient hypocalcaemia (27.1%) and 2 definitive hypoparathyroidism (1.0%). No other complications occurred. Moreover, no postoperative bleeding and/or haematoma requiring reoperation was observed. No perioperative or postoperative CVA was seen.

HR-DU findings

No preoperative evidence of clinically significant stenosis of internal and external carotid arteries and of the vertebral artery was observed. Preoperative mean IMT was 1.01 ± 0.18 mm (range: 0.9-1.3) on the right side and 0.98 ± 0.22 mm (range: 0.9-1.3) on the left side. On the right side, IMT pattern was type I in 125 patients (62.5%),

Table I. Demographic, clinical, surgical and pathological characteristics of patients.

N	200
Age mean \pm SD (years) (range)	54.1 ± 10.5 (40-84)
Sex Males/Females	45/155
Risk factors for atherosclerosis [§]	
Diabetes/smoking/hypertension	13/52/46
Pre-operative diagnosis	
Euthyroid multinodular goitre	97
Toxic multinodular goitre	25
Graves' disease	12
Indeterminate or suspicious nodule	49
Papillary thyroid carcinoma	17
Final histology	
Benign disease	133
Papillary thyroid carcinoma	62
Operative time mean \pm SD (min) (range)	61.1 ± 23.5 (27-140)
Complications	
Transient recurrent laryngeal nerve palsy	3
Transient hypocalcaemia	54
Definitive hypoparathyroidism	2

SD: Standard deviation; [§] 16 patients had a combination of risk factors.

type II in 50 (25.0%), type III in 15 (7.5%) and type IV in the remaining 10 cases (5.0%). Patients with a pattern IV had a mean stenosis of $41.3 \pm 6.7\%$ (range: 35-55%). On the left side, IMT pattern was type I in 106 patients (53.0%), type I in 55 (27.5%), type III in 27 (13.5%) and type IV in the remaining 12 cases (6.0%). Patients with pattern IV had a mean stenosis of $41.2 \pm 6.0\%$ (range: 35-50%). Overall, preoperatively no haemodynamically significant stenosis ($> 70\%$) was observed. Postoperative HR-DU showed no modification of pre-operative findings. In particular, postoperative HR-DU patterns were the same as in the preoperative evaluation in all 199 patients. No intimal tearing, thrombus formation, plaque ulceration, or turbulent flow was observed postoperatively.

Discussion

The incidence of perioperative stroke depends on the type and complexity of the surgical procedure². Perioperative strokes are predominantly ischaemic and embolic^{14,15}. The timing of embolic postoperative strokes has a bimodal distribution. Approximately 45% of perioperative strokes are identified within the first day after surgery, while the remaining 55% occur from the second postoperative day onward². Cardiac and vascular surgeries, in particular combined cardiac procedures, are associated with higher risks².

Despite the relative infrequency of stroke complicating general surgical procedures, the incidence of stroke in surgical patients exceeds what would be expected in similar populations not undergoing intervention¹⁶⁻¹⁹. The incidence of perioperative stroke following general surgical procedures is between 0.08 and 0.7% in patients without a previous history of cerebrovascular disease^{2,18,20} and appears to be confined to those with a cardioembolic source or to patients with CAS^{15,19,21}.

It is well known that CAS, especially if symptomatic, is a risk factor for postoperative CVA². The estimated prevalence of CAS in the general population over the age of 65 is about 1%²². Studies have found that carotid artery stenosis is more prevalent in older adults, smokers, and in those with hypertension and/or heart disease²². Research has not found any individual risk factor or clinically useful risk stratification tool that can reliably and accurately identify people with clinically important CAS.

Moreover, asymptomatic CAS has been proposed to be a special risk factor for increased morbidity for patients undergoing unrelated surgery¹⁹. However, there are currently no definitive data to assess the contribution of CAS to complications in general surgical procedures²³. In a general surgical population, carotid stenosis of at least 50% has been associated with ischaemic stroke in approximately 3.6% of patients²⁴. Indeed, this risk markedly exceeds the risk reported for the general population and patients with bruits^{16-18,25} and approximates the 1-year risk

for stroke in patients with asymptomatic high grade carotid lesions²⁶. However, a greater degree of stenosis did not result in an increased risk²⁴. Moreover, in a retrospective study of 38 patients with a history of vertebrobasilar ischaemia undergoing general surgical operations under general anaesthesia, the risk of perioperative stroke was 6.0% in the vertebrobasilar territory, which is notably higher than the risk for patients with other patterns of cerebrovascular disease²⁷.

Similarly, the type and nature of the surgical procedure influence the risk of CVA. Perioperative stroke may result from extracranial carotid or vertebral artery dissections resulting from neck manipulation and hyperextension during anaesthesia and neck surgery or from dislodgement of arterial atherosclerotic plaques from manipulation of extracranial internal carotid or vertebral arteries during neck surgeries².

Among patients who undergo non-cardiovascular procedures, those undergoing head and neck surgery are considered at higher risk of postoperative stroke^{2,20}. Nonetheless, only a few studies have addressed the incidence of CVA in patients undergoing head and neck surgery^{1,3,28,29}. The higher incidence of postoperative CVA in patients undergoing neck dissection for head and neck surgery is usually attributed to concomitant significant risk factors for CAS (i.e. hypertension, diabetes, peripheral vascular disease, smoking, age, external irradiation), to exposure and manipulation of vascular and neurologic structures and to neck hyperextension and rotation^{1,3,28}. In addition, neck dissection may involve haemodynamic instability, blood loss, exposure and manipulation of vascular and neurologic structures of the neck, all of which may increase the risk¹.

Perioperative stroke in patients undergoing head and neck surgery has been reported in 0.2-4.8% of cases¹⁻³. This wide spectrum of incidences could be related to variations in surgical technique, with consequent differences in neck hyperextension and rotation and in different amounts of carotid artery retraction²⁸.

Thyroidectomy is the most frequently performed head and neck surgical procedure⁴. Even if CVA following thyroid surgery has been anecdotally described^{6,7}, it has been recently reported that embolic stroke represents the source of malpractice claims litigation following thyroidectomy in 3% of case⁴. This rate is the same as for hypoparathyroidism⁴. Obviously, this implies that post-thyroidectomy CVA following thyroidectomy is rare, but not exceptional. The risk of stroke related to retraction of the cervical neurovascular bundle is well known and described, especially in older patients with large goiters⁸. It has also been reported that voluminous cervico-thoracic goitres may determine compression of the common carotid artery with subsequent cerebral ischaemia³⁰. Moreover, as already seen, the neck hyperextension required for thyroidectomy may determine extra-cranial carotid or vertebral-artery

dissections or dislodgements of arterial atherosclerotic plaques^{27,31}.

Unfortunately, we recently observed a post-thyroidectomy stroke that evolved into the death of a 45-year-old patient with no significant CAS or risk factors. Following this serious complication, we designed the present study with the primary aim of evaluating if surgical manipulation during thyroidectomy is associated any alteration of the CCA wall, which implies a potential increased risk of postoperative stroke. As a secondary aim, we determined the prevalence of CAS in an asymptomatic consecutive series of patients scheduled for thyroidectomy.

Morphological abnormalities of arterial walls can be imaged by B-mode ultrasonography. This high-resolution, non-invasive technique is one of the best methods for detection of early stages of atherosclerotic disease, because it is easily applicable, readily available and demonstrates wall structure with better resolution than magnetic resonance angiography or conventional angiography³². Accordingly, ultrasound has been used to monitor the IMT of carotid arteries, which is associated with risk factors for cardiovascular accidents³². IMT reflects not only atherosclerosis, but also non-atherosclerotic intimal reaction such intimal hyperplasia and intimal fibrocellular hypertrophy³². This differentiation is important because epidemiological studies have shown that wall thickening as depicted by ultrasonographic measurement of IMT is different from atherosclerotic plaque regarding localisation, risk factors and predictive value of cardiovascular events³². Standard use of IMT measurement was recently recommended in all epidemiological and interventional trials dealing with cardiovascular disease³². All of these reasons lead us to include IMT measurement in the present study.

The results of this study demonstrated that in a general asymptomatic population aged ≥ 40 years the prevalence of CAS is very low, even in the presence of at least one risk factor (47% of cases). Indeed, a plaque with stenosis $> 35\%$ was observed only in a minority of patients (5% on the right and 6% on the left side). Moreover, no significant stenosis ($> 70\%$) was observed. Obviously these findings, even if based on a relatively small patient series, confirmed, in a prospective study design, that screening for asymptomatic CAS does not seem to be beneficial in a general asymptomatic population. This is in agreement with the recommendations of the U.S. Preventive Services Task Force, which recently expressed against screening for asymptomatic CAS in the general adult population²². However, the most important finding of this study is that surgical manoeuvres during thyroidectomy do not determine any alterations in the carotid artery wall, at least in the absence of significant stenosis. This is of utmost importance since we strongly demonstrated for the first time with HR-UD examination that neck hyperextension and surgical manipulation during thyroid procedure³³ do not

appear to be associated with an increased risk of CVA. Obviously, manipulation of the cervical vascular bundle during thyroidectomy is minimal and not comparable to that of neck dissection and the operative time is relatively short. Further studies should be performed to verify if longer duration of surgery or more extensive manipulation of vascular neck structures in other kinds of head and neck procedures (i.e. lateral neck dissection) might determine alteration of the carotid artery wall and consequent increased risk of CVA, as suggested by previously published studies on this topic.

Conclusions

In the absence of significant CCA stenosis, thyroid surgery does not affect the presence and extent of arterial wall disease and the consequent risk of cerebrovascular accidents. Screening with HR-DU does not seem to be beneficial in a general asymptomatic population without significant risk factors.

References

- 1 Thompson SK, Southern DA, Mckinnon JG et al. *Incidence of perioperative stroke after neck dissection for head and neck cancer*. Ann Surg 2004;239:428-31.
- 2 Selim M. *Perioperative Stroke*. N Engl J Med 2007;356:706-13.
- 3 Nosan DK, Gomez CR, Maves MD. *Perioperative stroke in patients undergoing head and neck surgery*. Ann Otol Rhinol Laryngol 1993;102:717-23.
- 4 Abadin SS, Kaplan EL, Angelos P. *Malpractice litigation after thyroid surgery: the role of recurrent laryngeal nerve injuries, 1989-2009*. Surgery 2010;148:718-23.
- 5 Lombardi CP, Raffaelli M, De Crea C, et al. *Complications in thyroid surgery*. Minerva Chir 2007;62:395-408.
- 6 Shai SE, Chen CY, Hsu CP, et al. *Surgical management of substernal goiter*. J Formos Med Assoc 2000;99:827-32.
- 7 Houghton SG, Farley DR, Brennan MD, et al. *Surgical management of amiodarone-associated thyrotoxicosis: Mayo Clinic experience*. World J Surg 2004;28:1083-7.
- 8 Reeve T, Thompson NW. *Complications of thyroid surgery: How to avoid them, how to manage them, and observations on their possible effect on the whole patient*. World J Surg 2000;24:971-5.
- 9 Papa A, Santoliquido A, Danese S, et al. *Increased carotid intima-media thickness in patients with inflammatory bowel disease*. Aliment Pharmacol Ther 2005;22:839-46.
- 10 Bland JM, Altman DG. *Statistical methods for assessing agreement between two methods of clinical measurement*. Lancet 1986;1:307-310.
- 11 Yang EH, Holmes DR. *Surgical and percutaneous management of carotid artery stenosis*. Curr Probl Cardiol 2008;33:291-316.
- 12 Bellantone R, Lombardi CP, Bossola M, et al. *Total thyroidectomy for management of benign thyroid disease: review of 526 cases*. World J Surg 2002;26:1468-71.

- ¹³ Raffaelli M, De Crea C, Ronti S, et al. *Substernal goiters: Incidence, surgical approach, and complications in a tertiary care referral center.* Head Neck 2011;33:1420-5.
- ¹⁴ Likosky DS, Marrin CA, Caplan LR, et al; *Northern New England Cardiovascular Disease Study Group.* *Determination of etiologic mechanisms of stroke secondary to coronary artery bypass graft surgery.* Stroke 2003;34:2830-4.
- ¹⁵ Limburg M, Wijdicks EF, Li H. *Ischemic stroke after surgical procedures: clinical features, neuroimaging, and risk factors.* Neurology 1998;50:895-901.
- ¹⁶ Larsen SF, Zaric D, Boysen G. *Postoperative cerebrovascular accidents in general surgery.* Acta Anaesthesiol Scand 1988;32:698-701.
- ¹⁷ Landercasper J, Merz BJ, Cogbill TH, et al. *Perioperative stroke risk in 173 consecutive patients with a past history of stroke.* Arch Surg 1990;125:986-9.
- ¹⁸ Parikh S, Cohen J. *Perioperative stroke after general surgical procedures.* NY State J Med 1993;93:162-5.
- ¹⁹ Hagino RT, Rossi PJ, Rossi MB, et al. *Asymptomatic carotid stenosis and unrelated operations: should we be more aggressive?* J Am Coll Surg 2001;192:608-13.
- ²⁰ Kam PC, Calcroft RM. *Peri-operative stroke in general surgical patients.* Anaesthesia 1997;52:879-83.
- ²¹ Hart R, Hindman B. *Mechanisms of perioperative cerebral infarction.* Stroke 1982;13:766-73.
- ²² U.S. Preventive Services Task Force. *Screening for carotid artery stenosis: U.S. Preventive Service Task Force recommendation statement.* Ann Int Med 2007;147:854-9.
- ²³ Szeder V, Torbey MT. *Prevention and treatment of perioperative stroke.* Neurologist 2008;14:30-6.
- ²⁴ Evans BA, Wijdicks EF. *High-grade carotid stenosis detected before general surgery: is endarterectomy indicated?* Neurology 2001;57:1328-30.
- ²⁵ Ropper AH, Wechsler LR, Wilson LS. *Carotid bruit and the risk of stroke in elective surgery.* N Engl J Med 1982;307:1388-90.
- ²⁶ Meissner I, Wiebers DO, Whisnant JP, et al. *The natural history of asymptomatic carotid artery occlusive lesions.* JAMA 1987;258:2704-7.
- ²⁷ Blacker DJ, Flemming KD, Wijdicks EFM. *Risk of ischemic stroke in patients with symptomatic vertebral stenosis undergoing surgical procedures.* Stroke 2003;34:2659-63.
- ²⁸ Atik MA, Ates M, Akkus NI et al. *Preoperative Doppler sonography for prevention of Perioperative stroke in head and neck cancer patients undergoing neck dissection: is it beneficial?* J Clin Ultrasound 2007;35:38-9.
- ²⁹ Rechtweg J, Wax MK, Shah R et al. *Neck dissection with simultaneous carotid endarterectomy.* Laryngoscope 1998;108:1150-3.
- ³⁰ Ribet ME, Mensier E, Caparros-Lefebvre D, et al. *Cerebral ischemia from thoracic goiter.* Eur J Cardiothorac Surg 1995;9:717-8.
- ³¹ Paciaroni M, Bogousslavsky J. *Cerebrovascular complications of neck manipulation.* Eur Neurol 2009;61:112-8.
- ³² Touboul PJ, Hennerici MG, Meairs S, et al. *Mannheim carotid intima-media thickness consensus (2004-2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006.* Cerebrovasc Dis 2007;23:75-80.
- ³³ Giugliano G, Proh M, Gibelli B, et al. *Central neck dissection in differentiated thyroid cancer: technical notes.* Acta Otorhinolaryngol Ital 2014;34:9-14.

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OTOLOGY

First experience in Italy with a new transcutaneous bone conduction implant

Prima esperienza in Italia con una nuova protesi impiantabile a conduzione ossea

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SUMMARY

Since 2011, transcutaneous bone-anchored auditory implants have been an alternative to the classic percutaneous implant (Baha) for bilateral conductive/mixed hearing loss that cannot be corrected by surgery. Recently, a new transcutaneous device has been approved for clinical use. Its internal component is made of the classic titanium Baha fixture, coupled to a 27 mm diameter subcutaneous circular magnet. The external component includes a second circular magnet 29 mm in diameter and a digital sound processor. To date, there are no reports describing the results of the application of this device. The aim of the present study is to report on the anatomical and functional results of transcutaneous Baha implantation in three patients: two adults, one with syndromic aural atresia and one with bilateral conductive hearing loss due to bilateral tympanomastoidectomy, and an 8-year-old child with non-syndromic aural atresia. No major intraoperative or post-operative complications were observed. The three patients tolerated the external magnet, with no signs of skin irritation. Functional results were good: median unaided free-field PTA (0.5-3 kHz) was 50 dB HL (range = 41-66 dB HL); with the transcutaneous Baha median PTA (0.5-3 kHz) was 27 dB HL (range = 25-30 dB HL) and median gain was 25 dB HL (range = 11-39 dB HL). Preliminary results encourage use of the device as a valuable alternative to other implantable devices in these patients. To ensure the success of treatment, several precautions are suggested including gradually increasing use during the first post-operative months to favour skin adaptation to magnet pressure. In addition to skin reactions, in a paediatric age most concerns are related to the curvature of the skull, which may induce tenting of the skin over the internal magnet.

KEY WORDS: Transcutaneous • Bone conduction implant • Baha

RIASSUNTO

Nei pazienti affetti da ipoacusia trasmissiva o mista bilaterale che non trovano indicazione in una ricostruzione chirurgica, sono state nuovamente reintrodotte protesi ad impianto osseo di tipo transcutaneo, in alternativa a quelle percutanee di uso corrente (Baha). Di recente, un nuovo dispositivo Baha transcutaneo è stato approvato per uso clinico. Esso è composto da una parte impiantabile, che consta della classica vite Baha accoppiata ad un magnete circolare sottocutaneo di 27 mm di diametro, e da una porzione esterna, costituita da un secondo magnete circolare di 29 mm e dal processore digitale del suono. Ad oggi non vi sono studi clinici che descrivano i risultati dell'applicazione del Baha transcutaneo. Il presente lavoro riporta i risultati anatomici e funzionali dell'impianto in tre pazienti operati presso l'Ospedale Pediatrico "Bambino Gesù" di Roma: due adulti, uno affetto da atresia auris sindromica ed uno da ipoacusia trasmissiva bilaterale (esiti di timpanoplastica aperta bilaterale), ed una bambina di 8 anni con atresia auris bilaterale non sindromica. Non sono state osservate complicanze intra- o post-operatorie. Tutti e tre i pazienti hanno ben tollerato il magnete esterno senza segni di irritazione cutanea. I risultati funzionali sono apparsi incoraggianti: il PTA (0.5-3 kHz) mediano con il Baha transcutaneo è di 27 dB HL (range = 25-30 dB HL) e il guadagno mediano di 25 dB HL (range = 11-39 dB HL). In considerazione di ciò, il Baha transcutaneo sembra proporsi come una valida alternativa alle protesi impiantabili a conduzione ossea nei pazienti con ipoacusia trasmissiva bilaterale. Tuttavia, affinché il trattamento abbia successo sembrano opportuni alcuni accorgimenti, come in particolare un graduale incremento nell'utilizzo del dispositivo durante i primi mesi post-operatori allo scopo di favorire l'adattamento della cute sottostante al magnete ed evitare reazioni locali. Motivo di particolare attenzione soprattutto in età pediatrica è la spiccata curvatura della teca cranica, che potrebbe causare una sporgenza dei margini del magnete sottocutaneo, determinando una maggiore sofferenza locale dei tessuti.

PAROLE CHIAVE: Transcutaneo • Impianto a conduzione ossea • Baha

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Introduction

For decades, bone conduction implants have been the mainstay of treatment of bilateral conductive hearing loss that cannot be corrected by otomicrosurgery. By allowing

activation of the cochlea by bone vibration, they bypass the air conduction impairment and restore good quality hearing. Percutaneous implants, which imply a direct coupling of the external and the implanted component through an interrupted skin, have been highly successful

both in adult and paediatric subjects¹⁻⁶, allowing direct transmission of sound vibrations through the bone. However, related drawbacks include the need for a complete osseointegration, the risk of local infection or skin overgrowth, and poor aesthetic outcomes.

Recently, transcutaneous bone conduction implants have been available for the same indications as percutaneous devices. Compared to the latter, they are abutment-free, thus stimulating bone vibration through an intact skin thanks to the magnetic coupling between an external and an implantable component. In turn, this allows a better cosmetic result and elimination of the risk of local infection and extrusion, while maintaining good functional gain⁷⁻⁹. These are the principles that could drive the indication for such a device and the main reasons for shifting the choice from percutaneous to transcutaneous.

In 2013, a new transcutaneous bone conduction implant designed on pre-existing Baha implants obtained CE mark and Food and Drug Administration approval (www.fda.gov) for subjects aged 5 and older. The device is a non-active one, in which vibration of a “passive” implant is driven by an external mechanical transducer. The internal (implantable) component is made of a 3- or 4-mm titanium fixture of the BI300™ series and of a circular magnet (BIM400™) 27 mm in diameter and 2.4 mm in thickness, which is coupled to the fixture. The external component includes a digital multi-channel sound processor and a 29.5 mm large and 4.9 mm thick magnet, which adapts to the underlying skin thanks to a pad that is 1.5 mm thick. The external magnet can be chosen among six different strengths.

Indications are identical to those of other transcutaneous bone-conduction implants: bilateral conductive hearing loss, bilateral mixed hearing loss with bone-conduction PTA (0.5-3 kHz) \leq 45 dB HL (up to 55 dB HL if appropriate sound processor is used) and single-sided sensorineural deafness.

The potential advantage of the transcutaneous Baha compared with other currently available passive transcutaneous implants is the possibility of conversion to a percutaneous solution in case of major local complications or special conditions in which the magnet has to be removed. At any rate, this should be considered a minor advantage, because the procedure would likely require general anaesthesia.

Possible device-related drawbacks are common to all other transcutaneous implants, i.e. skin complications due to use of a magnet that is too powerful and lower hearing gain compared with a percutaneous device.

To date, there are no published reports in the literature on the anatomical and functional outcome of transcutaneous Baha.

“Bambino Gesù” Pediatric Hospital is a tertiary care Italian centre for paediatric disease, with long-standing experience with bone-anchored hearing aids⁴. Since Sep-

tember 2013, the Audiology and Otology Unit of the Institution has started implanting transcutaneous Baha and is therefore the first centre in Italy and one of the first in Europe to try this device. The aim of the present study is to describe three cases, focusing on surgical procedure and anatomical and functional outcomes.

Description of clinical cases

Our methods were reviewed and approved by the Institutional Review Board and are in accordance with the ethical standards laid down in the Declaration of Helsinki. Patients or their parents gave their informed consent to inclusion in the study.

Candidates for the Baha Attract™ (Cochlear Bone-Anchored Solutions, Molnlicke, Sweden) were selected amongst patients followed in the Audiology and Otology Unit of Bambino Gesù Pediatric Hospital. Only subjects with pure bilateral conductive hearing loss were enrolled in the study. Anatomical criteria were a presumed scalp thickness of at least 5 mm (confirmed intraoperatively) and skull thickness \geq 3 mm as assessed by a pre-operative high-resolution CT of the temporal bones.

The senior otosurgeon gave patients and/or their parents the possibility to choose between a percutaneous or a transcutaneous device among those commercially available.

Three patients, two adults and one 8-year-old child, were implanted. Demographic and clinical characteristics are shown in Table I. Before being implanted, patients 1 and 2 had been using an external, steel band bone-conduction hearing aid; for them Baha Attract™ implantation was the only surgical procedure of the operating session. Patient 3 had been using no hearing aid, but gave consent for implantation to be performed in the same session as left-sided canal-wall down tympanomastoidectomy, after experiencing the bone conduction by the classic Rod Test. The surgical steps common to all patients were:

- Measurement of skin thickness by a needle gauge before local anaesthetic infiltration
- External marking of the site for the fixture and the magnet (Fig. 1), paying particular attention to distancing the site of incision at least 1.5 cm from the edge of the magnet.
- C-shaped incision approximately 5-6 cm postero-superiorly to the auricle.
- Periosteum exposure and cross-shaped incision.
- Drilling and countersinking of a hole and 3 or 4 mm BI300™ fixture placement.
- Coupling of the magnet to the fixture head (Fig. 2)
- Suture of the wound and compression medication

All subjects received 3 mm fixtures because skull thickness did not allow placement of a 4 mm one. In patient 1, the internal magnet was not placed in full contact with the skull bone, due to the steeper curvature of the child calvarial bone, which caused minimal tenting of the skin

Table I. Demographic and clinical characteristics of implanted patients.

Pt	Sex	Age (yr)	Side	R-ACPTA	L-ACPTA	Aetiology	Pre-operative BCHA
1	F	8	R	58	52	Bilateral aural atresia	Steel band
2	M	22	R	69	69	Treacher-Collins syndrome	Steel band
3	M	44	L	39	45	Bilateral CWD TPL	None

L: left; R: right; ACPTA: Air-conduction pure-tone average; BCHA: conventional bone conduction hearing aid

**Fig. 1.** Marked surgical site.**Fig. 2.** Coupling and calibrated wrenching of the internal magnet to the implanted fixture.

covering the magnet. In patient 3, due to thin skull bone, drilling of two holes was necessary before a suitable place for fixture insertion could be found. One week post-operatively, patient 2 presented with mild swelling of the sub-

cutaneous tissue above the magnet, associated with fever and flu-like symptoms, which resolved after intravenous antibiotic and corticosteroid treatment.

Patients 1 and 2 received their external Baha 4™ processor one month after surgery, whereas switch-on was pre-cautionally planned two months after surgery in patient 3 because of the frequent ear medications that were needed after tympanomastoidectomy.

On the day of processor loading, each patient was invited to try magnets of increasing strength in the clinic, until one allowing good hearing and processor stability on the scalp at the same time was found (magnet N.1 in patient 1 and N.2 in patients 2 and 3). The Baha 4™ processor was fitted by means of the Cochlear® Baha Fitting Software™ (Cochlear Bone-Anchored Solutions AB, Mölnlycke, Sweden). Subjects were instructed to use the processor for a maximum of 4 hours a day for the first two months. They were also advised to check the skin area under the magnet daily and to suspend processor use immediately in case they should notice any redness or feel pain. Follow-up visits were planned 1 and 2 months after loading: the skin under the magnets was found intact and healthy in all subjects.

All patients reported using their processor comfortably for the recommended time with no skin hyperaemia in the area of magnet contact (Fig. 3). Functional results in the unaided condition with the external bone conduction hearing aid and with Baha Attract™ are reported for each subject in Table II: median unaided PTA was 50 dB HL, median Baha PTA was 27 dB HL and median gain with Baha was 25 dB HL. Speech recognition scores were obtained by administering lists of bisyllabic Italian words¹⁰ in quiet. Figure 4 illustrates the mean hearing threshold in the unaided and Baha Attract-aided conditions for each frequency.

Discussion

This is the first report in the literature describing transcutaneous Baha surgery and functional outcomes. Overall, the cases presented in this study suggest that Baha Attract™ surgery is safe and that the device can be a valuable alternative to traditional percutaneous bone implants as well as other transcutaneous devices. In our patients, no skin complications were observed following fitting, differently from our recent series on Sophono™ (Sophono Inc., Boulder, CO, USA)¹¹ and from other studies report-



Fig. 3. Paediatric patient #1 with and without the Baha 4™ sound processor.

Table II. Functional results with transcutaneous Baha.

Pt	Unaided PTA	Unaided speech recognition	BCHA PTA	BCHA speech recogn	Baha PTA	Baha speech recognition	Baha Attract™ gain
1	50	20	40	80	25	100	25
2	66	30	48	90	27	100	39
3	41	60	-	90	30	100	11

BCHA: conventional bone conduction hearing aid; PTA: pure tone average

ing a magnet lesion rate as high as 36%¹². Possibly, the soft pad interface under the external magnet and the skin may have favoured better pressure distribution on the underlying skin. Moreover, previous experience with transcutaneous bone conduction implants in our centre was important in choosing the right magnet and in counselling patients and parents correctly as to progressive processor use in the 2-3 months following activation.

The audiological results of our series are comparable to those obtained with other passive transcutaneous bone conduction implants¹¹⁻¹⁴. In particular, a better gain for central frequencies (500-2000 Hz) and a smaller gain for lower (250 Hz) and higher (4000 Hz) frequencies was found, as expected. Overall, the gain appears to be 10-15 dB HL lower than what can be obtained with percutaneous implants, due to skin and soft tissue interposition. For this reason, even though our series is too small to draw any conclusions, it can be hypothesised that subjects with a moderate degree of hearing loss are expected to obtain a greater benefit from the device than patients with an unaided PTA exceeding 70 dB HL in the better ear, such as patient n. 2 in our series.

After the short follow-up of these cases, the typical advantages of passive transcutaneous implants over traditional percutaneous device appear to be confirmed. First, healed skin eliminates the risk of local infection and allows reducing the number of post-operative medications; secondly, life-long care of the peri-abutment skin is no longer

required; third, the timing and level of osseointegration is less crucial with a transcutaneous implant, because of a much lower risk of extrusion, which enables it to fit in a 3 mm fixture in thin skulls.

One specific concern with Baha Attract™ relates to feasibility in very young children for two reasons: first, the thickness of the internal magnet may determine a poor

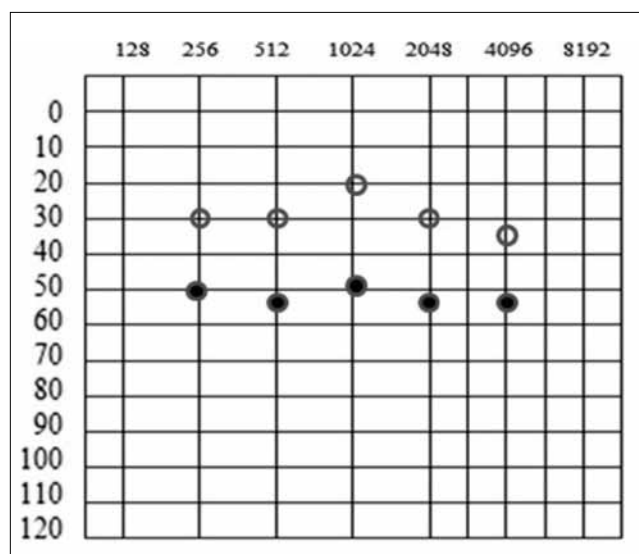


Fig. 4. Average frequency-specific PTA in unaided and Baha-aided conditions.

aesthetical outcome, owing to magnet bulging under very thin skin; second and more important, the internal magnet may not fit the highly curved skull typical of very young children or the irregular skull of syndromic subjects. More specifically, intraoperative placement of the fixture in a perfectly perpendicular plane with the skull emerged as a crucial point. If caution is not taken, there may be a significant tilting of the internal magnet causing a tenting of the skin, and secondary soft tissue injury and necrosis. Although this complication was not observed in our cases, this risk was especially evident in the paediatric case. In conclusion, the present series shows encouraging functional results of Baha Attract™. However, whereas implantation of the device can be considered to be a safe procedure in adults, further studies are needed to eliminate concerns and demonstrate its safety in very young children.

References

- 1 Rasmussen J, Olsen SØ, Nielsen LH. *Evaluation of long-term patient satisfaction and experience with the Baha® bone conduction implant*. Int J Audiol 2012;51:194-9.
- 2 de Wolf MJ, Shival ML, Hol MK, et al. *Benefit and quality of life in older bone-anchored hearing aid users*. Otol Neurotol 2010;31:766-72.
- 3 Barbara M, Biagini M, Lazzarino AI, et al. *Hearing and quality of life in a south European BAHA population*. Acta Otolaryngol 2010;130:1040-7.
- 4 Marsella P, Scorpecci A, Pacifico C, et al. *Pediatric BAHA in Italy: the "Bambino Gesù" Children's Hospital's experience*. Eur Arch Otorhinolaryngol 2012;269:467-74.
- 5 McDermott AL, Williams J, Kuo M, et al. *The Birmingham pediatric bone-anchored hearing aid program: a 15-year experience*. Otol Neurotol 2009;30:178-83.
- 6 Saliba I, Woods O, Caron C. *BAHA results in children at one year follow-up: a prospective longitudinal study*. Int J Pediatr Otorhinolaryngol 2010;74:1058-62.
- 7 Siegert R. *Partially implantable bone conduction hearing aids without a percutaneous abutment (Otomag): technique and preliminary clinical results*. Adv Otorhinolaryngol 2011;71:41-6.
- 8 Sprinzl G, Lenarz T, Ernst A, et al. *First European multi-center results with a new transcutaneous bone conduction hearing implant system: short-term safety and efficacy*. Otol Neurotol 2013;34:1076-83.
- 9 Barbara M, Perotti M, Gioia B, et al. *Transcutaneous bone-conduction hearing device: audiological and surgical aspects in a first series of patients with mixed hearing loss*. Acta Otolaryngol 2013;133:1058-64.
- 10 Turrini M, Cutugno F, Maturi P, et al. *Nuove parole bisillabiche per audiometria vocale in lingua italiana*. Acta Otorhinolaryngol Ital 1993;13:63-77.
- 11 Marsella P, Scorpecci A, Vallarino MV, et al. *Sophono in Pediatric Patients: The Experience of an Italian Tertiary Care Center*. Otolaryngol Head Neck Surg 2014;151:328-32.
- 12 O'Neil MB, Runge CL, Friedland DR, et al. *Patient outcomes in magnet-based implantable auditory assist devices*. JAMA Otolaryngol Head Neck Surg 2014 Apr 24. doi: 10.1001/jamaoto.2014.484 [Epub ahead of print].
- 13 Siegert R, Kanderske J. *A new semi-implantable transcutaneous bone conduction device: clinical, surgical, and audiological outcomes in patients with congenital ear canal atresia*. Otol Neurotol 2013;34:927-34.
- 14 Hol MK, Nelissen RC, Agterberg MJ, et al. *Comparison between a new implantable transcutaneous bone conductor and percutaneous bone-conduction hearing implant*. Otol Neurotol 2013;34:1071-5.

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OTOLOGY

Stretching stenoses of the external auditory canal: a report of four cases and brief review of the literature

“Stretching” della stenosi del condotto uditivo esterno: una serie di casi dopo una breve revisione della letteratura

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SUMMARY

Acquired stenosis of the external auditory canal may be caused by a variety of insults, all sharing a common pathogenesis, namely a cascade of inflammatory changes leading to medial canal fibrosis. Previous surgery (canaloplasty or meatoplasty) and radiotherapy, especially if associated with a history of parotid surgery extended to the external auditory canal, have been implicated as possible causes. The literature offers advice on the management of stenosis consequent to otosurgery for congenital and acquired defects, but nothing on forms secondary to radiotherapy to the head and neck region. The proposed solutions are often cumbersome and difficult to fabricate, and therefore expensive. The aim of this paper, in which the cases of four patients are reported, is to present a new technique initially used for the most severe form – i.e. external auditory canal stenosis after surgery and radiotherapy – and then extended to forms due to different causes. This new technique involves the use of a series of surgical steel tubes of increasing dimension commonly used for tissue expansion in a body piercing practice called stretching and known as ear stretching tunnels or ear stretchers. This innovative approach proved effective in solving external auditory canal stenosis in our patients, with the least discomfort for the patient and the lowest cost. We consider this new solution to be feasible and practical and are convinced that it provides a new approach to an old problem. Further studies are needed to increase the number of clinical cases to verify how long the ear stretcher should be kept in place for the stenosis to stabilise, and to establish whether surgery is always necessary after ear stretcher application and, if so, the best timing for surgery.

KEY WORDS: External auditory canal stenosis • Ear-Stretcher • Parotid surgery • Radiotherapy

RIASSUNTO

La stenosi acquisita del condotto uditivo esterno (CUE) può essere causata da molti insulti con una patogenesi comune che è rappresentata da una cascata di alterazioni infiammatorie che portano alla fibrosi della porzione mediale del condotto. Un precedente intervento chirurgico, cioè canoloplastica o meatoplastica e la radioterapia (RT), soprattutto se associata con precedente chirurgia parotidea estesa al CUE, sono state messe in relazione a questo problema. In Letteratura abbiamo trovato consigli su come gestire le stenosi conseguenti a otocirurgia per difetti congeniti e acquisiti, ma nulla per quelle secondarie a radioterapia applicata al distretto testa e collo; le soluzioni proposte, spesso non sono maneggevoli e sono difficili da fabbricare, perciò sono costose. Il nostro obiettivo è quello di presentare, attraverso l'esposizione dei casi di quattro pazienti, un nuovo metodo utilizzato per la prima volta per la condizione peggiore, ovvero stenosi del condotto uditivo esterno dopo intervento chirurgico e radioterapia, e poi esteso anche alla stenosi di origine diversa. Questa nuova tecnica utilizza una serie di tubi di acciaio chirurgico di diametro crescente solitamente usati in una pratica di espansione cutanea del body piercing chiamata “stretching” e conosciuti come “ear stretching tunnels” o “ear stretchers”. Questo approccio innovativo si è dimostrato efficace nel risolvere la stenosi del condotto uditivo esterno nei nostri pazienti, con il più basso costo e il minimo disagio per il paziente. Pensiamo che questa nuova soluzione sia pratica e dimostri come il contributo di tutti sia essenziale nella ricerca di nuovi approcci a vecchi problemi. Ulteriori studi sono necessari per aumentare il numero di casi clinici, per verificare quanto tempo lo “stretcher” debba essere mantenuto in sede ovvero in quanto tempo la stenosi si stabilizza, in modo da definire se l'intervento sia sempre necessario dopo l'applicazione dello “stretcher” e quale sia il momento giusto per effettuarlo.

PAROLE CHIAVE: Stenosi del condotto uditivo esterno • Stretcher-auricolare • Chirurgia parotidea • Radioterapia

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Introduction

Stenosis of the external auditory canal (EAC) can be congenital, due to abnormalities of the first gill cleft, or acquired as a result of inflammation, trauma and the effects of radiotherapy (RT), all sharing a common pathogenesis,

namely a cascade of inflammatory changes leading to medial canal fibrosis¹. Inflammatory causes of EAC stenosis are chronic and relapsing otitis externa, perichondritis and periostitis. EAC tumours can cause EAC stenosis and their excision can lead to postoperative restenosis (traumatic

Table 1. Hearing outcomes are presented as the mean of threshold by air conduction (TAC) and threshold by bone conduction (TBC) before and after insertion of the stretcher. ABG pre and post indicate the air-bone gap before and after insertion of the stretcher, respectively; Δ ABG indicates the difference between air-bone gaps before and after insertion of the stretcher.

Patient n	TAC pre	TBC pre	TAC post	TBC post	ABG pre	ABG post	Δ ABC
1	23.8	16	19.6	16	7.8	3.6	4.2
2	87.9	49	69.2	49	38.9	20.2	18.7
3	89.6	46.5	75	46.5	43.1	28.5	14.6
4	71.7	57	60.8	57	14.7	3.8	10.9

cause). RT for the treatment of head and neck cancers including those affecting the temporal bone area can induce pathological changes in the EAC that can be divided into: bony changes (resorption, fibrosis, empty lacunae, sequestration) and soft tissue changes (ulceration of the epithelial lining, thickening of the epithelium in the canal and in the tympanic membrane, subepithelial fibrosis, atrophy of ceruminous glands)². These changes may appear clinically as a persistent otitis externa, with otorrhoea and otalgia, resulting in EAC stenosis that prevents adequate examination and cleaning of the ear and is associated with hearing loss. RT, especially if associated with previous parotid surgery, has been related to EAC stenosis³.

Different stenting materials have been successfully used to prevent early, but not delayed, EAC stenosis, including absorbable gelatine sponge (Gelfoam®), backing strips and expandable wicks. Postoperative care is not, however, commonly discussed in the literature. After removal of the packing material about 1 week postoperatively, if the canal is oedematous, it may be necessary to place a Pope wick; in addition, otological antibiotic/steroid drops may help to prevent early restenosis¹. Postoperative EAC restenosis is the most common complication after surgery on the EAC. The use of stents can provide a solution to this problem.

Materials and methods

Technique

Our approach was to use a surgical steel tube that allowed progressive expansion of the stenotic EAC using devices of increasing dimension called ear stretching tunnels or ear stretchers. These are surgical steel tissue expanders (Fig. 1) commonly used in a body piercing practice called stretching and involving the progressive and gradual expansion of a skin area; this process can be applied to every piercing site, but the earlobe is the most frequently involved. Dilatation of the piercing hole is obtained gradually, usually 1 mm per month for the earlobe, by pushing a taper (conical rod) as far as it will go through the piercing hole and replacing it with a stretching tunnel of the appropriate size to be worn between stretches. The history of earlobe stretching is very old: it is a ritual that has been practised by indigenous peoples all over the world since ancient times.

Tribes in various countries (Africa, Eurasia, America) have practised this ritual for cultural, religious and traditional aesthetic purposes. Bone, horn, wood and stone were generally carved for earlobe stretching. King Tutankhamen is one of the earliest individuals known to have stretched earlobes. Although ear stretchers are commercially available in different materials (surgical steel, nickel-free titanium and glass), we decided to test only surgical steel stretchers to keep our clinical records uniform.

Case 1

In July 2012, a 47-year-old Caucasian man was referred to our ENT Department by his general practitioner because of a sudden increase in volume of a lateral neck mass, which had developed three months earlier. The mass was painless, located behind the right rising branch of the jaw, 30–40 mm in size, with a parenchymatous texture, fixed to deep tissues and covered by normal skin. Fine-needle aspiration biopsy (FNAB) of the mass was positive for squamous cell carcinoma. The patient underwent further investigations consisting of panendoscopy of the upper aerodigestive tract, computed tomography (CT) and magnetic resonance imaging (MRI) of the head, neck and chest, total body positron emission tomography (PET)-CT, and electroneurography (ENG) of the facial nerve. Clinical-radiological staging was right parotid carcinoma with EAC erosion and dermal infiltration. Therefore, a right radical parotidectomy and ipsilateral modified radical neck dissection type III (levels II–IV) were carried out. The tumour was leaning against the EAC, adherent to the cortical mastoid and the bony part of the EAC. These structures were drilled for oncologi-



Fig. 1. Commercially-available ear stretching kit including surgical steel tapers and tunnels of increasing gauges.

cal eradication. Part of the concha, cartilaginous EAC and skin were removed, and the deficiency of the submeatus region was filled with a temporo-occipital flap. Gelfoam[®] was used to protect the tympanic membrane (TM), and a silastic foil was fashioned containing a haemostatic plug (Pope wick) to maintain the patency of the new and shorter EAC. The patient had a regular postoperative course except for the onset of delayed facial nerve palsy. The final histological examination was undifferentiated adenocarcinoma of the parotid gland with squamous aspects and neoplastic neurotropism, pT3 N0 R0 M0 G3. Adjuvant radiation therapy, 60 Gy in 30 days, was planned. The patient began RT during which he developed an EAC stenosis due to hypodermic oedema. The stenosis grew so tight that it precluded retention of the Pope wick. Two weeks after the end of RT the EAC diameter was 2 mm (Fig. 2A). Corpuscular serum otorrhoea, eczema and subcontinuous fullness were associated with the EAC stenosis. The TM was no longer visible. Initially, a 2-mm stiff perforated silicon tube was placed, but it was expelled every 4-6 days. Thereafter, a 2.5-mm surgical steel ear stretching tube was used. This second device was retained in the stenotic EAC for one month, after which it was replaced with a 3.2-mm tube for 3 months, and then with a 4-mm tube that is still in place (Fig. 2B). The patient does not come to our clinic for medications because he is able to manage them autonomously, and only comes for his monthly follow-up appointments. Thanks to the ear stretcher, he no longer complains of otorrhoea, fullness, or hearing deficit; cultural buffers are negative for infection, and half of the TM is again visible (Fig. 3). His last follow-up visit was in May 2014, for an overall follow-up period of 21 months. One year has passed since the ear stretcher was positioned, and we think it should be kept in place for at least one year after the end of RT. We decided against an early surgical approach due to the risk of relapse and the expected local effects of RT that could influence surgical outcome. Surgical correction of the stenosis could be proposed 2 years after the first operation. Encouraged by this good result, we decided to extend the use of this new device in different situations.

Case 2

The second patient who was treated with an ear stretcher was a 90-year-old man who underwent surgery in August 2013 for a squamous cell carcinoma of the ear infiltrating the skin and the external part of the parotid gland. A subtotal amputation of the ear was performed, maintaining only the bony portion of the EAC with its skeletonisation up to the TM. Adjuvant RT was excluded because of the patient's general condition. To avoid local complications, in the operating room we covered the residual bony canal with a temporal muscle flap over which we positioned a silastic foil with a Pope wick inside. Finally, the skin defect was closed directly. One week after surgery we in-



Fig. 2. A: External auditory canal (EAC) diameter two weeks after the end of RT (2 mm), the tympanic membrane is not visible; B: 4-mm stretcher placed in the right EAC: it can be seen that it is self-retaining and aesthetically pleasing as it does not protrude from the EAC.

serted an ear stretching tunnel into the EAC which had already started to narrow in the sutured skin area, reaching a diameter of 3.2 mm. EAC patency was checked during the monthly oncological follow-up visits, the last of which took place in January 2014 since the patient died in February 2014; during that visit the diameter was 4 mm.

Case 3

The third patient was a 60-year-old woman with an EAC stenosis (3.5 mm in diameter) consequent to frequent otitis externa (Fig. 4A). During October 2013 she underwent canaloplasty with removal of the scar tissue, underlying epithelium and the epithelial part of the TM. The pre-operative CT scan demonstrated the absence of chronic otitis or middle ear illness, undamaged ossicular chain, normal ventilation of the mastoid and normal appearance of the scutum so that only exploratory myringotomy was sufficient. Bone drilling was not required because the bony part of the EAC was not stenotic. Tiersch fragments taken from the supraclavicular area were used to cover the bone. Gelfoam[®] was positioned over the TM, and si-

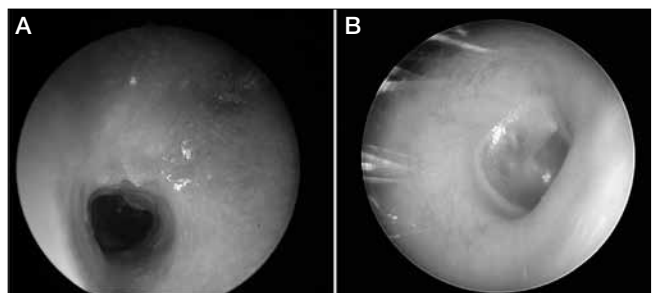


Fig. 3. A: EAC stenosis after removal of the stretcher; B: beyond the remaining stenosis the ear is clean and the tympanic membrane is visible again.

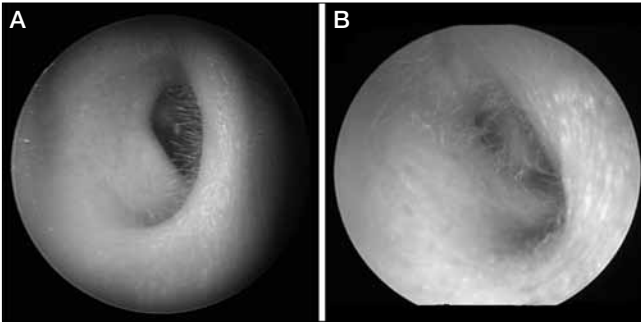


Fig. 4. A: EAC before the insertion of the stretcher, it appears narrowed and the TM is difficult to visualise; **B:** EAC after the use of stretcher, the diameter is larger and the TM is simpler to visualise.

lastic foil with a Pope wick was placed inside the EAC. One week later an ear stretcher of 4 mm was inserted to avoid narrowing. Her follow-up visits are scheduled every 3 months, and on her last visit in May 2014 the EAC appeared patent (Fig. 4B).

Case 4

The fourth patient we treated was a 90-year-old man with a squamous cell carcinoma of the concha. In November 2013, after amputation of the concha and antitragus with superficial parotidectomy and selective lateral neck dissection, the defect was rebuilt by transposition of a muscular-skin island flap based on the retroauricular muscle; an advancement flap was used for the skin defect of the mastoid region. Histological examination was pT1N0. To avoid stenosis of the distal tract of the cartilaginous canal, we adopted the same procedure as used in the other three cases, starting with a 2.5-mm diameter ear stretcher progressively replaced with larger stretchers. During monthly oncological follow-up examinations, the last of which took place in May 2014, the EAC did not appear to be narrowing; the stretcher now in place is 4 mm in diameter.

Discussion

A brief review of the literature revealed the lack of innovative solutions for the management of EAC stenosis. Furthermore, we found no advice on the treatment of post-RT EAC stenosis, but only on the management of post-surgical stenosis. As reported by Carls et al., we observed that the combination of high-dose radiation and previous parotid surgery is related to the risk of EAC stenosis ($p = 0.0059$), with a higher incidence during the earliest period after RT³.

Paparella and Kurkjian introduced the basic surgical principles of excising the fibrous plug, enlarging the cartilaginous and bony canal, and then re-covering it. Since then, modifications of this technique have been introduced primarily to address the most common postoperative complication, i.e. restenosis⁴.

The use of soft stents with injection of triamcinolone may be advantageous in the meatus that is beginning to stenose. Several splints and expanding techniques have been described; some of the problems encountered include availability of the materials, costs, expertise in fabrication and patient compliance.

A case report by Miller described the use of an expanding cellulose wick for EAC narrowing, changed monthly for 4 months. Otologic drops of a mixture of steroids were used to reduce scar formation. One year later the EAC size was normal⁵. A Foley catheter was used to maintain the patency of the EAC after resection of a preauricular squamous carcinoma and after ear reconstruction in microtia⁶. A North American group presented 6 cases of patients treated with medium-density viscosity dental impression material as an initial support device after surgery, followed by a hard, acrylic, removable stent to be worn for the following few months to maintain patency and prevent restenosis⁷. The Jerusalem Hospital group described meatal stenosis after mastoidectomy in 3 patients; to prevent it, they inserted an Optosil® template after surgery, which was left in place for the first postoperative week, and then replaced with an acrylic stent worn during most of the day for a period of 6 months, until epithelisation occurred around it⁸. Savion et al. produced an acrylic resin conformer to solve a stenosis of the cartilaginous part of the EAC, with the possibility to gradually dilate it by using progressively larger speculi⁹.

Our approach was to use a surgical steel tube that allowed progressive expansion of the stenotic EAC, by using devices of increasing dimension called ear stretching tunnels or ear stretchers. The idea was borrowed from the world of tattoos and body piercing, since these are surgical steel tissue expanders (Fig. 1) commonly used in a body piercing practice called stretching and involving the progressive and gradual expansion of a skin area, for example the earlobe. Dilatation of the piercing hole is obtained gradually (usually 1 mm per month) by pushing a taper as far as it will go through the piercing hole and then replacing it with a stretching tunnel of the appropriate size to be worn between stretches.

Although ear stretchers are commercially available in different materials (surgical steel, nickel-free titanium and glass), we decided to test only surgical steel stretchers to ensure that our clinical records were uniform.

In our experience, despite the limited number of patients treated, the use of an ear stretcher made it possible to preserve ventilation of the EAC, resulting in auditory improvement, reduced otorrhoea and secretion stasis, and thus preventing local infection. Because the principal morbidity of the EAC stenosis is hearing loss, we decided to objectively assess the efficacy of the new proposed treatment by comparing the auditory examinations before and after the insertion of the stretcher. The hearing outcomes were evaluated using the criteria stated by the

Committee on Hearing and Equilibrium Guidelines¹⁰, and closure of the air-bone gap was considered. In all 4 patients we obtained closure of the air-bone gap.

In our cases, the aetiology of EAC stenosis was different: consequent to repeated inflammation, to surgery alone or to a combination of surgery and RT. The use of an ear stretcher can be helpful in patients who have developed EAC stenosis as a consequence of surgery, because a second operation to resolve the condition after canaloplasty or meatoplasty could in itself lead to a worsening of the stenosis.

The possible disadvantages of the use of an ear stretcher include the following:

- it is not an approved medical device, so patients would have to buy it themselves;
- it may cause minimal discomfort at night because it is rigid and the tragus presses against it;
- its small size could make it difficult to handle for an elderly patient, but the device can easily be managed by the patient's caregivers;
- in the case of RT, the expected results are inferior since RT worsens EAC stenosis; however, we think this problem is common to all of the previously used devices.

In our opinion, the advantages of the ear stretcher, also in comparison with other stenting devices, are as follows:

- it is made of surgical steel and therefore it is nickel-free and cannot cause allergic reactions;
- it is non-degradable because of the prevalence of chrome which has antioxidant and noncorrosive properties so that the patient can also wear it while bathing;
- compared to the Foley catheter, it is safer as it is not porous and micro-organisms are less likely to colonize its surface; it is easily sterilisable; it is hard and incompressible, ensuring constant patency of the duct; it is aesthetically pleasing because it does not protrude from the EAC and it is self-retaining, while the Foley catheter is larger and needs to be fixed all around the auricle. This feature ensures good patient compliance;
- it is a cost-saving method that cuts direct and indirect costs. Ear stretchers are on sale at any tattoo shop and are very cheap; they come in different shapes and sizes so they do not need to be produced ex-novo and are readily adaptable to every EAC. Ear stretchers are handy and practical, and positioned within minutes in expert hands, so that outpatient follow-up visits are shorter; once inserted, they remain in place so that close follow-up is not necessary. Patients can individually clean the ear stretcher by removing it when it is obstructed by horny scales and sterilising it by boiling.

For this reason, this method is also time saving (indirect costs).

- the use of an ear stretcher is compatible with patients' personal hobbies and we think it is important not to alter patients' quality of life.

In conclusion, maintaining EAC patency is a basic component of the postoperative management of patients with EAC stenosis consequent to surgery with or without RT who are awaiting reconstructive surgery after local stabilisation. Our experience, albeit based on only 4 patients with a limited follow-up period, suggests that the surgical steel ear stretcher borrowed from body piercing practice can be successfully used to expand stenoses due to different causes.

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References

- ¹ Luong A, Roland PS. *Acquired external auditory canal stenosis: assessment and management*. *Curr Opin Otolaryngol Head Neck Surg* 2005;13:273-6.
- ² Adler M, Hawke M, Berger G, et al. *Radiation effects on the external auditory canal*. *J Otolaryngol* 1985;14:226-32.
- ³ Carls JL, Mendenhall WM, Morris CG, et al. *External auditory canal stenosis after radiation therapy*. *Laryngoscope* 2002;112:1975-8.
- ⁴ Paparella MM, Kurkjian JM. *Surgical treatment for chronic stenosing external otitis*. *Laryngoscope* 1966;56:232-45.
- ⁵ Miller GW. *Treatment of acute ear canal stenosis with an expanding cellulose wick*. *Arch Otolaryngol* 1978;104:55-6.
- ⁶ Karanth SK, Mokai NJ. *Silicone Foley's catheter: a useful splint in ear surgery*. *Indian J Plast Surg*. 2008;41:51-4.
- ⁷ Weber PC, Davis B, Adkins WY Jr. *Canal atresia reconstruction with dental impression material*. *Am J Otolaryngol* 1999;20:236-40.
- ⁸ Hocwald E, Sichel JI, Sela M, et al. *Prevention of post-mastoidectomy meatal stenosis by an acrylic prosthesis*. *Laryngoscope* 2002;112:1892-4.
- ⁹ Savion I, Good J, Sharon-Buller A. *An acrylic resin conformer for the prevention of external auditory meatus stenosis*. *Laryngoscope* 2005;115:2006-9.
- ¹⁰ Monsell EM. *New and revised reporting guidelines from the Committee on Hearing and Equilibrium*. *American Academy of Otolaryngology Head and Neck surgery Foundation, Inc*. *Otolaryngol-Head Neck Surg*. 1995;113:176-8.

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OTOLOGY

Efficacy and safety of ofloxacin and its combination with dexamethasone in chronic suppurative otitis media. A randomised, double blind, parallel group, comparative study

Efficacia e sicurezza dell'ofloxacina e della sua associazione con desametasone nell'otite media cronica purulenta. Uno studio comparativo, a gruppi paralleli, doppio cieco, randomizzato

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SUMMARY

The role of corticosteroid in patients of chronic suppurative otitis media (CSOM) is unknown. In the present study, the efficacy and safety of ofloxacin alone (OA) and the ofloxacin + dexamethasone combination (ODC) is compared by studying clinical cure rates and adverse drug reactions in patients with CSOM. After prior permission from the Institutional Review Board and written informed consent from patients, pre-treatment clinical assessment and bacteriology of the middle ear discharge were done. The middle ear was categorised into active, mucoid or inactive according to the type of discharge. Grades of otorrhoea and size of tympanic membrane perforation were noted. CSOM with organisms sensitive to ofloxacin were treated either with OA or ODC eardrops for a period of 15 days. Post-treatment clinical cure (when grade of otorrhoea become 0) was recorded on the 5th, 10th and 15th days and bacteriological assessment was recorded at the last visit. All parameters were analysed using Fisher's exact test. A total 110 patients were randomised. The most common microorganism associated with CSOM was *Pseudomonas aeruginosa* (45.45 %). Clinical improvement was seen in 84.61% and 86.79% of cases, but bacteriological improvement in only 82.69% and 77.35% of cases treated with OA and ODC, respectively. Shift of middle ear discharge from active to inactive was noted in 71.15% and 64.15% patients by the 10th day in the OA and ODC groups, respectively. As there was no difference in clinical or bacteriological improvement, it may be unnecessary to combine steroids with topical antibiotic preparations for management of CSOM.

KEY WORDS: Antimicrobial agents • Ofloxacin • Ofloxacin + dexamethasone • Chronic suppurative otitis media

RIASSUNTO

*Il ruolo dei farmaci corticosteroidi nei pazienti affetti da Otite Media Cronica Purulenta (OMCP) è sconosciuto. Nel presente studio sono state confrontate efficacia e sicurezza della terapia con Ofloxacina da sola (OS) con l'associazione di Ofloxacina + Desametasone (ODA), valutando il tasso di guarigione clinica e le reazioni avverse al farmaco in pazienti con OMCP. Previo consenso da parte del Institutional Review Board e adesione dei pazienti allo studio tramite consenso informato scritto, sono state effettuate valutazioni cliniche pre-trattamento ed esame colturale delle secrezioni provenienti dall'orecchio medio. In base alla tipologia di otorrea l'orecchio è stato classificato come attivo, mucoide o inattivo. Sono stati inoltre valutati il grado di otorrea e la dimensione della perforazione timpanica. I pazienti con OMCP in cui i microrganismi identificati risultavano sensibili all'Ofloxacina sono stati trattati in maniera randomizzata o con la sola Ofloxacina o con associazione Ofloxacina + Desametasone in gocce auricolari per 15 giorni. Il tasso di guarigione clinica alla fine del trattamento (ovvero quando il grado di otorrea risultava 0) è stato registrato al 5°, 10° e 15° giorno e in occasione dell'ultima visita è stata eseguito un esame colturale delle secrezioni. Tutti i parametri sono stati analizzati mediante il Test di Fisher. Sono stati reclutati in maniera randomizzata 110 pazienti. Il microrganismo associato più frequentemente al OMCP è risultato *Pseudomonas aeruginosa* (45,45%). È stato registrato un beneficio clinico in 84,61% dei casi trattati con OS e in 86,79% dei casi trattati con ODA ma la risoluzione dell'infezione all'esame batteriologico si è verificata solo nel 82,69% e nel 77,35% dei pazienti con OS e ODA rispettivamente. Il passaggio della forma attiva a quella inattiva è stato evidenziato al 10° giorno nel 71,15% e 64,15% dei pazienti trattati rispettivamente con OS e ODA. Dal momento che non è stata dimostrata nessuna differenza nel beneficio clinico e microbiologico, la combinazione di antibiotici topici e steroidi risulta sconsigliata nella terapia del OMCP.*

PAROLE CHIAVE: Agenti antimicrobici • Ofloxacina • Ofloxacina + desametasone • Otite media cronica purulenta

Introduction

Chronic suppurative otitis media (CSOM) is one of the leading causes of acquired and preventable hearing loss. It is estimated to affect 65 to 330 million people worldwide mainly involving South East Asia, Western Pacific, Africa and ethnic minorities. Of these, 60% have significant hearing loss¹. CSOM is associated with mucoid or mucopurulent discharge that impairs healing of tympanic membrane perforation. Surgery is necessary for the definitive management of CSOM, and is also needed to convert wet ear into dry ear for good surgical outcomes². In addition, otorrhoea may become a complication of many surgical procedures such as tympanoplasty, myringoplasty and mastoidectomy³. For these reasons, many ototopical antimicrobial with or without steroids are widely used for the treatment of otorrhoea in patients with CSOM⁴. Antimicrobial and steroid combinations are also commonly used for the treatment of otorrhoea. It has been claimed that it reduces oedema of middle ear mucosa which prevents microbial colonisation within the middle ear and reduces the allergic sensitivity of the antibiotic component in ear drops⁵. There are a few studies to claim the advantage of adding steroids in CSOM⁶. The disadvantage of adding the steroid is that it increases fungal overgrowth in some steroid treated ears due to reduction in local tissue resistance⁵. Thus, the role of steroids in the treatment of CSOM has always remained controversial. There is paucity of literature about the efficacy of an antimicrobial-steroid combination in CSOM. Hence, we designed the present study to compare the efficacy and safety of ofloxacin otic drops (0.3% w/v) with ofloxacin - dexamethasone otic drops (0.3% w/v & 0.1% w/v) for improved clinical status and bacteriological cure in CSOM patients.

Methods

Ethical approval was obtained from the Institutional Review Board, Government Medical College, Bhavnagar, Gujarat, India. Patients were thoroughly informed about the nature of the study and written informed consent was obtained prior to enrolment of subjects. This was a randomised, double blind, active control, parallel group, comparative study.

Subjects

Patients > 18 years of age including both genders, having ear discharge with tympanic membrane perforation and willing to give written informed consent were screened in the outpatient department of otorhinolaryngology. Patients with a history of sensitivity to any of the trial drugs, tuberculosis, diabetes mellitus, immunosuppressive disease, fungal or viral diseases, any clinically significant systemic diseases, chronic nasal obstruction, persistent rhinorrhoea, cholesteatoma, active atticofacial disease and pregnant or lactat-

ing women were excluded from the study. Patients with ear surgery in the preceding 12 months, congenital ear or hearing problems, middle ear obstruction (e.g., polyp) were also excluded. Patients who had taken systemic steroids, high dose of topical steroids and /or antibiotics in the previous one week and had temperature > 38°C were also excluded.

Study design

Investigators were responsible for subject enrollment. Subjects were randomised by Rando software at a 1:1 ratio to receive either ofloxacin or ofloxacin + dexamethasone ear drops for 10 days. Containers of ofloxacin and ofloxacin + dexamethasone combination ear drops were identical in appearance. The label was covered and coded according to the randomisation sequence by a third person who was not involved in the study. Neither the participants nor the investigators knew the sequence. At the time of screening, a pus sample from the ear was collected from the middle ear in a sterile container for culture and sensitivity report. Those patients whose pus culture and sensitivity report showed sensitivity to ofloxacin were randomised and assigned to one of the two treatment groups. Group A patients received ofloxacin 0.3% w/v ear drops (12 drops twice a day); whereas, Group B patients received ofloxacin (0.3% w/v) + dexamethasone (0.1% w/v) combination (12 drops twice a day); for 10 days. The pus sample was again collected after 5 days of completion of treatment (on day 15th). After cleaning the ear discharge, the patient was instructed to instill five drops in the affected ear in a supine position with that ear facing the ceiling. The same position was maintained for 10 min, tragus was massaged repeatedly and whole procedure was repeated twice daily. Patients were assessed on day 0 (prior to treatment), day 5, day 10 and day 15.

Outcomes

The primary endpoint was clinical cure rate and secondary endpoints were subjective assessment of otorrhoea, change in size of perforation, isolated organisms, bacteriological improvement and safety analysis. Clinical cure was defined as conversion of wet ear into dry ear. According to grades of otorrhoea by otoscopic examination, patients were categorised into severe (the discharge totally obscuring any view of the tympanic membrane), moderate (partial obscuring tympanic membrane), mild (weeping ear with little to no obscuring of the tympanic membrane or middle-ear cavity) and no symptom categories on day 5, day 10 and day 15³. Subjective assessment was categorised into active, mucoid and inactive ears by the investigator⁷. Presence of purulent discharge was considered as an active discharge, the presence of mucopurulent and mucous discharge was considered as mucoid and absence of ear discharge was considered as an inactive ear. The different sizes of perforation were estimated and divided into categories of small (0-25%), medium (25-75%) and large (75-100%) according to its proportion to intact tym-

panic membrane. Adverse drug reactions were recorded at every follow-up visit and compared between groups.

Statistical analysis

Data were expressed in proportions. Sample size calculations by nMaster software indicated that 100 participants would be needed to achieve 80% power with an alpha level of 0.05 (two tailed), if the minimal expected difference in clinical cure rate is 20% and the anticipated clinical cure rate in ofloxacin group is 70%. Fisher's exact test was applied for comparison of all qualitative data. All subjects who had one follow-up visit after giving study medication were included in the efficacy analysis (intention-to-treat). All subjects who instilled ear drops at least once were included in the safety analysis. A $P < 0.05$ was considered statistically significant. All statistical calculations were performed using GraphPad InState 3 (version 3.06) software.

Results

There were 55 subjects in each study arm (Fig. 1). Among these, 52 in the ofloxacin group and 53 in the ofloxacin + dexamethasone group were analysed in the intention-to-treat analysis. Table I shows baseline data and demographic characteristics of subjects in both groups. The prevalence

of medium perforation was high (51/105 = 48.57%). 84.61% subjects in the ofloxacin group and 86.79% subjects in the ofloxacin + dexamethasone group were clinically cured. Subjective assessment shows the distribution of patients with active, mucoid and inactive disease (Table II).

Subjective assessment of active discharge did not show any significant difference in both the groups when compared at day 0, 5, 10 and 15 (Fig. 2).

Shift of middle ear discharge from active to inactive was seen in 71.15% and 64.15% patients within the 10th day in the ofloxacin and ofloxacin + dexamethasone groups, respectively. The majority of patients were improved by day 10. A small number of patients continued to improve at day 15. The disease remained active in only 15 patients in the ofloxacin group and 20 patients in the ofloxacin + dexamethasone group at the end of the 15th day ($p = 0.41$, Fisher's exact test). No any serious adverse events were reported during the study and other adverse events were described in Table IV.

Bacteriological evaluation

Pseudomonas aeruginosa was found to be the most common organism associated with CSOM (40.95%) followed by *Staphylococcus aureus* (24.76%). Bacteriological improvement was seen in 82.69% and 77.35% of cases

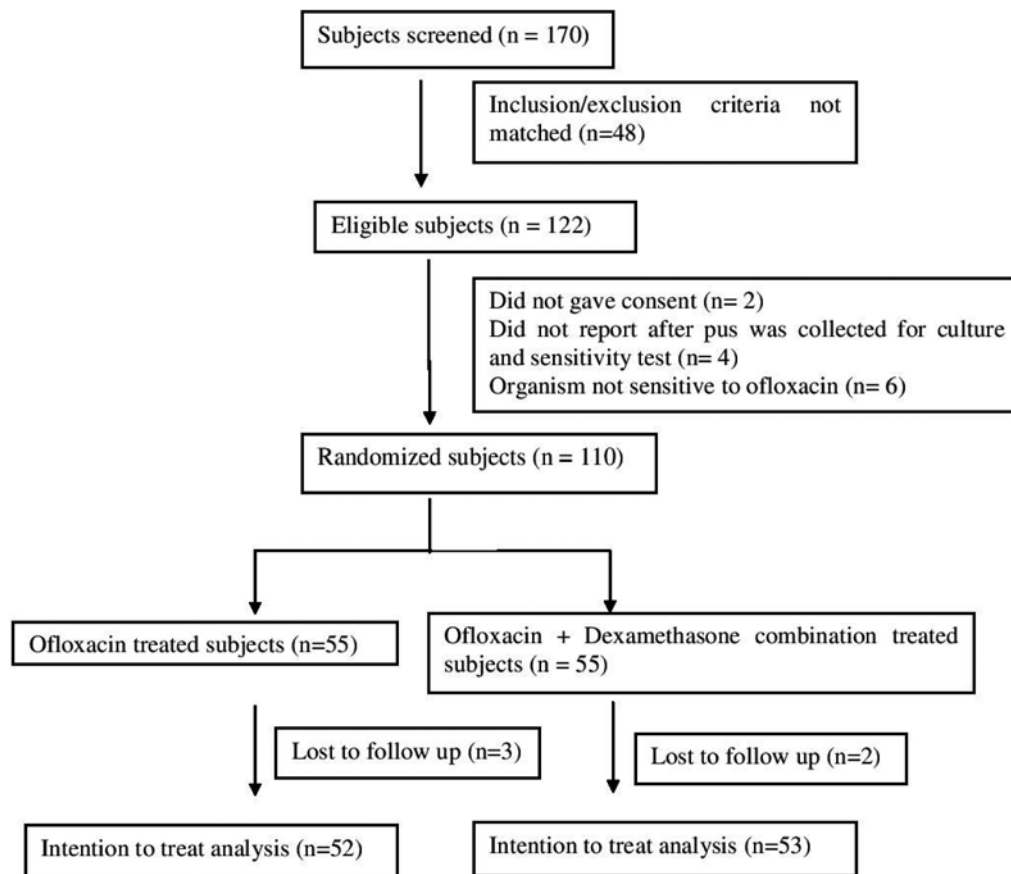


Fig. 1. CONSORT statement.

Table I. Baseline demographic characteristics of patients in both groups.

	Ofloxacin (n =55)	Ofloxacin + Dexamethasone (n = 55)	P value
Gender			
Male	24 (43.6%)	26 (47.2%)	0.5
Female	31 (56.3%)	29 (52.7%)	
Side of ear			
Right	33 (60%)	27 (49%)	0.11
Left	22 (40%)	28 (50.9%)	
Size of tympanic membrane perforation			
Small	04 (7.2%)	09 (16.3%)	0.63
Medium	32 (58.1%)	28 (50.9%)	
Large	19 (34.5%)	18 (32.7%)	
Otorrhoea			
Severe	18 (32.8%)	18 (32.8%)	0.99
Moderate	26 (47.2%)	26 (47.2%)	
Mild	11 (20%)	11 (20%)	
Status of middle ear			
Active	44 (80%)	40 (72.7%)	0.82
Mucoid	11 (20%)	15 (27.2%)	

Data were expressed in absolute numbers. Groups were compared by Fisher's exact test.

Table II. Cure rate of patients.

	Ofloxacin (n = 52)	Ofloxacin + Dexamethasone (n = 53)	p value
Cured at day 5	Grade 3 to 0 = 1	Grade 3 to 0 = 3	0.61
	Grade 2 to 0 = 7	Grade 2 to 0 = 5	0.55
	Grade 1 to 0 = 10	Grade 1 to 0 = 8	0.61
Cured at day 10	Grade 3 to 0 = 5	Grade 3 to 0 = 3	0.48
	Grade 2 to 0 = 10	Grade 2 to 0 = 14	0.48
	Grade 1 to 0 = 1	Grade 1 to 0 = 2	0.49
Cured at day 15	Grade 3 to 0 = 5	Grade 3 to 0 = 9	0.39
	Grade 2 to 0 = 5	Grade 2 to 0 = 2	0.16
	Grade 1 to 0 = 0	Grade 1 to 0 = 0	1.0

Data are expressed in absolute numbers. Groups were compared by Fisher's exact test.

treated with ofloxacin and ofloxacin + dexamethasone, respectively. The organisms associated with CSOM are listed in Table III. The rate of bacterial eradication was higher in the ofloxacin group.

Discussion

CSOM is most commonly a pseudomonal / staphylococcal disease^{8,9} which implicates the use of antipseu-

domonal drugs. Thus, fluoroquinolones are the best choice for topical use¹⁰⁻¹². Yuen et al. have shown that only 26% patients had dry ears with amoxicillin + clavulanic acid, whereas 76% of patients had dry ears using topical ofloxacin¹³. Our study also showed similar rates of improvement: 84.61% in the ofloxacin arm and 86.79% in the ofloxacin + dexamethasone arm. Esposito et al. compared oral ciprofloxacin with topical ciprofloxacin and found that 40% and 85% patients had cure of otorrhea,

Table III. Bacteria isolated and bacteriological cure rate.

Organism	Number of patients (%) Ofloxacin (n = 52)	Number of patients (%) Ofloxacin + Dexamethasone (n = 53)
Pseudomonas	15/17 (88.2%)	23/26 (88.4%)
Staphylococcus aureus	16/18 (88.8%)	6/8 (75%)
Coagulase -ve Staphylococcus aureus	5/6 (83.3%)	2/4 (50%)
Proteus	1/2 (50%)	1/2 (50%)
Klebsiella	4/6 (66.6%)	7/10 (70%)
E. coli	2/3 (66.6%)	2/3 (66.6%)

Numerator indicates the number of patients with bacteriological cure. The denominator indicates total number of patients showing total number with that organism.

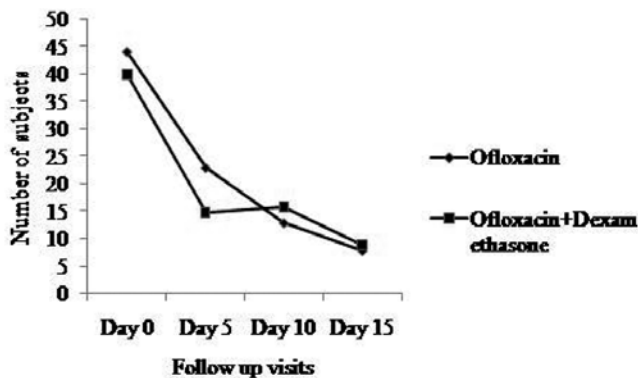


Fig. 2. Comparison of subjective assessment of active discharge. Subjective assessment of active discharge at day 0 compared with day 5, day 10 and day 15 in both groups.

respectively, which favours the use of eardrops¹⁴. Another study also showed the superiority of topical ciprofloxacin over intramuscular gentamicin¹⁵. Accordingly, we used otological medications instead of oral medications. The susceptibility of microorganisms to ofloxacin and aminoglycosides are similar except that ofloxacin has a higher efficacy for staphylococcal and pseudomonal infections. Hence, we selected ofloxacin instead of other antimicrobials¹⁶. The role of anaerobes in CSOM has recently gained widespread attention. The isolation rate of anaerobes in CSOM varies from no anaerobes^{17,18} to 50% of isolated anaerobes^{19,20}. The reason for not finding anaerobes may be due to inclusion of only those cases whose microorganism was sensitive to ofloxacin.

There is no standardisation regarding the duration and type of eardrops in patients with CSOM. Indudharan et al. reported 82.5% and 75% of bacteriological improvement with gentamicin or gentamicin-steroid ear drops when used for 3 weeks. Our study had a similar bacteriological cure rate when topical ofloxacin with or without steroid was used for 10 days, which may be because of the higher efficacy of ofloxacin. Overall clinical improvement was 84.61% & 86.79%, and bacteriological improvement was 82.69% and 77.35%, respectively, with ofloxacin and ofloxacin-dexamethasone at 10 days. This confirms that 10 days of therapy demonstrates significant clinical cure and less bacteriological cure because of persistent of infection in CSOM. There was also no statistically significant difference in clinical or bacteriological improvement if ofloxacin

or ofloxacin + dexamethasone was used. The size of tympanic membrane perforation was not reduced, which may be due to healing of tissue and may take a longer time, but in this study there was a shorter duration of follow-up.

The most commonly isolated organisms in our study were gram-negative organisms, which were about twice as frequent as the gram positive agents isolated from middle ear discharge. The pattern of bacterial isolates showed that *Pseudomonas aeruginosa* was the most common organism found in middle ear discharge, which is similar to the findings of other studies²¹⁻²³. We also compared the antimicrobial response to ofloxacin alone and ofloxacin + dexamethasone by assessing the bacteriological cure at the end of visit. Because both medications contained the same antibiotic, the difference in bacteriological cure rates was not expected.

Crowther and Simpson demonstrated improvement in ear discharge in 29% of patients when betamethasone ear drops were used, while 80% improvement in ear discharge in of patients when gentamicin-hydrocortisone was used. Using only a topical steroid preparation is not better than placebo²⁴. Spandow demonstrated the possibility of ototoxicity by glucocorticoids related to an impaired auditory brainstem response threshold in the high frequency range in an animal model²⁵. However, our study indicates no advantage of using an ofloxacin – steroid combination. This could be due to inhibition of its entry into cochlear hair cells in CSOM patients. Clinical as well as bacteriological improvement also showed similar results whether ofloxacin alone or ofloxacin + dexamethasone combination was used. It shows that the addition of steroids does not have any advantage over ofloxacin ear drops alone. On the contrary, it may allow fungal colonisation in the external ear canal⁵. Lastly, some of the limitations of the study warrant consideration. Firstly, since the duration of follow-up was relatively short, recurrence of otorrhoea and healing of perforation was not evaluated. In addition, as patients were assessed on days 5, 10 and 15, the exact day when ear discharge stopped is not known. In this regard, patients should keep a symptom diary so that a more precise time can be obtained for resolution of ear discharge.

Conclusions

Our data suggest that *Pseudomonas aeruginosa* is the most common organism causing CSOM. Because clinical im-

Table IV. Adverse events in both groups.

Adverse events	Ofloxacin (n = 52)	Ofloxacin + Dexamethasone (n = 53)
Headache	2	3
Vertigo	1	2
Local itchiness	1	1
Other	1	-
Total	9.61%	11.32%

provement of patients with topical ofloxacin eardrops was good in our study, we recommend its use for a period of 10 days, even if the ear becomes dry, to improve bacteriological cure. There is no added advantage of using a topical ofloxacin + dexamethasone combination over ofloxacin alone in terms of clinical and bacteriological cure.

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References

- 1 Acuin J. *Chronic suppurative otitis media: Burden of illness and management options*. Geneva: World Health Organization (WHO) 2006.
- 2 Tong MC, Woo JK, van Hasselt CA. *A double-blind comparative study of ofloxacin otic drops versus neomycin-polymyxin B-hydrocortisone otic drops in the medical treatment of chronic suppurative otitis media*. J Laryngol Otol 1996;110:309-14.
- 3 Gydé MC. *A double-blind comparative study of trimethoprim-polymyxin B versus trimethoprim-sulfacetamide-polymyxin B otic solutions in the treatment of otorrhea*. J Laryngol Otol 1981;95:251-9.
- 4 De Louvois J, Gortvai P, Hurley R. *Bacteriology of abscesses of central nervous system: a multicentric prospective study*. Br Med J 1977;2:981-4.
- 5 Ramunnikutty I, Kamaru Ambu V, Suraparaju Sivachandra R. *Role of glucocorticoids in ototopical antibiotic-steroid preparations in the treatment of chronic suppurative otitis media*. Arch Med Res 2005;36:154-8.
- 6 Miró N. *Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisonesuspension*. Otolaryngol Head Neck Surg 2000;123:617-23.
- 7 Browning GG, Picozzi GL, Calder IT, et al. *Controlled trial of medical treatment of active chronic otitis media*. Br Med J (Clin Res Ed) 1983;287:1024.
- 8 Fliss DM, Dagan R, Meidan N, et al. *Aerobic bacteriology of chronic suppurative otitis media without cholesteatoma in children*. Ann Otol Rhinol Laryngol 1992;101:866-9.
- 9 Papastavros T, Giamarellou H, Varlejides S. *Role of aerobic and anaerobic microorganism in chronic suppurative otitis media*. Laryngoscope 1986;96:438-42.
- 10 Browning GG, Gatehouse S, Calder IT. *Medical management of active chronic otitis media: a controlled study*. J Laryngol Otol 1988;102:491-5.
- 11 Kasemsuwan L, Clongsuesuek P. *A double blind, prospective trial of topical ciprofloxacin versus normal saline solution in the treatment of otorrhea*. Clin Otolaryngol 1997;22:44-6.
- 12 Indudharan R, Haq JA, Aiyar S. *Antibiotics in chronic suppurative otitis media—a bacteriologic study*. Ann Otol Rhinol Laryngol 1999;108:440-5.
- 13 Yuen PW, Lau SK, Chau PY, et al. *Ofloxacin eardrop treatment for active chronic suppurative otitis media. Prospective randomized study*. Am J Otol 1994;15:670-73.
- 14 Esposito S, D'Errico G, Montanaro C. *Topical and oral treatment of chronic otitis media with ciprofloxacin. A preliminary study*. Arch Otolaryngol Head Neck Surg 1990;116:557-9.
- 15 Esposito S, Noviello S, D'Errico G, et al. *Topical ciprofloxacin vs intramuscular gentamicin for chronic otitis media*. Arch Otolaryngol Head Neck Surg 1992;118:842-4.
- 16 Ikeda K, Takasaka T. *In vitro activity of ototopical drops against middle ear pathogens*. Am J Otol 1993;14:170-1.
- 17 Cooke ETM, Raghuvaram G. *Clindamycin in conjunction with surgery of the chronic suppurative ear*. Br J Clin Pract 1974;28:57-9.
- 18 Deka RC, Kacker SK. *Chronic otitis media: a clinical and bacteriological study*. Eye Ear Nose Throat Man 1975;54:198-201.
- 19 Brook I. *Chronic otitis media in children: microbiological studies*. Am J Dis Child 1980;134:564-6.
- 20 Erkan M, Aslan T, Sevuk E, et al. *Bacteriology of chronic suppurative otitis media*. Ann Otol Rhinol Laryngol 1994;103:771-4.
- 21 Brook I, Frazier E. *Microbial dynamics of persistent purulent otitis media in children*. J Pediatrics 1996;128:237-40.
- 22 Ologe FE, Nwawolo CC. *Prevalence of chronic suppurative otitis media (CSOM) among school children in a rural community in Nigeria*. Nig Postgrad Med J 2002;9:63-6.
- 23 Bluestone CD. *Pathogenesis and epidemiology of chronic otitis media*. WHO/CIBA foundation workshop, report on prevention of hearing impairment for chronic otitis media held at CIBA foundation, London 1996;pp. 14-17.
- 24 Crowther JA, Simpson D. *Medical treatment of chronic otitis media: Steroid or antibiotic with steroid eardrops?* Clin Otolaryngol Allied Sci 1991;16:142-4.
- 25 Spandow O. *Are glucocorticoids in ear drops ototoxic?* Ada Oto-Laryngologica 1992;493(suppl):89-91.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Utility of Glidescope® videolaryngoscopy in surgical procedures involving the larynx

Utilità del videolaringoscopio Glidescope® nelle procedure chirurgiche sulla laringe

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SUMMARY

Glidescope® is a recently developed videolaryngoscope that helps to achieve a good view of the laryngeal inlet and the vocal cords. Videolaryngoscopy has been proven effective in patients with unusual anatomical or pathological features, suggesting the possibility of a difficult endotracheal intubation. This device may also be useful for otorhinolaryngologists by facilitating access to the larynx and tongue base, especially in selected cases, where good visualisation of disease-altered structures is vital. According to the current literature, Glidescope® has been used for surgical procedures involving the tongue base, such as biopsies, foreign body removal and radiofrequency treatment of obstructive sleep apnoea. We believe that the use of this kind of videolaryngoscopy might be also indicated for laryngeal surgery as a valid alternative to the placement of a direct laryngoscope. This technique, especially in those cases with anatomical issues or important comorbidities, may be preferred to ambulatorial flexible or rigid laryngoscopy, and in planning surgical procedures in "difficult" patients due to the operating room setting comprising constant anaesthesiological support. In our experience, we performed five procedures involving the larynx with the Glidescope® in patients presenting unusual clinical characteristics that potentially compromised surgical outcome. No complications related to videolaryngoscopy were found. We recommend the use of Glidescope® for small surgical procedures involving the larynx in selected patients.

KEY WORDS: Videolaryngoscopy • Laryngeal Surgery • Difficult Intubation

RIASSUNTO

Il Glidescope® è un videolaringoscopio di recente sviluppo, che permette di visualizzare in maniera ottimale l'aditus ad laryngem ed il piano glottico. La videolaringoscopia con l'ausilio del Glidescope® è indicata in pazienti con caratteristiche anatomiche delle vie aeree superiori (VADS) o con patologie che possano far prevedere una intubazione difficile. Questo strumento può essere di grande aiuto anche per lo specialista otorinolaringoiatra, in quanto l'accesso alla laringe ed alla base della lingua è facilitato, soprattutto in casi selezionati, nei quali una buona visualizzazione delle strutture interessate da patologia è di vitale importanza. In letteratura il Glidescope® è stato utilizzato per procedure chirurgiche sulla base linguale, come biopsie, rimozione di corpi estranei e trattamento con radiofrequenze delle apnee ostruttive del sonno. Crediamo che la videolaringoscopia possa essere indicata anche per la chirurgia della laringe, come valida alternativa all'utilizzo del laringoscopio convenzionale. Questa tecnica, soprattutto in caso di comorbidità importanti o di alterazioni anatomiche, è da preferire alla fibrolaringoscopia ambulatoriale, in quanto si esegue in ambiente operatorio e con supporto anestesiológico. La nostra esperienza consta di cinque casi di chirurgia laringea con l'utilizzo del Glidescope®, in pazienti con caratteristiche cliniche potenzialmente pregiudicanti il successo chirurgico. Non sono state riscontrate complicanze dovute all'utilizzo del videolaringoscopio. Raccomandiamo pertanto l'utilizzo del Glidescope® per procedure di piccola chirurgia laringea, in pazienti selezionati.

PAROLE CHIAVE: Videolaringoscopia • Chirurgia laringea • Intubazione difficile

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Introduction

Glidescope® (Verathon Medical, Bothell, WA, USA) is a recently developed videolaryngoscope, which allows easier airway management in difficult conditions, such as neonatal intubation, morbidly obese patients or a restricted view of the laryngeal inlet. This device can be useful for several clinical situations due to its particular features: 1) multiple sizes are available; 2) it can be

used even in preterm/small children; 3) the possibility to record the video images makes it suitable for academic purposes; and 4) the anti-fog system prevents poor visualisation due to secretions and the device can be operational in seconds, when needed (Fig. 1). While videolaryngoscopy has been proven effective in achieving a better view of the glottis, the success rate of intubation seems to be essentially the same as conventional direct

laryngoscopy (DL): for this reason, at present GlideScope® is recommended with strong evidence only as a rescue choice after a failed intubation attempt using DL¹. Nonetheless, GlideScope® can be helpful not only for the anaesthesiologist, but also for other scenarios of upper airway management. For example, a perfect view of the vocal cords is vital in laryngeal surgery, and it is frequent for the ENT specialist to experience technical issues due to the misplacement of the laryngoscope, due to particular anatomical or pathological features (i.e. traumatic injuries, cervical spine immobilisation, etc.). The use of the GlideScope® can help in managing these issues and facilitate the execution of several procedures in addition to simple endotracheal tube placement. According to the current scientific literature, GlideScope® has been used for examination and biopsies of the tongue base, removal of foreign bodies, and radiofrequency treatment of obstructive sleep apnoea². The aim of this study was to explore selected laryngeal and hypopharyngeal procedures as other conditions in which GlideScope® may help achieving an optimal view, thus providing greater ease for surgeons. We believe that the GlideScope®, for certain surgical procedures, may be preferred to surgical procedures performed with fiberoptic laryngoscopy in those patients regarded as 'complex' for anatomical issues or relevant comorbidities. The procedure is

executed in an operating theatre, which may be important in case of complications: furthermore, using GlideScope®, intubation is not generally required, thus making the procedure faster and less invasive for the patient. In the recent medical literature, no data were found about GlideScope®-guided surgical procedures involving the larynx. In our department, we performed laryngeal surgery with the use of GlideScope® on five patients.

Clinical technique

Case 1

An 84-year-old man came to our observation with a long history of dysphonia. Fibre optic laryngoscopy revealed a 5 mm mass involving the middle third of the left vocal cord. The patient was scheduled for a surgical biopsy but, due to severe cardiovascular and respiratory comorbidities, general anaesthesia was not possible. Under GlideScope® view, the procedure was rapidly executed in an operating theatre setting (Fig. 2), under mild sedation, and the patient did not need further hospitalisation. Bleeding was minimal and no respiratory problems occurred.

Case 2

A 21-year-old woman with Down syndrome was admitted to our department with increasing dysphonia. Indirect laryngoscopy was impossible due to the characteristic macroglossy, while with fibre optic laryngoscopy visualisation of the vocal cords was partial (Cormack-Lehane grade II) and spoiled by vivid reflexes. A large cyst involving the anterior third of the right vocal cord was visualised, and surgery was scheduled. Intubation proved hard to achieve, so GlideScope® videolaryngoscopy was used. With the device still in, we proceeded with the removal of the cyst, thus sparing all the time and the difficulties associated with direct laryngoscope positioning. The procedure was brief and with no immediate complication. The patient was hospitalised and went home the following day.



Fig. 1. The GlideScope videolaryngoscope.



Fig. 2. The GlideScope device helped in achieving correct visualisation of a laryngeal mass, under mild sedation, without needing to place a direct laryngoscope (this picture refers to case 1).

Case 3

A 44-year-old man with pathological obesity (BMI = 38) underwent fibre optic laryngoscopy in our department for complaints of dysphagia. A medial epiglottic cyst measuring about 1 cm was found. Microlaryngoscopy surgery was programmed, but DL with the Macintosh blade was especially difficult to perform due to the patient's physical structure. The GlideScope® was used and a good view of the aditus ad laryngem was obtained. The cyst was successfully removed in a short period of time.

Case 4

A 28-year-old woman came to our observation with a history of dysphonia. Indirect and fibre optic laryngoscopy showed the presence, in the middle third of the right vocal cord, of two small, exophytic lesions, compatible with a diagnosis of laryngeal papillomatosis. Due to the possibility of respiratory obstruction, the patient was scheduled for surgical removal of the lesions. The patient presented severe prognathism and a very short interincisive distance (1.9 cm), and thus the intubation procedure required several attempts, and was achieved with the use of the GlideScope®. We decided to maintain the inserted device and an excisional biopsy of both lesions was performed. The procedure ended with consistent time savings. Histology confirmed clinical diagnosis, and the patient was discharged without hospitalisation.

Case 5

A 74-year-old man with a long history of smoking and increasing dysphonia came to our observation. Fibre optic laryngoscopy revealed a bulky, 2 cm mass in the left pyriform sinus which imposed surgical biopsy. The patient suffered from a severe form of congestive heart failure and preoperative risk was assessed as high (ASA class 4). We decided to perform a biopsy under mild sedation with the use of GlideScope® videolaryngoscopy. The procedure was brief and without complications. Histology revealed a squamous cell carcinoma, for which radiotherapy treatment was programmed.

Discussion

The GlideScope® videolaryngoscopy device is frequently helpful in airway management, especially in achieving a better view of the glottis in difficult intubations. It is currently used as a primary or a rescue device for several kinds of patients, from paediatric cases to those with cervical spine immobilisation. Moreover, the numerous features in common with direct laryngoscopes make it easy to use without any special training³. Furthermore, the chance of registering the procedure with good video quality should be regarded as useful for both academic teaching in university hospitals and forensic issues (Fig. 3). Few complications related to the use of GlideScope® have



Fig. 3. Videolaryngoscopy offers the possibility to record the procedure on the monitor, which can be of great interest for both academic and medico-legal purposes.

been described, the majority of which concern difficulties in placing the endo-tracheal tube for ventilation, due to the presence of potential blind spots. However, less intensity is needed to expose the glottis in comparison to direct laryngoscopy, and the GlideScope® is considered safe⁴. We encountered no particular anatomical difficulty while performing these procedures, and we always obtained a good view of the anatomical district. Surgery using the GlideScope® can be performed with one hand, while the other hand holds the instrument, or with both hands, with a second operator holding the device: both operators can see the images on the screen, which can be useful in an academic setting for teaching purposes. No evidence of the use of a GlideScope® in laryngeal surgery seems to have been published in the medical literature: this may be due to the relatively recent introduction of this device, which may not yet be available in all institutions. In our experience, GlideScope® videolaryngoscopy has considerably shortened the duration of surgical procedures because the operation can start immediately, without the time needed for intubation. Moreover, while performing a biopsy, GlideScope® allows a better view and no need for general anaesthesia, with the possibility of easier access to some delicate regions like the pyriform sinuses and better patient compliance. We performed upper aerodigestive tract surgery (excisional biopsies) on five patients, all of whom were difficult to intubate for either anatomical or pathological reasons. We managed to achieve an optimal view of the glottis (Cormack and Lehane grade I) in all procedures we performed. For all procedures, we used the instrumentation commonly needed for microlaryngoscopy with the addition of some instruments from our endoscopic sinus surgery set (due to the fact that their curvature is more suitable). Thus, we think that it would be helpful to have a new set of instruments specifically de-

signed for GlideScope®-guided surgery, and have started the designing process. The outcome was generally satisfying; no particular complication related to use of the GlideScope® was encountered. We believe that GlideScope® videolaryngoscopy should be considered for lesions suitable for biopsy, diagnosed with traditional fibre optic endoscopy, for which surgery in direct microlaryngoscopy or in fiberoptic laryngoscopy is not optimal due to the patients' conditions. GlideScope® allows a complete acquisition of clinical data, with a reduced risk in these types of patients. Nevertheless, we believe that direct suspension microlaryngoscopy should remain the gold standard for the treatment of laryngeal lesions; GlideScope® can be considered as an alternative to local ambulatory surgical procedures, once a biopsy is necessary, to perform surgery in presence of unfavourable anatomy or high risk associated with endotracheal intubation.

Conclusions

GlideScope® videolaryngoscopy offers several opportunities in many fields other than airway management for difficult intubations. A good exposure of upper aero-digestive tract, the possibility to register images and the short learning curve make it an interesting device to use in academic settings. Recently, tongue base surgery and foreign body removal were attempted under GlideScope® view, and seemed to show positive results. We believe that the advantages this technology may bring in upper airway surgery are numerous; for this reason, we tested a new potential use of GlideScope®, by performing laryngeal surgery in selected cases. The results were good, with no additional complication and a consistent time savings. Moreover, thanks to the possibility of achieving an optimal view of the laryngeal inlet, we could perform a relatively easy procedure even in patients with complicated anatomical features. We believe that this technique should be preferred over ambulatorial procedures, due to the easier handling of unforeseen complications such as bleeding or respiratory problems needing



Fig. 4. GlideScope-guided procedures are executed in an operating theatre setting, with the help of an anaesthesiologist. We believe this makes this technique preferable over ambulatorial fibre optic laryngoscopy, especially in patients with relevant comorbid conditions.

intubation (Fig. 4). We suggest limited use of GlideScope® videolaryngoscopy for selected patients who must undergo a surgical procedure for diagnostic and/or therapeutical reasons and present a high risk of intubation or adverse anatomical features.

References

- 1 Healy DW, Maties O, Hovord D, et al. *A systematic review of the role of videolaryngoscopy in successful orotracheal intubation.* BMC Anesthesiol 2012;12:32.
- 2 Shenoy PK, Aldea M. *The use of GlideScope for biopsies of the tongue base.* J Laryngol Otol 2012;7:1-2.
- 3 Xue FS, Zhang GH, Liu J, et al. *The clinical assessment of Glidescope in orotracheal intubation under general anesthesia.* Minerva Anesthesiol 2007;73:451-7.
- 4 Niforopoulou P, Pantazopoulos I, Demestihia T, et al. *Video-laryngoscopes in the adult airway management: a topical review of the literature.* Acta Anaesthesiol Scand 2010;54:1050-61.

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CLINICAL TECHNIQUES AND TECHNOLOGY

Intracapsular microenucleation technique in a case of intraparotid facial nerve schwannoma. Technical notes for a conservative approach

Enucleazione mediante tecnica di svuotamento intracapsulare al microscopio in un caso di neurinoma del VII nervo facciale intraparotideo.

Note tecniche per un approccio conservativo

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SUMMARY

We report a rare case of a large intraparotid facial nerve schwannoma (IFNS) in a 51-year-old female who presented with a painless, slow growing left parotid mass without peripheral facial nerve palsy, with non-specific findings at preoperative diagnostic work-up, that was treated with conservative surgery. Management of IFNS is very challenging because the diagnosis is often made intra-operatively, and in most cases resection may lead to severe facial nerve paralysis, with important aesthetic sequelae. Our experience suggests a new surgical option, namely intra-capsular enucleation using a microscope, currently used for schwannomas arising from a major peripheral nerve, which should be a safe and reliable treatment for IFNS. This surgical technique is the first experience of intracapsular microenucleation of facial nerve schwannoma described in the literature and allows preservation of the nerve without resection and reconstruction.

KEY WORDS: Parotid tumour surgery • Intraparotid facial nerve schwannoma • Facial nerve palsy • Microenucleation in peripheral nerve

RIASSUNTO

Descriviamo un raro caso di un neurinoma intraparotideo del nervo facciale in una donna di 51 anni giunta alla nostra osservazione per una voluminosa neoformazione parotidea sinistra, non dolente, senza deficit periferico del nervo facciale. L'agoaspirato e la RM della regione parotidea, eseguiti prima dell'intervento chirurgico, non si sono dimostrati diagnostici, pertanto poiché l'esame istologico estemporaneo rilevava cellule fusiformi compatibili con neurinoma la paziente è stata sottoposta a trattamento conservativo. La gestione degli schwannomi intraparotidei è molto difficile perché la diagnosi viene spesso fatta intraoperatoriamente e nella maggior parte dei casi, l'asportazione può procurare lesione del nervo facciale, con importanti conseguenze estetiche. La nostra esperienza suggerisce una nuova opzione chirurgica: l'utilizzo di microdissezione ed enucleazione con preservazione dell'epinevrio, eseguita con microscopio, attualmente utilizzata per gli schwannomi dei grandi nervi periferici. Questa tecnica potrebbe rivelarsi utile ed applicabile anche ai neurinomi intraparotidei del nervo facciale. Tale opzione chirurgica è la prima esperienza di microenucleazione intracapsulare che consente di preservare il nervo facciale senza resezione e ricostruzione descritta in letteratura.

PAROLE CHIAVE: Chirurgia dei tumori parotidei • Neurinoma intraparotideo • Paralisi del nervo facciale • Microenucleazione nei nervi periferici

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Introduction

Facial nerve schwannoma (FNS) is a benign tumour arising from Schwann cells of the facial nerve sheath. Intraparotid FNS is very rare and comprises 0.2-1.5% of all parotid tumours¹. From an histological point of view, schwannomas usually grow eccentrically from the nerve sheath and do not contain nerve fibres intramurally. The clinical symptoms of a schwannoma of the facial nerve vary depending on the location. Within the parotid gland, schwannomas may reach significant size without causing any symptoms other than parotid swelling. In the major-

ity of cases, these tumours present as an asymptomatic intraparotid mass, mobile to the skin and lower layers. However, signs of facial paralysis have been reported as the initial presenting symptom in a small number of cases, mainly when the tumour is located close to the stylomastoid foramen³. Preoperative fine-needle aspiration cytology (FNAC) is very often not diagnostic, and in some cases can give an incorrect diagnosis³. MRI diagnosis of intraparotid facial nerve schwannoma (IFNS) remains difficult. MRI characterises such heterogeneous lesions with isointensity in T1-weighted images

and hyperintensity in T2-weighted images, which are not specific for schwannoma and can be found in other neoplasms, such as pleomorphic adenomas⁴. Alicandri-Ciuffelli et al.³ in 2009 published a classification of FNS based on position and adherences of the neoplasm with respect to the nerve and post-operative function of the facial nerve. This classification includes type A neoplasms (tumour that can be resected without any sacrifice of the nerve), type B neoplasms (tumour that cannot be resected without sacrifice of the nerve, involving a main division or a distal branch of the nerve), type C neoplasms (tumour that cannot be resected without sacrifice of the nerve, involving the main trunk of the nerve), type D neoplasms (tumour that cannot be resected without sacrifice of the nerve, involving either the main trunk and its main divisions).

During surgical treatment, if these tumours are recognised, the surgeon is faced with a number of dilemmas regarding treatment policy. Because of its rarity, only a few clinicians have experience in the surgical management of intraparotid schwannomas. In addition, the results of facial nerve repair after resection of schwannoma are rarely described². It is critical to have a diagnostic and management algorithm when a suspected facial nerve tumour is encountered during parotidectomy⁵. We present such a case and discuss the management strategy used.

Case report

A 51-year-old woman presented with a 6-year history of a slowly growing, asymptomatic, mass in her left parotid gland. There was no history of facial nerve weakness. Physical examination revealed a large, 4 cm, painless,

slightly mobile mass, just inferior to the cartilaginous auditory canal. Fine needle aspiration cytology (FNAC) was not diagnostic, describing a spindle-cell morphology possibly of mesenchymal origin. MRI showed a well defined lesion that appeared hyperintense on fat-suppressed T2-weighted images (T2WI) and hypointense on T1-weighted images (T1WI), with marked enhancement on gadolinium-enhanced T1WI and cystic changes inside the lesion localised in the superficial and deep lobe of the parotid gland, which measured approximately 3.2 × 3.5 cm (Fig. 1). The patient underwent parotidectomy using a modified Blair incision. After elevation of the superficial musculoaponeurotic system (SMAS), flap a bulky, yellowish tumour appeared in the parotid gland with prolongation to the deep lobe. Intraoperatively under microscopic view (using conventional landmarks: i.e. pointer) problems were encountered in identifying and isolating the proximal main trunk of the facial nerve, so we attempted to identify it by retrograde dissection of the peripheral branches using nerve stimulation. Finally, we observed that the tumour was adherent to the facial nerve trunk and that the peripheral branches could not be separated from the tumour mass. It became apparent that the facial nerve branches in this location were intimately associated with the mass and were not simply lying on its surface. The nerve stimulator was used again, and facial motion occurred with stimulation of the mass. Intraoperative frozen section analysis from an incisional biopsy revealed spindle cells compatible with schwannoma. We carefully made a longitudinal incision in the epineurium, and the uninvolved nerve fibres that splayed around the tumour were dissected and retracted extracapsularly (Fig. 2). The onion

skin-like epineurial tissue layers were meticulously peeled out until the shiny surface of the tumour was exposed. Gentle dissection along the plane of the tumour capsule from the epineurial layers allowed the tumour to be shelled out en bloc without disturbing the nerve fascicles. Intra-operative nerve stimulation during the dissection was performed. Haemostasis was carefully checked by delicate bipolar to prevent secondary compression of the affected nerve by haematoma. Suction drainage was positioned at the end of the procedure and closure was made in layers taking care to not entrap the nerve, and finally an aesthetic intradermal suture was used.

Histological features showed spindle shaped Schwann cells arranged in interlacing fascicles, and immunohistochemical analy-

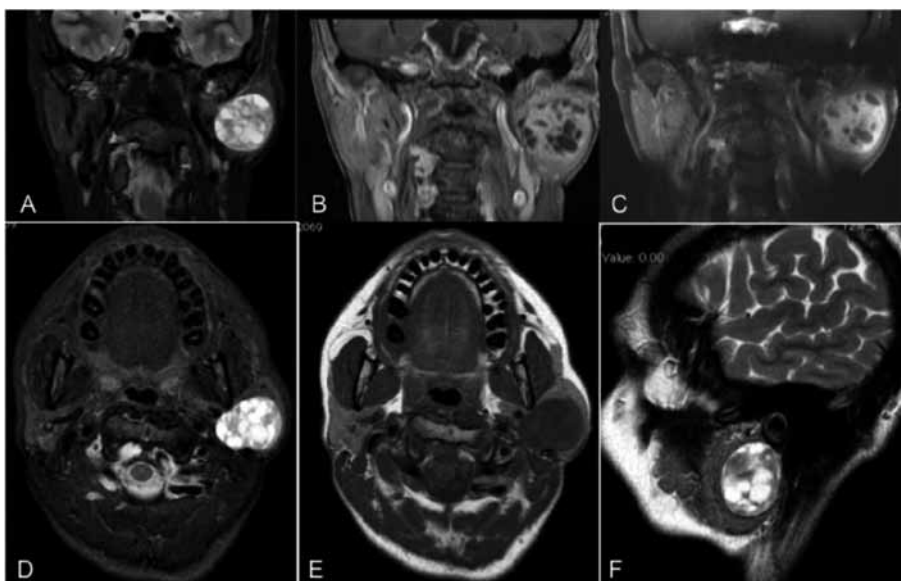


Fig. 1. MRI images showing left parotid lesion with extension in the deep parotid lobe close to the stylo-mastoid process (as appears in the axial, coronal and sagittal plane). The lesion appears on hyperintense fat-suppressed T2-weighted images (T2WI) and hypointense on T1-weighted images (T1WI), with marked enhancement on gadolinium-enhanced T1WI with cystic changes inside the lesion. All these features are similar to those observed in cases of pleomorphic adenoma.

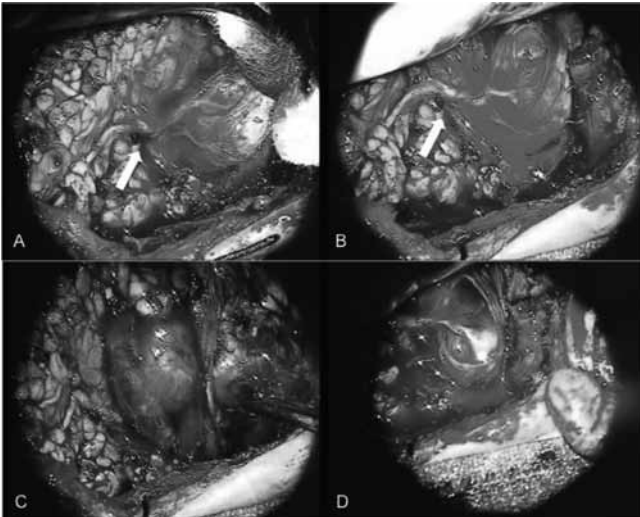


Fig. 2. Intra-operative microscopic view of the lesion dissected from the peripheral branch (inferior branch) of the facial nerve (arrow) after carefully dissected preserving the pseudocapsule (epinevrium) (A-B). Intraneural microdissection of the nerve at both the proximal and distal poles of the tumour with preserved perineurium of fascicles (C-D).

sis confirmed strong expression of S-100 protein by tumour cells, low expression of CD99, while AE1/AE3, CAM 5.2, SMA, HNF-35, caldesmone, calponine and CD 34 were negative; these confirmed diagnosis of schwannoma.

Postoperatively the patient developed facial nerve dysfunction on her left side (House-Brackmann grade IV facial nerve paralysis). Three months later, after physiotherapy rehabilitation, facial nerve function improved to grade II-IIIa on the House-Brackmann grading system. No recurrence was observed after 6 months.

Discussion

In this report, FNS is described as a slow growing, painless parotid mass, mimicking at preoperative imaging the most common benign parotid tumour, pleomorphic adenoma. Preoperatively, it is very difficult to differentiate intraparotid FNS from other parotid tumours, but preoperative diagnosis of FNS is essential for treatment planning⁶. From an imaging point of view, in diagnosing intraparotid FNS there is no evidence that any radiological method is of particular assistance. CT usually shows a smooth, sharply circumscribed lesion in the parotid, which is difficult to differentiate from other tumours. It is not the preferred imaging modality for FNS, but it may reveal osseous changes especially in the extension through the stylomastoid foramen⁷. MRI shows intraparotid FNS as a mass with an isointense signal to muscle on T1 and hyperintense to muscle on T2 sequence, respectively, and also gadolinium-enhancement on T1 sequences, although with MRI it is not always possible to make preoperative diagnosis of FNS, especially in lesions located purely in the gland⁶.

A diagnosis of FNS is often made intraoperatively, and is frequently only recognised while exploring a “parotid mass”. When the surgeon, using landmarks, encounters an intraparotid tumour in which the main trunk of the facial nerve is not easily identified, with retrograde dissection the presence of a facial nerve schwannoma should also be considered. Macroscopically, nerve fibres that disappear entering into the mass and also displaced over it strongly suggest the presence of this tumour. Generally, in case of schwannoma electrical stimulation of the tumour will elicit facial movement. In this event, frozen section analysis should always be performed². If presence of schwannoma is confirmed, according to a critical literature review on the management of FNS, the surgeon should opt in the case of type A or B neoplasms, or in the case of a pre-operative FN HB grade IV or worse, for resection and (where necessary possible primary reconstruction of the FN with nerve graft. In the case of pre-operative HB grade III or higher and in type C or D neoplasms, patients should undergo an intra-operative biopsy to rule out malignancy, and conservative management should be considered³.

Stereotactic radiosurgery shows promising preliminary results for treatment of intra-temporal FN schwannomas, even if at the moment the role of stereotactic radiotherapy remains to be determined⁸. If sacrifice of the nerve is necessary, a sural nerve interposition graft or a hypoglossal-facial nerve anastomosis can be performed. Better results are obtained in young patients and when there is a short time interval between paralysis and reconstructive surgery⁹.

Our experience suggests another possible surgical option: intra-capsular enucleation by microscope, which is currently used for schwannomas arising from a major peripheral nerve, and should be a safe and reliable treatment for FNS (Fig. 3). The surgical technique generally used in peripheral nerves involves exposure of the nerve beginning in a region of normal anatomy and extends into a region of tumour formation. Loop magnification or an operating microscope is essential for identification of the fascicles coursing over the tumour. Electrical nerve stimulation is also used to differentiate fascicles from tumour. A dissection plane is now established by gently separating and elevating the fascicles from the surface of the tumour. There may be a thin capsule (epinevrium) that requires opening to allow easier dissection of tumour from the nerve. As the tumour is mobilised, there may be single fascicles seen entering and exiting the mass. Electrical stimulation will determine if these are motor fascicles and still functional. Most schwannomas can be removed en bloc. Although often splayed and thinned, the intact fascicles should still function. The tumour bed is inspected for any evidence of divided fascicles. No attempt is made to remove remaining tumour capsule because the presence of tumour capsule is not associated with tumour recurrence^{10 11}.

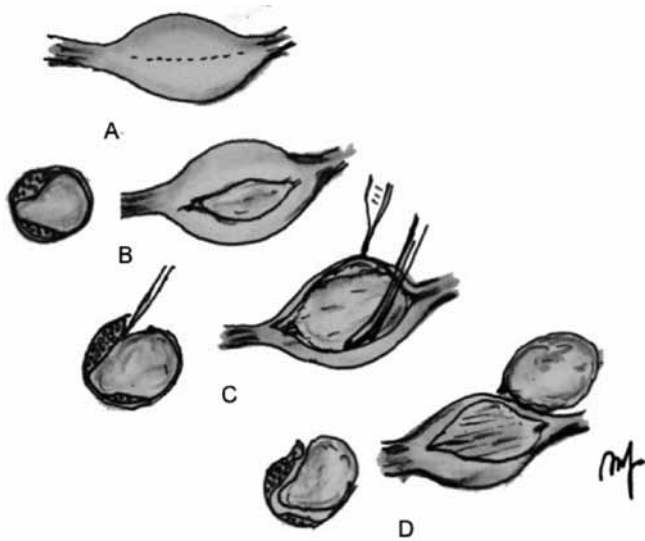


Fig. 3. Axial cuts of a neuroma and nerve are shown. A, longitudinal incision is made on the capsule of the mass; B schwannoma is seen and on axial plane the fascicles are displaced laterally by the tumour mass. C, the nerve fascicles must be separated or dissected from the abnormal tumour mass. D, fascicles that have been dissected away and spared are seen below the tumour, which is elevated away from the tumour bed. The tumour has been elevated away from the fascicular bed, leaving the coagulated ends of the entering and leaving fascicles and spared fascicles behind.

In our case report, after 3 months neurological deficits following enucleation are lower using the intra-capsular compared with a resection and reconstruction of the facial nerve. Therefore, further reports on additional cases might help to better understand if this conservative option is feasible in treating schwannomas of the facial nerve.

When dealing with lesions of the parotid gland suspected to be FNS, informed consent of the patient should include this possibility (intracapsular microenucleation by microscope) to preserve the nerve without resection and reconstruction, considering the benign nature of the lesion as suggested by frozen sections, and in particular when there is no preoperative facial nerve palsy.

The surgical technique used in our patient is the first reported experience of intracapsular microenucleation by

microscope of facial nerve schwannoma. Informed consent and good clinical judgement may lead the surgeon to subtotal excision or to retreat after biopsy without any definitive surgery, preserving nerve functionality and avoiding medico-legal issues.

References

- ¹ Fyrmipas G, Konstantinidis I, et al. *Hatzibougias D, Intraparotid facial nerve schwannoma: management options.* Eur Arch Otorhinolaryngol 2008;265:699-703.
- ² Kreeft A, Schellekens PP, Leverstein H., et al. *Intraparotid facial nerve schwannoma. What to do?* Clin Otolaryngol 2007;32:125-9.
- ³ Alicandri-Ciuffelli M, Marchioni D, Mattioli F, et al. *Critical literature review on the management of intraparotid facial nerve schwannoma and proposed decision-making algorithm.* Eur Arch Otorhinolaryngol 2009;266:475-9.
- ⁴ Shimizu K, Iwai H, Ikeda K, et al. *Intraparotid facial nerve schwannoma: a report of five cases and an analysis of MR imaging results.* Am J Neuroradiol 2005;26:1328-30.
- ⁵ Mehta RP, Deschler DG. *Intraoperative diagnosis of facial nerve schwannoma at parotidectomy.* Am J Otolaryngol 2008;29:126-9.
- ⁶ Ma Q, Song H, Zhang P, et al. *Diagnosis and management of intraparotid facial nerve schwannoma.* J Craniomaxillofac Surg 2010;38:271-3.
- ⁷ Jäger L, Reiser M. *CT and MR imaging of the normal and pathologic conditions of the facial nerve.* Eur J Radiol 2001;40:133-46.
- ⁸ Gross BC, Carlson ML, Moore EJ. *The intraparotid facial nerve schwannoma: a diagnostic and management conundrum.* Am J Otolaryngol 2012;33:497-504.
- ⁹ Salemis NS, Karameris A, Gourgiotis S, et al. *Large intraparotid facial nerve schwannoma: case report and review of the literature.* Int J Oral Maxillofac Surg 2008;37:679-81.
- ¹⁰ Belzberg AJ, Dorsi MJ. *Neoplasms of peripheral nerves.* In: Fessel RG, Sekhar L, editors. *Atlas of neurosurgical techniques - Spine and peripheral nerves.* New York: Thieme; 2007.
- ¹¹ Kim DH, Hudson AR, Kline DG, et al. *Surgical technique for nerve tumors.* In: *Atlas of Peripheral nerve surgery.* Amsterdam: Elsevier-Saunders; 2012.

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CASE SERIES AND REPORTS

Laryngotracheal reconstruction in glottic-subglottic stenosis associated with DiGeorge syndrome in a four and a half-month-old infant

Ricostruzione laringotracheale in stenosi subglottica associata a sindrome di DiGeorge in un neonato di 4 mesi e mezzo

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SUMMARY

Neonatal subglottic stenosis still remains a substantial challenge for paediatric ENT surgeons. Herein, we present a case of a single stage laryngotracheal reconstruction for a glottic-subglottic stenosis in an 18-week-old, 7.2 kg infant with DiGeorge syndrome. Our surgical approach was compared with those reported in the literature. Paediatric airway surgery should be tailored to individual patients according to age, weight, comorbidities and family collaboration, with the ultimate objective to minimise the invasiveness of the procedure.

KEY WORDS: Laryngotracheal reconstruction • Neonatal glottic-subglottic stenosis

RIASSUNTO

La stenosi subglottica neonatale rimane ancora una grande sfida per i chirurghi di ORL pediatrica. In questo lavoro presentiamo un caso di ricostruzione laringo-tracheale di una stenosi glottica-subglottica in un neonato di 18 settimane di età con sindrome di DiGeorge di 7,2 kg di peso corporeo. Il nostro approccio chirurgico è stato confrontato con la letteratura. La chirurgia delle vie aeree pediatrica dovrebbe essere adattata al singolo paziente in base all'età, al peso, alla comorbidità ed alla collaborazione familiare, con l'obiettivo ultimo di ridurre al minimo l'invasività della procedura.

PAROLE CHIAVE: Ricostruzione laringo-tracheale • Stenosi neonatale glottica-subglottica

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Introduction

Neonatal subglottic stenosis still remains a substantial challenge despite the significant surgical improvements that have been made in the last 40 years, especially in the effort to carry out less invasive procedures.

According to the literature, the estimated rate of paediatric subglottic stenosis ranges from 1 to 8%, and has remained relatively stable in the past 2 decades^{1,2}. The first cause of acquired stenosis is still long-term intubation in need of mechanical ventilator assistance, especially among premature infants. Congenital malformations, caused by failure of laryngotracheal opening mechanisms during embryological life, are relatively rare, accounting for 5% of patients with subglottic stenosis³. It is clear that, frequently, these congenital malformations are the manifestation of a genetic aberration, such as 22q11.2 deletion syndrome^{4,5}.

A recent 12-year review of tracheotomies, performed in a neonatal care unit at a tertiary care institution, reported

that subglottic stenosis was the most common indication in neonates (one third of all cases)⁶.

Nowadays it is well known that tracheostomy, besides portending a mortality risk of about 1%, may cause long term sequelae in children such as impairment in speech development, social integration and overall development¹. This concept is even more important for small infants in whom early vocalisation is critical to overall development. Moreover, it has a strong impact in the context of a congenital syndrome determining other impairments affecting normal speech and voice development besides overall growth.

Open or endoscopic surgical procedures used to correct subglottic stenosis are a safe alternative to tracheotomy and allow avoiding the negative consequences of tracheostomy in neonates and infants.

Herein, we present the case of a 4.5-month-old boy affected by glottic-subglottic stenosis in the context of DiGeorge syndrome who underwent single stage laryngotracheal reconstruction and compared our surgical approach with those reported in the literature.

Case report

The patient was referred to our paediatric otorhinolaryngology clinic at 4.5 months of age with a diagnosis of DiGeorge Syndrome. On admission he presented with severe dysphonia and recurrent croup crisis. The baby was delivered full term and his mother's pregnancy was not complicated. His father was affected by Gilbert Syndrome and chronic obstructive pulmonary disease, and his mother by Hashimoto thyroiditis and Von Willebrand disease. There was also a predisposition to autoimmune diseases in the extended family.

DiGeorge syndrome was suspected at birth because of the patient's facial dysmorphism and the severe cat-cry dysphonia that appeared to clear from his first wail. He had no history of severe difficulty in breathing at birth or intubation.

Moreover, a detailed neonatal assessment revealed patency of foramen ovale and a minimum ventricular septal defect, slight axial hypotonia, hypoparathyroidism without clinical manifestations, thrombocytopenia without coagulation defects and a few episodes of velopharyngeal insufficiency without cleft palate. Therefore, chromosome examination was performed, with a definitive diagnosis of 22q11 microdeletion by FISH (fluorescence in situ hybridisation) with diagnosis of DiGeorge syndrome.

A second assessment at 3 months of age found significant posterior plagiocephaly and bilateral nasolacrimal duct stenosis. Furthermore, the patient's growth curve was adequate and he had never had dysphagia.

After several croup crisis and many therapies with steroids and adrenalin, the baby was taken to the emergency department where he was admitted to our clinic.

We planned endoscopic examination to assess mobility of the vocal cords, craniocaudal extension of the stenosis and to evaluate the size of the airway residual lumen. Thus, we ruled out the presence of masses, fistulas, malacia and extrinsic compression. Moreover, endoscopy was performed to evaluate the condition of the "activity" of the mucosa to exclude the presence of an inflammatory status caused by viral infection or gastro-oesophageal reflux disease (GERD) or eosinophilic oesophagitis.

We performed transnasal fibre optic laryngo-tracheobronchoscopy with a 3.5 mm diameter flexible endoscope, under digital recording, during spontaneous breathing at first and during general anaesthesia through a catheter mouth by face mask secondly. Moreover, we performed a rigid videoendoscopy with a 4 mm 0° telescope, prior to glottic exposure by a Storz laryngoscope, during general anaesthesia plus topical anaesthesia, above and under the glottic plane, under digital recording.

The baby underwent computed tomography (CT) scan with a CT LightSpeed Pro 32 scanner (General Electric Healthcare, Milwaukee, WI, USA) after intravenous administration of contrast medium in wakefulness super-



Fig. 1. CT study (A, B).

vised by an anaesthesiologist. Technical parameters of acquisition were optimised for the patient size and clinical needs (Th 0.625 mm, kV 120, mAs mod., rotation time 500 msec, pitch 1); a scan range of 9 cm was covered in less than 3 sec. Source images were transferred to a computer workstation (Advantage Windows 4.5; GEMS, Milwaukee, WI, USA) to obtain multiplanar and three-dimensional reconstruction of the airway also using a virtual endoscopic technique. Consequently, after a careful re-evaluation of the clinical and pre-operative condition, we planned a combined endoscopic and open surgery. Endoscopy showed a glottic-subglottic stenosis. The glottic involvement consisted of an anterior fibrous web (III degree Choen) that significantly reduced vocal cord motility. The stenosis was extended to the subglottic area with an anterior fibro-cartilaginous lamina of 0.5 mm cranio-caudal length. The cricoid cartilage was normally shaped.

Airway residual lumen size was assessed to be 4.5 mm by a calibration with a 2.5 mm Mallinckrodt endotracheal tube. In accordance with Myer-Cotton classification, we defined grade III sub-glottic stenosis. We did not find other morphological anomalies of the trachea and bronchi. The CT study revealed a glottic-subglottic stenosis 5 mm in length with an extreme luminal narrowing (transverse diameter < 2 mm).

The infant's weight was 7.2 kg. At first, we performed a diode laser transection of the mucosa portion of the web, monitored by a 4 mm 0° telescope. We then performed a double stage laryngotracheal reconstruction with anterior costochondral cartilage grafting. The costochondral cartilage was harvested from rib 8 at the bony-cartilaginous junction of the sternum, just to achieve the best, slightly concave, surface of the graft. As a result, after cervical exposure of the larynx and trachea, the thyroid isthmus was divided and retracted laterally, preserving the cricothyroid muscles.

The ensuing laryngotracheal fissure included the thyroid cartilage, cricothyroid membrane, anterior cricoid arch and the first tracheal ring. An endoscopic control was performed to evaluate the outcome of the surgical correction. Because of the very small dimensions of the graft (only 2 cm, due to the age of the infant), the typical boat-shaped graft carving was impossible. Thus, a notch in the longitudinal side of the graft was routed with a cold lancet blade and brushed up with a drill used for ear surgery, bilaterally. The graft was positioned and fixed with nine prolene 4.0 stitches with the perichondral side of the graft facing the lumen.

A Portex N. 4 endotracheal tube was positioned by the naso-tracheal path to stent the graft.

After the procedure, the patient was admitted to the Intensive Care Unit. During the post-operative period no complications were recorded and the tube was removed 9 days after surgery.

The first videoendoscopic control, 14 days after surgery, revealed a 6.5 mm glottic-subglottic diameter and only minimal fibrous tissue in the anterior area. Three additional endoscopic evaluations were performed every 8 days. Only one balloon dilation was necessary (balloon dimension: 7-2.4 mm; pressure up to 10 atm). Pulsoxi-metry measure and functional respiratory tests performed in the post-operative period were negative. At the time of writing the child is at home and on daily proton pump inhibitor therapy. He is free from dysphagia and shows regular growth.

Discussion

During embryological life the respiratory tract is first obliterated by actively proliferating epithelial tissue that closes at 8 weeks of gestation starting with vacuolisation and autolytic dissolution. At this point in time, definitive



Fig. 2. Cervical exposure of the larynx and trachea.



Fig. 3. Laryngotracheal fissure and the stenosis.

opening of the airway begins. Congenital malformation of the larynx and trachea are caused by failure of that mechanism during embryological life. In some cases of congenital glottic and subglottic stenosis it is possible to define a genetic cause such as in the context of DiGeorge syndrome⁷.

DiGeorge syndrome is a chromosomal disorder associated with 22q11 deletion, the most frequent interstitial deletion in humans (incidence of 1/4000 live births). Deletion of 22q11 is inherited only in 6-28% of cases. In most cases, the mutation is somatic⁵. Allelic loss results in altered development of the pharyngeal pouch determining various pathologies of the head and neck⁸. Di George syndrome commonly comprises certain heart defects, facial dysmorphism (small mouth, broad nose root, small ears), al-

tered development of the thymus and parathyroid glands with neonatal hypocalcaemia and psychomotor development delay. Over the years many other clinical features and phenotypes have been reported including laryngeal and tracheal disease⁹.

According to the literature the exact frequency of laryngotracheal malformation in the context of 22q11 deletion is not well defined (in particular subglottic stenosis), although it is clear that laryngotracheal status needs to be assessed whenever 22 q11 deletion is suspected^{5,7}.

In our case, diagnosis of DiGeorge syndrome was suspected at birth because of the typical facial dysmorphism and severe dysphonia.

The rising number of acquired subglottic stenoses, due to the improvement of neonatal disease management in intensive care unit and long-term intubations, has led to the development of alternative techniques to avoid the high rate of morbidity and mortality associated with tracheotomy and the negative impact of tracheotomy on a child's life¹.

In 1953, John Conley published a summary of the known surgical methods for the treatment of stenosis at that time and for the first time used the term *reconstruction*. In fact, the real innovation was in 1956 when A. Rethi, who had had some experience with laryngeal stenosis in patients who suffered from injuries during World War I, described his techniques for laryngotracheal expansion by vertical median anterior and posterior division of the cricoid cartilage without touching the scar tissues, which was significantly different from previously described methods. His report did not include children.

It was not until 1958 that Holinger and Johnston published their case series on laryngotracheal reconstruction (LTR) in children and recommended complete removal of the scar and damaged tissues and a multi stage procedure that included skin graft and stent placement with tracheotomy tube. Next, Fearon and Cotton in 1972 well defined and encoded cricoid splitting and expansion of the subglottis by autologous cartilage graft. In 1988, Prescott presented the first description of single-stage LTR with laryngotracheal tube stenting of the reconstructed airway. These original basic concepts remain valid in the face of the many surgical improvements that have been brought about and allow performing many expansion procedures endoscopically^{8,10}.

According to the literature, during the past 30 years LTR has been the standard surgical method to treat subglottic stenosis in children. Endoscopic methods are limited to mild stenosis and to assist open surgery in case of glottis involvement; these approaches are contraindicated in case of congenital cartilaginous malformations. Actually, in cases with more severe stenosis (grade 3 and 4) the preferred surgical method is PCTR¹¹.

In the present case, upon admission to our paediatric otorhinolaryngology department, we performed a meticulous



Fig. 4. A-B: Positioning and fixation of the graft.

assessment to choose the correct surgical method for the particular condition.

First, general clinical assessment was done. Next, during the endoscopic evaluation, we were careful to ensure that the larynx and the trachea were not in an “activity” status, i.e. significant inflammation due to infection or acid or basic GERD because that could have minimised surgical efforts. Daily proton pump inhibitor therapy was established before scheduling the operation as suggested by the literature^{12,13}. After a consensus with intensive care unit paediatricians, cardiologists, endocrinologists and gastroenterologists, we decided to perform single-stage LTR.

Our choice was supported by the high consensus found in the literature and by the experience of our senior surgeons.

Indeed, many studies have confirmed that LTR is a safe and highly successful procedure for the management of congenital malformation, i.e. glottis-subglottic stenosis in infants and neonates because it allows a high rate of successful extubation and low complication rates¹.

The choice of a single-stage procedure is supported by the literature: firstly, it has been demonstrated to be a safe alternative to tracheostomy even in neonates^{12,11}, secondly, according to the literature, it allows a high grade of decannulation, decreases the risk of granulation and scar tissue re-stenosis and removes potential sources of infectious complications^{11,12}.

Our choice is also supported by a recent study showing similar outcomes between single and double stage LTR and the importance of an individualised approach to every case¹².

The infant herein was affected by a laryngotracheal malformation in the context of a genetic syndrome with other impairments. Fortunately, he demonstrated good general clinical conditions. Furthermore, the collaboration between surgeons, the anaesthesiologist and chest and speech language therapist allowed to choose the single stage performance and to maximise decannulation. Costal cartilage graft was chosen because of in our paediatric ENT unit we have never had complications with this technique, thus confirming previous reports¹⁴.

Finally, it is worthwhile underscoring that our patient was also very young, only 4.5 months old and weighing 7.2 kg. Thanks to multidisciplinary collaboration among our laryngotracheal team – surgeons, anaesthesiologist, physiotherapist and nurses – we embrace the concept that performing single stage LTR early in life [1] could avoid negative consequences of a tracheostomy, i.e. impairment in voice and speech development, inferior complexity and social integration⁷.

In conclusion, careful preoperative evaluation can influence the surgical outcome in the treatment of congenital laryngotracheal malformations. Therefore, we confirm the necessity to assess disease-specific airway condition with general clinical conditions to optimise the patient's status before surgery to minimise post-operative complications, according to the literature¹³.

Paediatric airway surgery is a “tailored surgery”, which means “tailored on” every single patient considering age, weight, comorbidities and family collaboration. In our case, all these considerations allowed performing the less invasive surgical treatment in a very young and underweight infant. This kind of surgical choice is possible only with good cooperation among all members of a multidisciplinary team¹¹.

References

- O'Connor TE, Bilish D, Choy D, et al. *Laryngotracheoplasty to avoid tracheostomy in neonatal and infant subglottic stenosis*. *Otolaryngol Head Neck Surg* 2011;144:435-9.
- White DR, Bravo M, Vijayasekaran S, et al. *Laryngotracheoplasty as an alternative to tracheotomy in infants younger than 6 months*. *Arch Otolaryngol Head Neck Surg* 2009;135:445-7.
- Meier JD, White DR. *Multisystem disease and pediatric laryngotracheal reconstruction*. *Otolaryngol Clin North Am* 2012;45:643-51.
- Sidman JD, Jaguan A, Couser RJ. *Tracheotomy and decannulation rates in a level 3 neonatal intensive care unit: a 12-year study*. *Laryngoscope* 2006;116:136-9.
- Marom T, Roth Y, Goldfarb A, et al. *Head and neck manifestations of 22q11.2 deletion syndromes*. *Eur Arch Otorhinolaryngol* 2012;269:381-7.
- Leopold C, De Barros A, Cellier C, et al. *Laryngeal abnormalities are frequent in the 22q11 deletion syndrome*. *Int J Pediatr Otorhinolaryngol* 2012;76:36-40.
- Koempel JA, Cotton RT. *History of pediatric laryngotracheal reconstruction*. *Otolaryngol Clin North Am* 2008;41:825-35.
- Santos D, Mitchell R. *The history of pediatric airway reconstruction*. *Laryngoscope* 2010;120:815-20.
- Bielecki I, Cofala M. *Single-stage laryngotracheoplasty in children*. *Auris Nasus Larynx* 2011;38:697-701.
- Digilio MC, Angioni A, De Santis M, et al. *Spectrum of clinical variability in familial deletion 22q11.2: full manifestation to extremely mild clinical anomalies*. *Clin Genet* 2003;63:308-13.
- Smith LP, Zur KB, Jacobs IN. *Single- vs double-stage laryngotracheal reconstruction*. *Arch Otolaryngol Head Neck Surg* 2010;136:60-5.
- Cheng AT, Beckenham EJ. *Congenital anterior glottic webs with subglottic stenosis: surgery using perichondrial keels*. *Int J Pediatr Otorhinolaryngol* 2009;73:945-9.
- De Alarcon A, Rutter MJ. *Revision pediatric laryngotracheal reconstruction*. *Otolaryngol Clin North Am* 2008;41:959-80.
- Nguyen CV, Bent JP, Shah MB, et al. *Pediatric primary anterior laryngotracheoplasty: Thyroid ala vs costal cartilage grafts*. *Arch Otolaryngol Head Neck Surg* 2010;136:171-4.

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CASE SERIES AND REPORTS

Mucoepidermoid carcinoma of the base of tongue

Carcinoma mucoepidermoide della base della lingua

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SUMMARY

Mucoepidermoid carcinoma (MEC) is the most common malignant, locally-invasive tumour of the salivary glands, and accounts for approximately 35% of all malignancies of the major and minor salivary gland. Minor salivary glands are scattered in different areas of the oral cavity such as palate, retromolar area, floor of the mouth, buccal mucosa, lips and tongue. MECs of tongue base are not common. We present a rare case of MEC localised at the tongue base in a 42-year-old Caucasian woman and discuss the histopathological types, management and review the literature. Adequate intra-oral excision was the treatment of choice in this case and in low-grade MEC. Prognosis of MEC is a function of the histological grade, adequacy of excision and clinical staging.

KEY WORDS: Mucoepidermoid carcinoma • Tongue base • Minor salivary glands • Intra-oral approach

RIASSUNTO

Il carcinoma mucoepidermoide è il più comune tumore maligno, localmente invasivo delle ghiandole salivari. Esso si presenta approssimativamente nel 35% di tutti i tumori delle ghiandole salivari maggiori e minori. Per le ghiandole salivari minori si localizza principalmente nella cavità orale, nel palato, nell'area retro molare, nel pavimento della bocca, sulla mucosa buccale, sulle labbra e sulla lingua. Il carcinoma muco epidermoide della base della lingua è alquanto raro. Presentiamo un raro caso di carcinoma muco epidermoide della base della lingua occorso in una donna di 42 anni giunta alla nostra osservazione. Un'adeguata escissione del tumore per via intraorale ha rappresentato il trattamento più adeguato per il nostro caso e per i carcinomi muco epidermoidi a basso grado di malignità. In generale la prognosi del carcinoma muco epidermoide è in relazione al grado istologico, all'adeguatezza dell'escissione chirurgica e allo stadio clinico.

PAROLE CHIAVE: *Carcinoma mucoepidermoide • Base lingua • Ghiandole salivari minori • Approccio intraorale*

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Introduction

Mucoepidermoid carcinoma (MEC) is malignant, locally-invasive tumour of the salivary glands¹. It accounts for approximately 35% of all malignancies of the major and minor salivary glands, especially in the parotid gland^{1,2}. MECs can also occur in the submandibular and minor salivary glands³. When MEC arises in minor salivary glands, it can be located in different areas such as palate, retromolar area, floor of the mouth, buccal mucosa, lips and tongue³⁻⁵. Although MECs of tongue base are not common, they constitute more than 50% of malignant lesions of salivary glands in this region⁶⁻⁹. The mean age of patients with MEC is 48 years (range 12-82 years) with peaks in the fifth and sixth decades of life, although it may occur at any age^{1,2}. In this report, we present a rare case of 42-year-old woman with MEC of the tongue base and discuss the histopathological types and management of MEC.

Case report

A 42-year-old woman was referred to the ENT Department of University of Naples. The patient complained of an asymptomatic nodule of the right side of tongue base for 4 months duration. The mass gradually increased in size during this time. The patient complained of dysphagia, but it was not associated with any bleeding or pain (Fig. 1). There was no history of weight loss. The patient denied the use of tobacco and alcohol at any point in her life. Clinical examination showed a non-ulcerated, firm, exophytic, oval mass on the dorsal surface in the right posterior-lateral base of the tongue that was seen easily when the patient protruded her tongue (Fig. 1). The mass was about 3.2 cm crossing the midline, and had an irregular surface. Neck examination showed no palpable lymph nodes. Clinical stage was established as II (T2N0M0).

Computed tomography (CT) showed a soft tissue mass on the right side of tongue base and crossing the midline. It was



Fig. 1. Asymptomatic, non-ulcerated, firm, exophytic, oval mass on the dorsal surface in the right posterior-lateral base of the tongue.

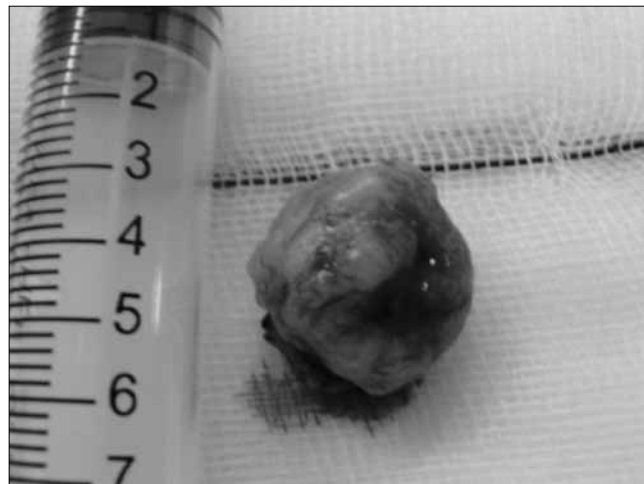


Fig. 3. Complete transoral excision of nodular lesion with intact overlying mucosa. Histological examination confirmed low-grade MEC.

infiltrating the muscles, but was not involving the whole thickness of the tongue. No loco-regional adenomegalies were detected. Magnetic resonance imaging (MRI) showed an irregular oval-shaped mass, 3 cm in diameter arising from the right tongue base (Fig. 2). Findings on chest radiographs and laboratory tests were within normal limits. Complete transoral excision (Fig. 3) was performed under general anaesthesia. The post-surgical course was uneventful. The patient started swallowing foods and water on the second postoperative day. Histopathological examination of the specimen confirmed a slightly raised nodular lesion with intact overlying mucosa measuring 3 x 1.6 x 1.8 cm

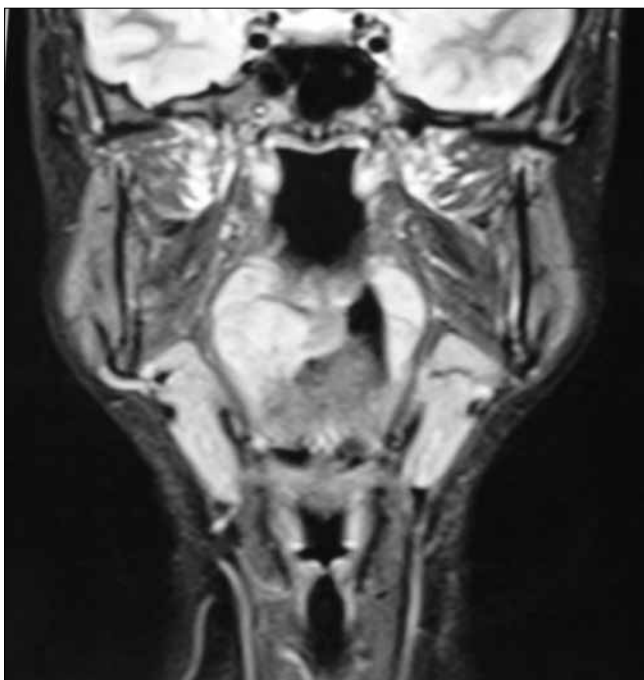


Fig. 2. MRI shows an irregular oval-shaped mass, 3 cm in diameter, arising from the right tongue base.

of a low-grade mucoepidermoid carcinoma with negative margins. No adjuvant therapy was offered due to the low histological grade and clear resection margins. Follow-up for 3 years showed no recurrence. Informed consent was obtained from the patient to publish the case.

Discussion

The first report on mucoepidermoid tumours was by Stewart³: he divided these tumours into relatively favourable and highly unfavourable. The classification of MECs into low, intermediate and high grade was based on the relative proportion of cell types^{1,2}.

MEC of the minor salivary glands is composed histologically of three cell types: mucous cells, epidermoid squamous cells and poorly differentiated intermediate cells that have the ability to differentiate into either mucous-producing or epidermoid cells^{1,2}. When the epidermoid element predominates, the histological appearance of the tumour may closely resemble that of squamous cell carcinoma on histological examination, and it is thus classified as a high-grade MEC tumour. Instead, the presence of mucin-producing cells within a predominantly cystic architecture is regarded as low-grade MEC tumour. Intermediate-grade tumours are less cystic and show a greater tendency to form large, more irregular nests or sheets of squamous cells and often have a more prominent intermediate cell population¹.

Auclair et al.⁶ studied the grading criteria of minor salivary glands MECs. The histopathological features that indicated high-grade behaviour were:

- an intra-cystic component of < 20% (+ 2 points);
- four or more mitotic figures per 10 high power field (+ 3 points);
- neural invasion (+ 2 points);
- necrosis (+3 points);

- cellular anaplasia (+ 4 points)².

According to this grading scale, tumours with a:

- score of 0-4 were considered low-grade;
- scores 5-6 were considered intermediate (between low-grade and high-grade);
- scores ≥ 7 indicated highly aggressive behaviour.

The standard treatment for all grades of MEC is surgical resection^{1,2,6,8,10}. The treatment of choice for MECs of minor salivary glands with low to intermediate-grade is a radical surgery alone by wide local excision intraoral, if it can be achieved, with adequate tumour-free margins. High-grade tumours require more aggressive surgery with or without postoperative radiotherapy and chemotherapy^{2,8}. The methods of surgical removal of neoplasm of base of the tongue include transmandibular and/or transcervical approaches and an intraoral route. The transmandibular approaches have the advantage of good exposure of the surgical site, but may result in complications such as extraoral scar formation, damage of joint components and more traumatic access with consequent high morbidity and poor cosmetic and functional outcomes. The intraoral route may avoid these problems and allow the possibility to deintensify adjuvant treatments, but provides a smaller surgical site. Recently, transoral robotic surgery has been used with good results in the treatment in selected T1-T2 cases of oropharyngeal tumours of the base of the tongue, but one of the main criticisms against using robotic surgery is related to the cost of the procedure¹¹.

During follow-up, patients often develop local or regional recurrence and distant metastases. Metastasis is primarily to subcutaneous tissues, lymph nodes, bone and lung^{4,10}. Generally, lymphatic spread can be common in high-grade MEC. Previously, high-grade MEC has been associated with poorer regional control because it frequently infiltrates surrounding structures, recurs, or metastasises⁴. Management of the neck and the need to assess it during long-term follow-up of MEC has been emphasised¹². Neck dissection is not indicated for patients with low grade mucoepidermoid carcinoma¹¹⁻¹³. In a study of 48 patients from the MD Anderson Cancer Center, the presence of lymphatic spread was closely correlated with increasing histological grade: 0% for low-, 22% for intermediate- and 72% for high-grade tumours¹⁴. Thus, many authors believe that adjuvant radiotherapy (RT) is recommended for high-grade tumours⁴. We believe that post-operative radiotherapy should be given to patients with high-grade tumours and in those invading or in close resection margins, lymph node metastases, perineural or lymphovascular invasion, or both. Treatment with chemotherapy is indicated for patients with metastatic disease and those who are not candidates for salvage surgery or RT^{4,14}. It is generally accepted that, for high-grade MECs, radiotherapy combined with surgery should achieve local control of the disease and good survival rates². We believe that the prognosis of MECs is a function of the histological grade, adequacy of excision and clinical staging.

Low-grade tumours have a 5-year survival rate of 76-95%, with the exception of the submandibular gland MECs that demonstrate a more benign nature². Intermediate and high-grade tumours have a tendency to infiltrate, recur and metastasise with reported 5-year survival of 30-50%^{4,14}. Most high-grade MECs show malignant behaviour within the first 5 years after surgery. Although it is rare, cases of recurrence have been reported 15 years after initial excision, indicating the requirement of long-term follow-up. In our case, surgical excision of the tumour was done transorally because there was no lymph node metastasis (clinically and radiologically), and there is no need to perform neck dissection as suggested by NCCN guidelines¹¹ in low-grade MEC. However, Conley¹⁰ reported that lymph node metastases occur in nearly three-quarters of patients with high-grade cancer. Thus, after surgery, radiotherapy may reduce the risk of loco-regional recurrence in cases of advanced tumours with positive resection margins or high-grade malignancy. Jones advised performance of selective neck dissection for patients with high-grade or large lesions and a N0 neck, and radical dissection for patients with positive neck nodes.

Follow-up of our case for 3 years showed no recurrence. However, some authors recommended follow-up for life as recurrence may be delayed for many years^{1,2,15}.

Conclusions

MECs are rare tumours of the salivary glands. No specific guidelines have evolved for the management of these tumours, but surgical excision is mandatory along with a long-term follow-up. In particular, low and intermediate-grade MECs of salivary glands tend to have a favourable outcome compared with high-grade MECs that have a greater tendency to recur and metastasise. The clinical stage continues to be both a prognostic factor for overall survival and a predictive factor of distant metastases. Therefore, both correct clinical staging and immunohistochemical findings associated with careful follow-up are important factors in minor salivary gland malignancies, especially high-grade MECs, for appropriate management of these tumours. In our case, surgical excision of the tumour was done transorally. This approach is safe and can radically remove limited oropharyngeal tumours of the tongue base with good functional outcomes compared with transmandibular and/or transcervical approaches.

References

- 1 Triantafyllidou K, Dimitrakopoulos J, Iordanidis F, et al. *Mucoepidermoid carcinoma of minor salivary glands: a clinical study of 16 cases and review of the literature*. Oral Dis 2006;12:364-70.
- 2 Brandwein MS, Ivanov K, Wallace DI, et al. *Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading*. Am J Surg

- Pathol 2001;25:835-45.
- ³ Stewart FW, Foote FW, Becker WF. *Mucoepidermoid tumors of salivary glands*. Ann Surg 1945;122:820-44.
 - ⁴ Eversole LR. *Mucoepidermoid carcinoma: review of 815 reports cases*. J Oral Surg 1970;28:490-45.
 - ⁵ Caccames JF, Ord RA. *Paediatric mucoepidermoid carcinoma of the palate*. Int J Oral Maxillofacial Surg 2002;31:136-9.
 - ⁶ Auclair PL, Goode RK, Ellis GL. *Mucoepidermoid carcinoma of intraoral salivary glands. Evaluation and application of grading criteria in 143 cases*. Cancer 1992;69:2021-30.
 - ⁷ Abdel-Aziz M. *Mucoepidermoid carcinoma of the tongue in a child*. Int J Pediatr Otorhinolaryngol Extra 2012;7:6-8.
 - ⁸ Sobani ZA, Junaid M, Ghaffar S, et al. *Mucoepidermoid carcinoma of the base of tongue*. J Pak Med Assoc 2011;61:945-7.
 - ⁹ Leong SCL, Pinder E, Sasae R, et al. *Mucoepidermoid carcinoma of the tongue*. Singapore Med J 2007;48:e272-4.
 - ¹⁰ Conley J, Tinsley PP. *Treatment and prognosis of mucoepidermoid carcinoma in the paediatric age group*. Arch. Otolaryngol 1985;111:322-4.
 - ¹¹ Mercate G, Ruscito P, Pellini R, et al. *Transoral robotic surgery (TORS) for tongue base tumours*. Acta Otorhinolaryngol Ital 2013;33:230-5.
 - ¹² Andrews KV, Eveson JW. *Myokymia (fasciculation) of the tongue as a unique presentation of mucoepidermoid carcinoma*. Int J Oral Maxillofac Surg 2007;36:79-81.
 - ¹³ *NCCN Guidelines: clinical practice guidelines in oncology. Head and Neck Cancer*. Version I. 2013.
 - ¹⁴ Mc Hugh CH, Roberts DB, El-Naggar AK, et al. *Prognostic factors in mucoepidermoid carcinoma of the salivary glands*. Cancer 2012;15:3928-36.
 - ¹⁵ Mesoletta M, Luce A, Marino A, et al. *Treatment of c-kit positive adenoid cystic carcinoma of the tongue: a case report*. Oncol Lett 2014;8:309-12.

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CASE SERIES AND REPORTS

Intra-operative sclerotherapy for treatment of a head and neck venous malformation

Trattamento di una malformazione venosa del distretto testa-collo mediante scleroterapia intraoperatoria

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SUMMARY

Venous malformations of the head and neck are congenital lesions that grow steadily without spontaneous regression. We describe the management of a 47-year-old woman with an extensive subcutaneous venous malformation of bilateral submandibular regions and the entire tongue, refractory to multiple surgical excisions and percutaneous sclerotherapy sessions. The tumour lacked prominent feeding arteries for embolisation, but maintained high blood outflow via a few substantial venous branches. Sclerotherapy to the lesion was prevented by major communicating branches from the mass to the internal jugular vein bilaterally. Our approach entailed direct surgical access to the malformation, ligation of these communicating veins and intraoperative sclerotherapy with ethanol injection into the vessel stumps.

KEY WORDS: Head and neck • Venous malformation • Recurrent • Sclerotherapy • Intra-operative

RIASSUNTO

Le malformazioni venose della testa e del collo sono lesioni congenite che crescono costantemente, senza regressione spontanea. Presentiamo il caso clinico di una donna di 47 anni con una estesa malformazione venosa sottocutanea delle regioni sottomandibolari e della lingua refrattaria a più escissioni chirurgiche ed a sedute di scleroterapia percutanea. Il nostro approccio ha permesso un accesso chirurgico diretto alla malformazione, la legatura delle vene comunicanti, e la scleroterapia intraoperatoria con iniezione di etanolo.

PAROLE CHIAVE: *Malformazioni venose della testa e del collo • Scleroterapia intraoperatoria*

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Introduction

Venous malformations are an ill-defined subgroup of congenital vascular anomalies that affect one in 22 children, primarily in the head and neck. In contrast with haemangiomas, which involute soon, vascular malformations persist into adulthood, being the source of distressing functional and aesthetic afflictions¹.

Treatment options for venous malformations classically include compression garments, laser therapy, percutaneous sclerotherapy and surgery². Whereas superficial lesions can be addressed successfully by the majority of these modalities, deeper subcutaneous masses might be amenable to surgical excision only. However, the latter approach is technically challenging, may compromise other vital structures and carries the risk of significant intraoperative haemorrhage³.

In the case of the extensive deep head and neck vascular malformation described here, we needed to utilise the combined approach of intra-operative sclerotherapy.

Case report

Our patient, a 47-year-old female, has been under our care for the past 7 years. She initially presented with a very long history, beginning in infancy, of a large neck vascular mass, extending to the lower face, which did not involute in childhood. She had undergone multiple surgical procedures, including repeated bilateral neck dissections, left parotidectomy and significant tongue resections. In spite of that, she was never disease-free, and presented to our Department with the complaint of progressing swelling and tenderness over the left parotid and upper neck area, as well as the tongue, odynophagia and severe episodic tongue bleeding.

On the initial physical exam, the oral cavity demonstrated notable hypertrophy of the anterior tongue, which was also tethered to the floor of mouth, due to post-operative scarring. Palpation of the neck, apart from extensive scarring, did not reveal any distinct masses, but rather diffuse soft enlargement of the left parotid and upper cervical re-

gion. Yet, the affected areas did not show any cutaneous lesions or pigmentation changes.

The initial magnetic resonance imaging (MRI) scan displayed multiple contrast-enhancing lesions, diffusely expanding into the tongue mass, as well as the submandibular and deep parotid spaces, mainly on the left side (Fig. 1). The aberrant vascular network seemed to be adherent to the internal jugular vein (IJV). A computed tomography angiography (CTA) showed a normal arterial branching pattern, but prominent venous drainage during the late phase. Next, we performed a direct venogram, which displayed a large varicose branch, merging into the IJV bilaterally (Fig. 2). Based on the above findings, interventional radiology proceeded with percutaneous sclerotherapy, as no obvious feeding arteries could be identified for embolisation. The sclerosing agent was injected into the submandibular and parotid regions. There was symptomatic improvement for two years, but eventually the swelling and bleeding recurred, and a second sclerotherapy session followed, with new temporary regression of the malformation. Unfortunately, both attempts were limited by the immediate drainage pattern from the lesion to the IJV, via bilateral venous branches. During the past year, the symptoms had been progressing slowly again.

Keeping in mind the multiple attempts to control the disease, both by either surgery or sclerotherapy alone, the diffuse infiltrating spread pattern along the deep and subcutaneous tissues and the large venous trunk draining into the IJV, we chose to perform direct intra-operative sclerotherapy through the main lesion vein, after division of the venous trunk, to avoid infusion of the sclerosing agent systemically. In detail, surgical exploration of the neck revealed the inferior aspect of the vascular mass and its large draining vessel, which was dissected down to its termination into the IJV (Fig. 3a). Three smaller venous branches were traced from the venous malformation to more superior points of entry into the IJV. The four branches were ligated. Then, interventional radiology performed sclerotherapy via the open neck wound. Specifically, into the proximal ligated end of the principal lesion vein, 4 mL of alcohol were injected (Fig. 3b). The entire procedure was also performed on the right side, where three considerably smaller veins than those on the left, were dissected between the vascular anomaly and IJV, and suture-ligated. Subsequently, 3 mL of alcohol were injected into the largest branch. Several minutes later, sclerosis of the vascular spaces was palpable. The patient's post-operative course was fortunately uneventful. Six months later, depletion of the malformation volume could be noted both clinically and radiographically (Fig. 4).

Discussion

“Vascular anomaly” is a generic, non-descriptive term, embracing a group of diverse lesions, which indicates dis-

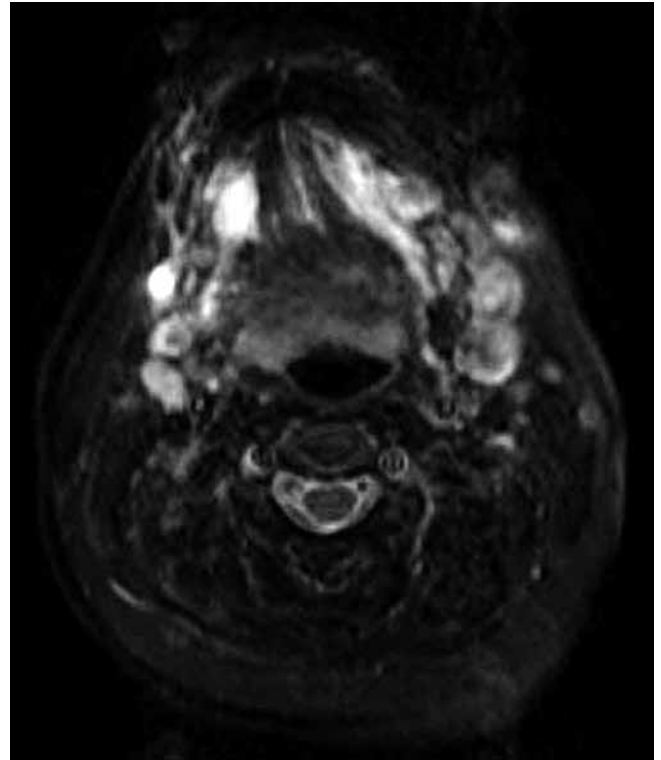


Fig. 1. This axial T2 fat-suppressed MRI scan depicts high signal intensity lesions surrounding the ramus and body of the left mandible. The lesion extends into the left lateral tongue. A smaller lesion involves the corresponding structures on the right. This “bunch of grapes” arrangement with septations is pathognomonic of a venous malformation.



Fig. 2. After the percutaneous injection of contrast into the vascular mass, digital venograms show a large varicose venous trunk on each side, draining briskly into the ipsilateral IJVs. The left malformation (a) is larger than the right (b).

tinct approaches. Therefore, a clear-cut classification precludes their misdiagnosis and mismanagement. According to the criteria established by Mulliken and Glowacki, vascular malformations are non-neoplastic, ectatic vessels, of venous, arterial or mixed origin¹. Their architecture can

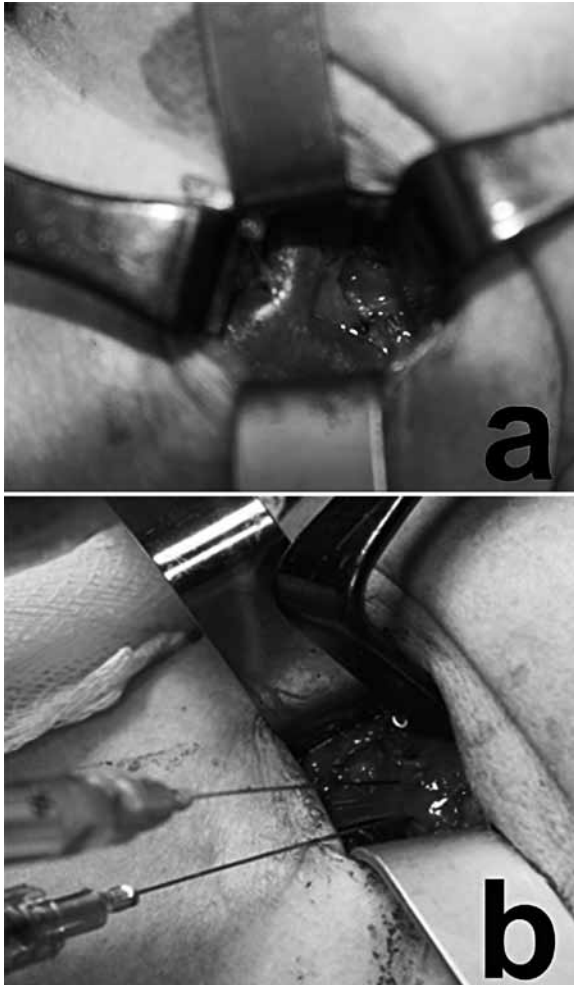


Fig. 3. Intraoperative snapshots from our approach: (a) The left IJV receives the venous outflow from the malformation, via a large-calibre vessel, which is about to be ligated. (b) After the ligation, ethanol is injected directly into the stump, and disseminates in the circulation of the lesion, to exert its toxic effect on the vascular endothelium.

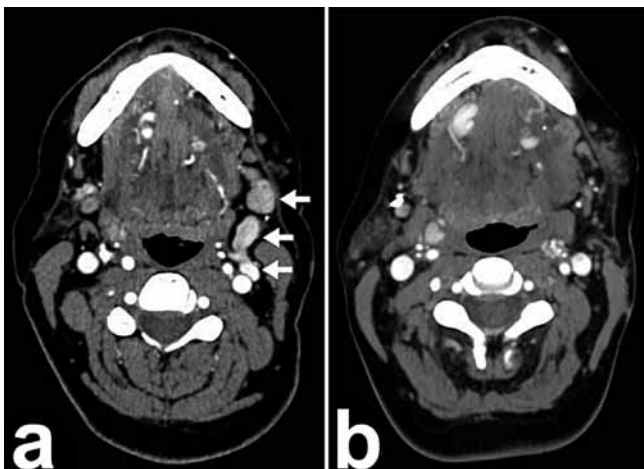


Fig. 4. (a) Axial CTA section before the intra-operative sclerotherapy: large enhancing vascular spaces (arrows) of the left submandibular triangle, which communicate readily with the IJV. (b) Post-treatment CT-image: the terminal venous branch of the malformation has been ligated and the direct injection of the sclerosing agent has led to substantial contraction of the abnormal vasculature.

be either well-defined, producing a sharply demarcated lesion, or as in the case of our patient, might demonstrate infiltrating margins into the deeper structures of the head and neck⁴. Perioral localisation can hamper food intake and permanently deform the lips.

The challenge in the management of such lesions is determining how far we can go with interventions, and which treatment modality is appropriate. Whereas the consensus regarding the treatment of these benign anomalies is to resect the malformation aggressively, for fear of recurrence, the magnitude of some cervicofacial lesions determines a debulking, palliative approach⁵.

Laser photothermolysis is the treatment of choice for mucosal or skin malformations. Subcutaneous masses may respond to interstitial Nd:YAG laser, but vessels deeper than 7-8 mm will not be coagulated sufficiently due to the limited penetration of the light beam. Moreover, when targeting beyond the superficial layers, the risk of injury to the facial and hypoglossal nerves should be considered⁶. High-flow arteriovenous malformations communicate profusely with the arterial tree and are amenable to embolisation either as a monotherapy, or an adjunct to surgery⁷. However, in our patient, no prominent arterial branch was identified angiographically, to be targeted for occlusion.

Percutaneous intra-lesional sclerotherapy is a useful adjunct to surgical resection. The sclerosing agent produces a successful fibrous change in the consistency of the venous anomaly, but only after prolonged contact with the endothelial lining of the vascular spaces⁸. By using novel sclerosing substances, such as sodium tetradecyl sulphate foam, transoral or percutaneous injection, significant regression of the malformation can be achieved in up to 83% of lesions. The advantage of a sclerosant with a foamy texture is its slow-paced clearance from the deposition site⁹. In the case presented here, several wide-calibre vessels, as outlined in the venogram, maintained a brisk out-flow of blood from the malformation to the IJV, thus rapidly clearing the sinusoidal compartment of the sclerosing substance. This also explains the temporary effect of the two sclerotherapy sessions performed in our institution.

Surgical intervention is the definitive treatment for small to moderate venous malformations¹⁰. In the case presented here, the operation would be a major undertaking with significant morbidity. Taking into account the multi-planar, infiltrating extent of the tortuous lesion, radical resection would require near-total glossectomy and extended submandibular resection. Consequently, the functional restoration of deglutition and articulation, as well as the aesthetic reconstruction would, in all probability, be sub-optimal, even with use of free tissue transfer.

Nevertheless, a minimal surgical intervention provides valuable direct access to the vein trunks of the mass. A sclerosing agent is then injected under direct vision

into the ligated vessels and saturates protractedly the dysplastic venous channels. The concept of depriving a vascular lesion of its main drainage pathways by surgical ligation, while addressing the numerous minute vascular spaces by long-standing sclerotherapy, has been efficiently applied in urology to treat varicoceles¹¹. In the head and neck however, to our knowledge, intra-operative sclerotherapy of venous malformations is first reported here. It has successfully treated an aneurysmal cyst of the sphenoid bone, however¹². Of course, a less complicated alternative to ligating the draining veins prior to the injection of ethanol would be simply to hold pressure transiently on the IJV, allowing the sclerosis to take place. Yet in our opinion, the combination of direct sclerotherapy with the elimination of main flow connections, provides a long-term effect on vascular space obliteration as the dilated malformed veins may not degenerate while still communicating widely with the circulation. The capacity of the sinusoidal vessels² and the blood reflux from the IJV¹³ would synergistically perpetuate the anomaly.

Naturally, direct injection of ethanol into the bloodstream carries a risk of substantial morbidity, which is already documented in percutaneous sclerotherapy. Local adverse effects include deep venous thrombosis, ulceration and necrosis, while systemic toxicity may escalate to pulmonary embolism and ventricular fibrillation^{14 15}. In the case described here, the major outflow pathways were surgically eliminated prior to ethanol administration to avoid rapid washout of the sclerosing substance. We carefully monitored our patient in the ICU for 24 hours, and fortunately her post-operative course was uneventful. Other sclerosants, such as sodium tetracycl sulphate, have demonstrated a safer adverse effect profile⁹.

The case we present demonstrates a multidisciplinary approach to a complex problem. Extended venous malformations which are not amenable to radical excision might be appropriate candidates for intra-operative sclerotherapy. Clearly, the modality described here is not recommended as a first-choice treatment, but rather as a backup technique only in selected cases that are refractory to transcatheter sclerotherapy. It is evident that in every aspect of this approach, close collaboration between the surgeons and interventional radiologists is cardinal.

References

- Mulliken JB, Glowacki J. *Classification of pediatric vascular lesions*. *Plast Reconstr Surg* 1982;70:120-1.
- Arneja JS, Gosain AK. *Vascular malformations*. *Plast Reconstr Surg* 2008;121:195e-206e.
- Buckmiller LM, Richter GT, Suen JY. *Diagnosis and management of hemangiomas and vascular malformations of the head and neck*. *Oral Dis* 2010;16:405-18.
- Eivazi B, Ardelean M, Baumler W, et al. *Update on hemangiomas and vascular malformations of the head and neck*. *Eur Arch Otorhinolaryngol* 2009;266:187-97.
- Glade RS, Richter GT, James CA, et al. *Diagnosis and management of pediatric cervicofacial venous malformations: retrospective review from a vascular anomalies center*. *Laryngoscope* 2010;120:229-35.
- Clymer MA, Fortune DS, Reinisch L, et al. *Interstitial Nd:YAG photocoagulation for vascular malformations and hemangiomas in childhood*. *Arch Otolaryngol Head Neck Surg* 1998;124:431-6.
- Gomes AS. *Embolization therapy of congenital arteriovenous malformations: use of alternate approaches*. *Radiology* 1994;190:191-8.
- Burrows PE, Mason KP. *Percutaneous treatment of low flow vascular malformations*. *J Vasc Interv Radiol* 2004;15:431-45.
- Stimpson P, Hewitt R, Barnacle A, et al. *Sodium tetracycl sulphate sclerotherapy for treating venous malformations of the oral and pharyngeal regions in children*. *Int J Pediatr Otorhinolaryngol* 2012;76:569-73.
- Kang GC, Song C. *Forty-one cervicofacial vascular anomalies and their surgical treatment--retrospection and review*. *Ann Acad Med Singapore* 2008;37:165-79.
- Lebed B, Packer M, Husmann D, et al. *Results and complications of adolescent varicocele repair with intraoperative sodium morrhuate sclerotherapy*. *J Urol* 2008;180:1837-41.
- Chartrand-Lefebvre C, Dubois J, Roy D, et al. *Direct intra-operative sclerotherapy of an aneurysmal bone cyst of the sphenoid*. *AJNR Am J Neuroradiol* 1996;17:870-2.
- Chung CP, Hsu HY, Chao AC, et al. *Flow volume in the jugular vein and related hemodynamics in the branches of the jugular vein*. *Ultrasound Med Biol* 2007;33:500-5.
- Lee BB, Do YS, Byun HS, et al. *Advanced management of venous malformation with ethanol sclerotherapy: mid-term results*. *J Vasc Surg* 2003;37:533-8.
- Mason KP, Michna E, Zurakowski D, et al. *Serum ethanol levels in children and adults after ethanol embolization or sclerotherapy for vascular anomalies*. *Radiology* 2000;217:127-32.

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Calendar of events – Italian and International Meetings and Courses

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Information, following the style of the present list, should be submitted to the Editorial Secretariat of Acta Otorhinolaryngologica Italica (actaitalicaorl@rm.unicatt.it).

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MARCH-DECEMBER 2015

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March 2-3, 2015 • Rome – Italy

Directors: Marco De Vincentiis and Gaetano Paludetti – Honorary President: Giorgio Iannetti – E-mail: segreteria@stilema-to.it – Website: www.aiocc.it

10th SURGICAL ANATOMY IN HEAD & NECK CANCER PROCEDURES • March 4-6, 2015 • Arezzo – Italy

Course Directors: Marco Benazzo and Fausto Chiesa – E-mail: info@iclo.eu – Website: www.iclo.eu

CORSO DI ANATOMIA E CHIRURGIA CERVICO-FACCIALE • March 4-6, 2015 • Nîmes – France

E-mail: pierfrancesco.pelliccia@hotmail.it

27th SVO INTERNATIONAL WINTER COURSE • March 15-21, 2015 • Sesto - Val Pusteria – Italy

President: Gregorio Babighian – Website: www.otologytoday.it

8° CORSO INTERNAZIONALE “BIENNALE MILANO MASTERCLASS”

A. CHIRURGIA ENDOSCOPICA RINOSINUSALE, ORBITA E BASE CRANICA

B. RINOPLASTICA: DA MINIMAMENTE INVASIVA A STRUTTURALE

March 20-24, 2015 • Milan – Italy

Direttori: Paolo Castelnovo e Pietro Palma – Segreteria Organizzativa: MZ Congressi, via C. Farini 81, 20159 Milano – Tel. +39 02 66802323 – Fax +39 02 49542900 – E-mail: mima@mzcongressi.com – Website: www.milanomasterclass.it

HANDS-ON COURSE ON ENDOSCOPIC MIDDLE EAR SURGERY

March 21-22, 2015 • Arezzo – Italy

March 23, 2015 • Modena – Italy

Directors: Livio Presutti and Daniele Marchioni – Tel. +39 0575 1948501 – Fax + 39 0575 1948500 – Email: info@iclo.eu

CENACOLO ITALIANO DI AUDIOVESTIBOLOGIA • March 21-May 16, 2015 • Chieti – Italy

Director: Giampiero Neri – E-mail: info@nsmcongressi.it – Website: www.nsmcongressi.it

3° MASTER DI LARINGOLOGIA OTOLOGICA • March 30 - April 2, 2015 • Vittorio Veneto (TV) – Italy

Director: M. Lucioni – Chairman: G. Rizzotto – E-mail: mail@nordestcongressi.it – Website: www.nordestcongressi.it

**INTERNATIONAL CONGRESS OF KOREAN SOCIETY OF OTORHINOLARYNGOLOGY-HEAD & NECK SURGERY
April 24-26, 2015 • Seoul – Korea**

President: Sang Hag Lee

**5th INTERNATIONAL HANDS-ON COURSE “TRANSNASAL CORRIDORS TO SKULL BASE AND ORBIT”
April 28-30, 2015 • Wien – Austria**

Course Directors: P. Castelnuovo, P. Nicolai, M. Tschabitscher – Organizing Secretariat: informazioni@attingo-edu.it – E-mail: www.attingo-edu.it

16th WORLD CONGRESS OF RHINOLOGY • April 30-May 2, 2015 • São Paulo – Brazil

President: Aldo Stamm – E-mail: secretaria@malulosso.com.br – Website: http://www.rhinology2015.com/Scientific-program.htm

**VI CONGRESO IBEROAMERICANO DE IMPLANTES COCLEARES Y CIENCIAS AFINES
May 20-23, 2015 • Sao Paulo – Brasil**

Tel. 55 11 5081 7028

VERTIGO ACADEMY INTERNATIONAL • May 22-23, 2015 • Moscow – Russia

Chairman: O. Nuri Ozgirgin (Turkey) – Website: www.vainternational.org

102nd NATIONAL CONGRESS SIO, ITALIAN SOCIETY OF OTORHINOLARYNGOLOGY HEAD AND NECK SURGERY • May 27-30, 2015 • Rome – Italy

President: Giuseppe Spriano – Organizing Secretariat: NordEst Congressi – Tel. +39 06 68807925 – Fax +39 06 68212211 – E-mail: nec@nordestcongressi.it – Website: www.sio2015.com

3rd CONGRESS OF EUR OPEAN ORL-HNS • June 7-11, 2015 • Prague – Czech Republic

President: Jan Betka – E mail: orl-hns2015@guarant.cz – Website: http://www.europeanorl-hnsprague2015.com

27° CONGRESSO NAZIONALE SPIGC • June 11-13, 2015 • Brescia – Italy

President: Gian Luca Pariscenti – Website: www.spigc.it

5th HANDS ON DISSECTION ADVANCED COURSE: “FROM REMOVAL TO RECONSTRUCTION IN HEAD & NECK CANCERS” • June 16-19, 2015 • Paris – France

Directors: Marco Benazzo, Department of Otolaryngology HN Surgery, University of Pavia; Fausto Giuseppe Chiesa, Department of Otolaryngology HN Surgery, IEO Milan. Organizing Secretariat: Bquadro Congressi srl, via S. Giovanni in Borgo 4, 27100 Pavia. Tel. +39 0382 302859 – Fax +39 0382 27697 – E-mail: bolla@bquadro-congressi.it – Website: www.bquadro-congressi.it

41° CONGRESSO CONVENTUS SOCIETAS ORL LATINA • July 6-8, 2015 • Torino – Italy

President: Francesco Pia

22nd INTERNATIONAL CONGRESS ON THE EDUCATION OF THE DEAF • July 6-9, 2015 • Athens – Greece

Website: www.iced2015.com

WORLD CONGRESS ON LARYNX CANCER 2015 • July 26-30, 2015 • Queensland – Australia

Website: www.wclc2015.org

SYMPOSIUM & 52nd INNER EAR BIOLOGY WORKSHOP • September 12-15, 2015 • Rome – Italy

Directors: Gaetano Paludetti and Diana Troiani – Website: www.ieb2015.it

2nd SIR (SOCIETÀ ITALIANA DI RINOLOGIA) NATIONAL CONGRESS • September 17-19, 2015 • Udine – Italy

President: Marco Piemonte – E-mail: nec@nordestcongressi.it – Website: www.nordestcongressi.it

V CORSO TEORICO-PRATICO DI AUDIOLOGIA E VESTIBOLOGIA**September 28-30, 2015 • Benevento – Italy**

Segreteria Scientifica: Luigi Califano, Maria Grazia Melillo – E-mail: luigi.califano@tin.it, vertigobn@hotmail.com

INTERNATIONAL WORKSHOP “OPEN PARTIAL HORIZONTAL LARYNGECTOMIES (OPHL) VERSUS TRANSORAL LASER MICROSURGERY (TLM) IN LARYNX CANCER”**October 8-10, 2015 • Castel Brando (TV) – Italy**

Chairman: G. Rizzotto – Email: mail@nordestcongressi.it – Websites: www.nordestcongressi.it, www.oncolarynx.it

XXXIX CONVEGNO NAZIONALE AOOI (ASSOCIAZIONE OTORINOLARINGOLOGI OSPEDALIERI ITALIANI)**October 16-17, 2015 • Genova – Italy**

President: Felice Scasso – E-mail: nec@nordestcongressi.it – Website: www.nordestcongressi.it

7th INTERNATIONAL SYMPOSIUM ON MENIERE’S DISEASE AND INNER EAR DISORDERS**October 17-20, 2015 • Rome – Italy**

Website: meniere2015.eu

VII INTERNATIONAL SYMPOSIUM ON RECENT ADVANCES IN RHINOSINUSITIS AND NASAL POLYPOSIS**October 22-25, 2015 • Panama**

Information: congresors2015@gmail.com

3rd VIS (SOCIETÀ ITALIANA DI VESTIBOLOGIA) CONGRESS • October 30-31, 2015 • Modena – Italy

Website: www.vestibologyitaliansociety.com

SIOP (SOCIETÀ ITALIANA DI OTORINOLARINGOIATRIA PEDIATRICA) NATIONAL CONGRESS**November 5-7, 2015 • Rome – Italy**

E-mail: info@formazioneeventisrl.it – Website: www.formazioneeventisrl.it

XXXV CONGRESSO NAZIONALE SIAF – AGGIORNAMENTI IN AUDIOLOGIA INFANTILE**December 16, 2015 • Milan – Italy**

Chairman: Antonio Cesarani – Website: www.sia-f.it

JANUARY-DECEMBER 2016**15th INTERNATIONAL MEETING OF THE MEDITERRANEAN SOCIETY OF OTOLGY AND AUDIOLOGY****April, 28-30, 2016 • Cappadocia – Turkey**

President: S. Armagan Incesulu – Website: www.msoa2016.org

INSTRUCTIONAL WORKSHOP EUROPEAN ACADEMY OF OTOLGY AND NEURO-OTOLGY**September 28 - October 1, 2016 • İzmir, Turkey**

President: O. Nuri Ozgirgin – Website: www.eaono.org