ACTA OTORHINOLARYNGOLOGICA ITALICA 2008;28:159-163

Rhinology

Italian multicentre study on intrathecal fluorescein for craniosinusal fistulae

Studio multicentrico italiano sull'uso della fluorescina intratecale nelle fistole rinoliquorali

G. FELISATI, A. BIANCHI, P. LOZZA, S. PORTALEONE
ENT Clinic, "San Paolo" Hospital, University of Milan, Italy

SUMMARY

Cerebrospinal fluid leak (CSF), clinical sign of a dural lesion of the skull base, is a relatively rare event that can present with a variety of symptoms. Every craniosinus fistula should be considered a serious, potentially life-threatening situation (even those cases with hidden CSF leak). Reports of experience concerning diagnosis and treatment of craniosinus fistulae have appeared in the Literature. In the last few years, the endoscopic nasal approach is proving effective as it makes diagnosis much easier and is the least invasive surgical approach, with the greatest percentage of success. Various classifications are being proposed to improve clinical evaluation of CSF leaks and to simplify the diagnostic and therapeutic approach. The most common parameters of classification are: aetiology (traumatic, iatrogenic, non-traumatic, etc.) site, type of flow (high or low pressure) and, as far as concerns treatment, the type of graft used, all of which have contributed to various diagnostic and therapeutic algorithms being proposed. Therefore, the subject seems to be widely schematized and the therapeutic attitude widely agreed. However, one of the diagnostic and therapeutic approaches is now being questioned. For some, it is the heart of the clinical approach, while for others, it is a useful tool yet too dangerous to be used on account of potential side effects: namely, the fluorescein test. This procedure, consisting of intrathecal injection of a colorant (fluorescein), is well known by the Food and Drug Administration (FDA) which neither explicitly prohibits it, nor allows it, intrathecal administration is, therefore. an off label use. As far as the Authors know, authorization of this procedure has not been forthcoming anywhere in the world although the procedure itself is widely employed. As far as concerns the use of intrathecal fluorescein, many scientific papers have been written, clearly supporting its clinical usefulness. One limit to the use of fluorescein derives from frequent reports of complications, often related to the intrathecal administration; such complications are, however, always due to an incorrect dosage. In order to perform correct monitoring of any complication related to the use of intrathecal fluorescein and to investigate in a strictly scientific fashion, the legal problem related to the off label use (intrathecal administration) of an authorised substance, the Authors coordinated an Italian multicentre study aimed at establishig the tolerability of the lumbar intrathecal administration of fluorescein. Aim of the study was to review the literature focusing on CSF leaks, to set up to date diagnostic and therapeutic indications of fluorescein and to report the preliminary results of the Italian multicentre study.

KEY WORDS: Craniosinusal fistula • Cerebrospinal fluid • Fluorescein • Nasal endoscopy

RIASSUNTO

La rinoliquorrea, segno clinico di lesione durale della base cranica, rappresenta una evenienza relativamente rara, che può presentare un'ampia variabilità di presentazioni cliniche. Tutte le fistole rinoliquorali (anche se la liquorrea è occulta) vanno considerate come situazioni cliniche gravi, con pericolo per la vita. La letteratura riporta una notevole esperienza relativa all'inquadramento diagnostico ed al trattamento delle fistole rinoliquorali. In questo ambito, da alcuni anni, si sta imponendo l'approccio nasale endoscopico che può facilitare la diagnosi e risulta essere la soluzione chirurgica meno invasiva e con le maggiori percentuali di successo. Varie classificazioni sono state proposte per migliorare l'inquadramento clinico delle fistole rinoliquorali e facilitarne l'approccio diagnostico-terapeutico. I parametri classificativi principalmente utilizzati sono: eziologia (traumatica, iatrogena, non traumatica, ecc.), la sede, le caratteristiche di flusso (alta o bassa pressione) e, per quanto riguarda il trattamento, le caratteristiche del graft utilizzato. Su queste basi sono stati proposti algoritmi diagnostici e terapeutici. Sembrerebbe quindi che l'argomento in oggetto sia largamente schematizzato e che l'atteggiamento clinico sia ampiamente condiviso. Nella realtà, ad oggi, risulta in discussione uno dei presidi diagnostici e terapeutici, che per alcuni rappresenta il cardine fondamentale dell'approccio clinico e per altri, pur costituendo un utile ausilio potenziale, è da proscrivere per le possibili complicanze cui essa espone: la prova della fluorescina. Tale procedura, che consiste nella somministrazione di un colorante per via intratecale (la fluorescina), risulta conosciuta dalla American Food and Drug Administration, non è da questa esplicitamente vietata, ma non è nemmeno autorizzata, pertanto si tratta di una somministrazione "off label". Per quanto noto agli Autori, l'autorizzazione a tale procedura non esiste in alcun Paese nel mondo anche se viene largamente e diffusamente praticata. Sulla utilizzazione della fluorescina per via intratecale sono state scritte peraltro molte pubblicazioni scientifiche che ne dimostrano con certezza l'utilità clinica. Un limite all'utilizzo nasce, in effetti, dalla comunicazione di numerose complicanze derivate dalla somministrazione intratecale; tali complicanze, peraltro, risultano invariabilmente legate ad un errore di dosaggio. Per consentire un corretto monitoraggio di eventuali complicanze legate all'applicazione della tecnica in questione e affrontare con serio spirito scientifico le problematiche medico-legali legate all'utilizzo di un prodotto autorizzato per una

via di somministrazione non autorizzata, gli Autori hanno attivato uno studio multicentrico volto a verificare la tollerabilità della fluorescina somministrata per via lombare. Scopo del presente lavoro è rivisitare la letteratura sulle rinoliquorree per fare il punto sulle attuali indicazioni diagnostico-terapeutiche della fluorescina e riportare i risultati preliminari dello studio multicentrico italiano.

PAROLE CHIAVE: *Fistole rinoliquorali • Liquor • Liquorrea • Fluorescina • Endoscopia nasale*

Acta Otorhinolaryngol Ital 2008;28:159-163

Introduction

Cerebrospinal fluid (CSF) fistulae represent a clear sign of a dural lesion of the skull base. Clinical presentation of CSF fistulae can vary considerably, ranging from small gaps with a hidden CSF leak, to high flow leaks (generally post-operative or post-traumatic). Neurosurgeons traditionally deal with these different situations using treatment that rapidly span from very conservative (CSF drainage) to very aggressive (craniotomy). CSF drainage, on the one hand has been widely used even when it could be avoided, while, on the other, the invasiveness of a craniotomic approach often delayed the performance of a resolutive surgical approach. This clinical attitude, caused by the limited choice of treatments, has, for several years, delayed efforts towards a precise diagnosis of the disease under examination. It is also important to remember that any fistula located in the skull base, even if the CSF leak is small and often not recognizable, can lead to potentially lethal complications. Bacterial meningitis is the main cause of morbidity and mortality, in these patients, and is often the first clinical sign of the disease. In view of all these considerations, early diagnosis of a dural defect, as well as its localization and surgical repair, are mandatory, also bearing in mind that the fistulae could be multiple. There are some preferential CSF leak sites: the roof of the anterior or posterior ethmoid, the olfactory groove, the roof and lateral wall of the sphenoid sinus and the posterior wall of the frontal sinus [1-4]. The site of the leak is related to the pathogenesis of the dural lesion and the most accredited classification is currently based upon pathogenesis. The classification of Har-El [5] refers to CSF leaks as traumatic (iatrogenic or accidental) and non-traumatic (congenital or idiopathic). A specific situation is related to high pressure CSF leaks, that may be either traumatic or non-traumatic. These are characterized by increased CSF pressure, as in the case of hydrocephalus or by the presence of an intracranial mass. The clinical presentation of patients with CSF-nasal fistulae varies considerably as the CSF leak may be intermittent, with occasional headache or nasal blockage and often meningitis (sometimes recurrent) as the most evident clinical sign of a dural lesion.

The diagnosis of a suspected CSF leak has two endpoints: 1) to demonstrate the presence of CSF rhinorrhea and 2) to identify the precise site of the leak [6]. A combination of several clinical tests may be used to confirm the diagnosis of a CSF nasal fistula: biochemical analysis (beta 2 transferrin, beta trace dosage, etc.), radiological investigation (high definition computerized tomography (CT) scan) and fluorescein nasal endoscopic evaluation. Various diagnostic algorithms have been proposed in the literature for guidance in the correct use of the different tests. In each of the diagnostic algorithms the fluorescein test has a precise indication whenever a CSF leak is suspected and its presence and site have to be demonstrated [6-8].

Personally, we agree with the simple algorithm of Locatelli et al. [6] that relies on the biochemical examination of a fluid sample (whenever possible), on nasal endoscopy and on imaging techniques (CT scan, magnetic resonance imaging (MRI)). When these first evaluations give positive results, there is the indication for surgical repair of the dural lesion, when the preliminary tests are negative, the fluorescein test follows in order to locate and to confirm or exclude a CSF leak.

In this and in every other algorithm, the fluorescein test is a fundamental diagnostic tool in cases of low pressure craniosinusal fistula with hidden or intermittent CSF leak.

As far as concerns treatment, many different techniques and materials for surgical repair have been proposed, but every variation relies on the endoscopic nasal approach that, today, has replaced the traditional craniotomic approaches due to its minimal invasiveness and to the optimal results obtained (≥ 90% success in sealing the dural gap after the first endoscopic intervention and ≥ 97% success after the second endoscopic attempt) [9 10].

The good results and the limited invasiveness, demonstrated by endoscopy, reduced the indication of conservative treatment, thus limiting the use of CSF drainage to acute post-traumatic fistulae [6]. The rules to optimize the endoscopic approach are a precise definition of the site and size of the fistula, as well as evaluation of the presence of multiple fistulae and adequate preparation of the area surrounding the gap in order to guarantee good adhesion of the graft. To obtain these results, the use of intrathecal fluorescein has again been proposed in the literature since it allows not only ideal visualization of the defect, but also intra-operative evaluation of the effectiveness of the repair. Recently. the use of intrathecal fluorescein, during skull base surgery, has been introduced in those cases at high risk of CSF leak or when a dural defect is programmed [11].

Fluorescein

Sodic fluorescein is a green fluorescent compound used for various applications in man, mainly in ophthalmology. The use of sodic fluorescein to detect a suspected CSF leak started back in 1960 to impart its fluorescence properties to CSF and facilitate its identification [12]. The introduction of endonasal techniques resulted in great importance being attributed to the use of this substance for diagnostic and surgical means purposes [13-18]. Wolf et al., in particular, reported, in 1997 [17], their experience on as many as 925

patients who underwent intra-thecal sub-occipital infusion of sodic fluorescein while referring to "over 250 more recent cases" where fluorescein had been administered via lumbar injection. Applying a blue filter on the light source and a yellow filter on the endoscope lens is a useful technique to enhance fluorescein in very low flow fistula [17].
To our knowledge, there is no clinical experience concerning other compounds used to stain the CSF fluid in order to more clearly reveal its presence during nasal endoscopy. Anyway, fluorescein gained consent by proving to be effective even at low doses. The nasal endoscopic approach can be applied even without using intrathecal fluorescein where the fistula is evident maintaining its effectiveness, whereas mistakes are more common when treating smaller defects or multiple fistulae that can never be excluded.
Based on these considerations, intrathecal fluorescein is, for most Authors, the clinical approach of choice to CSF leaks. For other Authors, use of fluorescein might be a valuable aid but should be avoided due to possible complications.
Although the label on the bottle of fluorescein states that it is "not for intrathecal administration", off label intrathecal use is neither indicated nor prohibited by the United States' Food and Drug Administration. The Authors are not aware of explicit authorization for intrathecal administration of fluorescein, in any country in the world, although the procedure is widely practiced worldwide, outside of the United States.
The major limitation to the use of fluorescein is a consequence of complications that have been attributed to intrathecal use; these include seizures but also death always related, however, to errors in dosing.
Recently, local administration of fluorescein through the nose has been proposed.
"A change in the colour of the fluorescein from yellow to green fluorescence and sometimes streaming the fluorescein over the nasal mucosa and blood denoted the presence of CSF, and the site of the leak could be traced" [19,20]. Further studies are needed on this technique, however, before being clinically approved.

Complications

Very few publications, in the literature, are significant as far as concerns the number of cases treated. The report of Wolf et al. [17] represents one of the most important papers published on this topic and, to date, refers to the largest series, analysing 925 cases where fluorescein had been administered suboccipitally and ≥ 250 cases where fluorescein had been administered through a lumbar injection.
The Authors insist that the dose of fluorescein should be equal to, or lower than, 1 ml in a 5% mixture (a total of 50 mg of sodic fluorescein). In the first 925 cases, 3 epileptic crises have been reported as a complication, while lumbar administration was free of side-effects. The Authors conclude that, if the suggested dosage is respected and lumbar administration is adopted, the technique is safe and without complications.
On the basis of Wolf's experience, many endoscopic surgeons adopted this technique. As far as complications are concerned, following the more widespread use of this technique, the results are extremely varying. Many contributors report the absence of side-effects, or the presence of only minor collateral effects, in thousands of cases treated with a total dose of fluorescein up to 50 mg. The side-effects also seem to be only marginally related to the use of fluorescein itself and are always temporary [6,21-28] (Table I).
The contribution of Meco and Oberascher [7] deserves attention as they did not report any complications in "more than 900" treated cases. On the other hand, many sporadic communications of severe complications can be found in the literature (epileptic crises, *grand mal* epilepsy, opisthotonos, peripheral nerve palsy). Severe complications are always related to the direct irritant action of fluorescein by way of chemical meningeal trauma due to overdose of the stain, as pointed out by Syms et al. [29], in an experimental study on dogs.
Relying on these experiences, literature expresses almost unanimously that pure sodic fluorescein should be administered in a 5% concentration up to 1 ml (50 mg) of total dose. Fluorescein should be mixed with previously withdrawn CSF (ideal quantity 9 ml) and slowly reinjected into the lumbar column.
Keerl et al. [24] published a paper analysing 420 cases that they had treated in different hospitals, but mainly described the cases reported to the FDA. Analysing these data it can be seen that 7 cases of major complications have been reported, including one death. All these complications appear, however, to be related to errors in dosage. In the worst outcome, resulting in death of the patient, it was impossible to define the exact amount of fluorescein administered, but it was certainly ≥ 500 mg, while in the less serious cases, it

Table I. Major publications on intrathecal administration of fluorescein with doses less than or equal to 50 mg.

	Intrathecal fluorescein ≤ 50 mg total dose	
Authors Year of publication	No. cases treated	Specific serious complications
Moseley et al. 1978	1	1 transient
Lanza et al. 1996	25	0
Wolf et al. 1997	250	0
Guimaraes and Becker 2001	23	0
Lund 2002	6	0
White et al. 2003	13	0
Keerl et al. 2004	420	2 transient ***
Meco and Oberascher 2004	900	0
Lindstrom et al. 2004	10	0
Silva et al. 2006	24	0
Locatelli et al. 2007	135	1 transient (cause unclear)
Demarco et al. 2007	18	0
Placantonakis et al. 2007	54	0
Tabaee et al. 2007	61	0
	1940	

*** 100 mg fluorescein and simultaneous intrathecal administration of radiographic contrast medium

was 100 mg or even more. It can, therefore, be assumed that a 50 mg dose should be safe.
Keerl et al. [24] always analysed the complications reported to the FDA and to the producers resulting from intravenous and local lacrimal administration of fluorescein. As far as intravenous (iv) administration is concerned, many adverse reactions have been reported, with 13 deaths, but only one major complication leading to death after a simple local lacrimal application. Obviously, these data are related to a very large number of treated cases and are not comparable to those obtained from the intrathecal administration of the stain.
It is worthwhile pointing out that exceptional cases have been reported such as that described by Moseley et al. in 1978 [30] where lower extremity weakness and numbness, cleared within 48 hours, was observed after intrathecal administration of only 25 mg of fluorescein. To avoid this risk Placantonakis et al. [27] propose that premedication of the patient, with diphenhydramine and dexamethasone, be systematically adopted to protect against such chemical meningeal irritation. Albeit, it is difficult to distinguish between side-effects due to to surgery and the patient's general conditions and those due to the use of fluorescein [27].

The Italian multicentre study

As already pointed out, it has been reported in the literature that low-dose intrathecal fluorescein is generally considered a safe procedure. In 2004, we started the administrative procedures to obtain the consent of the Ethics Committee to commence a multicentre observational study aimed at monitoring possible complications related to the use of the technique under examination, following a strict operative protocol using a total dose of fluorescein not over 50 mg, to be administered in a 5% solution (1 ml) in turn diluted in at least 9 ml of CSF. All patients enrolled in the study had to sign a detailed informed consent. In the past, it was difficult to obtain the fluorescein solution in the correct concentration, it was necessary to dilute the commercialized fluorescein solutions in a 10% or 20% concentration. This was frequently the cause of mistakes. Monico SpA (Mestre-Italy) currently produces and distributes the correct preparation of fluorescein for adult intrathecal administration (1 ml, 5% solution), even if the indication remains "off label".
The Ethics Committee of San Paolo Hospital in Milan (HSP) authorized a first experimental study, in March 2005, limited to HSP itself and to a limited number of cases (total 8) in order to assess the safety of the procedure, before allowing the extension of the study to other centres. All procedures were performed according to the previously described protocol, all of which without any complications. In March 2006, the Ethics Committee of HSP finally authorized the start of a long Multicentre Study aimed at evaluating adverse reactions related to the use of fluorescein.

To date, 6 centres have obtained approval from their Ethics Committee to join the study: Clinica Otorinolaringoiatrica Polo San Paolo, University of Milan; Clinica Otorinolaringoiatrica, Ospedale San Gerardo, Monza, University of Milan Bicocca; Clinica Otorinolaringoiatrica and Clinica Neurochirurgica, University of Bologna; Otorinolaringoiatria, Ospedale Bassini, Cinisello Balsamo; Otorinolaringoiatria, Istituto Clinico Humanitas, Rozzano. A preliminary analysis of data, from the centres taking part in the study was performed: 53 cases (22 females, 31 males, mean age 46.8 yrs). The aetiology of the CSF leaks in the patients who underwent the procedure is shown in Table II. There were no adverse reactions when fluorescein was used for diagnostic (6 cases) or therapeutic purposes (47 cases), with doses of fluorescein less than or equal to 50 mg.

Table II. Aetiology of CSF leaks in the Italian Multicentre Study.

Traumatic	15
Iatrogenic	12
Spontaneous	20
Expansive neoplasm	2
Negative test	4
Total no. cases	53 (31 males, 22 females)

Conclusions

From a review of the literature and the preliminary results of the Italian multicentre study, it can be seen that lumbar intrathecal fluorescein administration is a safe procedure provided that the following criteria are respected: maximal dose of 50 mg of fluorescein, further dilution of the colorant in CSF, and slow administration. With the exception of sporadic cases, the literature clearly shows the usefulness of the test, both in the diagnostic and intra-operative phase, as well as for preventive purposes, when surgical procedures on the skull base are performed with risk of dural damage.
Many Authors have demonstrated that the off-label use of fluorescein, administered intrathecally, can be performed safely, in hundreds of patients, without any morbidity and mortality provided the correct solution is used, properly diluted, and carefully administered. Hopefully, the addition of other centres will provide meaningful data regarding the true risks of intrathecal fluorescein, as employed by the otolaryngology community.
These preliminary data are reported on behalf of all the colleagues taking part in the study. Together, we invite every surgeon, already using fluorescein, to take part in the study by obtaining permission from their respective Ethics Committees. The Otolaryngology Department of HSP is available for all colleagues requiring scientific documentation, the protocol for the study and the informed consent statement for the approval process.

References

1 Beckhardt RN, Setzen M, Carras R. *Primary spontaneous cerebrospinal fluid rhinorrhea*. Otolaryngol Head Neck Surg 1991;104:425-32.

2 Binhammer RT. *CSF anatomy with emphasis on relations to nasal cavity and labyrinthine fluids*. Ear Nose Throat J 1992;71:292-4.

3 Castelnuovo P, Mauri S, Locatelli D, Emanuelli E, Delu G, Giulio GD. *Endoscopic repair of cerbrospinal fluid rhinorrhea: learning from our failures*. Am J Rhinol 2001;15:333-42.

4 Castelnuovo PG, Delu G, Locatelli D, Padoan G, Bernardi

FD, Pistochini A, et al. *Endonasal endoscopic duraplasty: our experience*. Skull Base 2006;16:19-24.

5 Har-El G. *What is spontaneous cerebrospinal fluid rhinorrhea? Classification of cerebrospinal fluid leaks*. Ann Otol Rhinol Laryngol 1999;108:323-6.

6 Locatelli D, Rampa F, Acchiardi I, Bignami M, De Bernardi F, Castelnuovo P. *Endoscopic endonasal approaches for repair of cerebrospinal fluid leaks: nine-year experience*. Neurosurgery 2006;58(Suppl 2):ONS-246-56.

7 Meco C, Oberascher G. *Comprehensive algorithm for skull base dural lesion and cerebrospinal fluid fistula diagnosis*. Laryngoscope 2004;114:991-9.

8 Lund VJ. *Endoscopic management of cerebrospinal fluid leaks*. Am J Rhinol 2002;16:17-23.

9 Hegazy HM, Carrau RL, Snyderman CH, Kassam A, Zweig J. *Transnasal endoscopic repair of cerebrospinal fluid rhinorrhea: a meta-analysis*. Laryngoscope 2000;110:1166-72.

10 Senior BA, Jafri K, Benninger M. *Safety and efficacy of endoscopic repair of CSF leaks and encephaloceles: a survey of the members of the American Rhinologic Society*. Am J Rhinol 2001;15:21-5.

11 Tabaee A, Placantonakis DG, Schwartz TH, Anand VK. *Intrathecal fluorescein in endoscopic skull base surgery*. Otolaryngol Head Neck Surg 2007;137:316-20.

12 Kirchner FR, Proud GO. *Method for the identification and localization of cerebrospinal fluid, rhinorrhea and otorrhea*. Laryngoscope 1960;70:921-31.

13 Messerklinger W. *Therapy of recurring meningitis*. Monatsschr Ohrenheilkd Laryngorhinol 1972;106:11-5.

14 Messerklinger W. *Nasal endoscopy: demonstration, localization and differential diagnosis of nasal liquorrhea*. HNO 1972;20:268-70.

15 Reck R, Wissen-Siegert I. *Results of fluorescein nose endoscopy in the diagnosis of cerebrospinal rhinorrhea*. Laryngol Rhinol Otol 1984;63:353-5.

16 Stankiewicz JA. *Cerebrospinal fluid fistula and endoscopic sinus surgery*. Laryngoscope 1991;101:250-6.

17 Wolf G, Greistorfer K, Stammberger H. *Endoscopic detection of cerebrospinal fluid fistulas with a fluorescence technique. Report of experiences with over 925 cases*. Laryngorhinootologie 1997;76:588-94.

18 Stammberger H, Greistorfer K, Wolf G, Luxenberger W. *Surgical occlusion of cerebrospinal fistulas of anterior skull base using intrathecal sodium fluorescein*. Laryngorhinootologie 1997;76:595-607.

19 Jones ME, Reino T, Gnoy A, Guillory S, Wackym P, Lawson W. *Identification of intranasal cerebrospinal fluid leaks by topical application with fluorescein dye*. Am J Rhinol 2000;14:93-6.

20 Saafan ME, Ragab SM, Albirmawy OA. *Topical intranasal fluorescein: the missing partner in algorithms of cerebrospinal fluid fistula detection*. Laryngoscope 2006;116:1158-61.

21 Lanza DC, O'Brien DA, Kennedy DW. *Endoscopic repair of cerebrospinal fluid fistulae and encephaloceles*. Laryngoscope 1996;106:1119-25.

22 Guimaraes R, Becker H. *A new technique for the use of intrathecal fluorescein in the repair of cerebrospinal fluid rhinorrhea using a hypodense diluent*. Rev Laryngol Otol Rhinol 2001;122:191-3.

23 White DR, Dubin MG, Senior BA. *Endoscopic repair of cerebrospinal fluid leaks after neurosurgical procedures*. Am J Otolaryngol 2003;24:213-6.

24 Keerl R, Weber RK, Draf W, Wienke A, Schaefer SD. *Use of sodium fluorescein solution for detection of cerebrospinal fluid fistulas: an analysis of 420 administrations and reported complications in Europe and the United States*. Laryngoscope 2004;114:266-72.

25 Lindstrom DR, Toohill RJ, Loehrl TA, Smith TL. *Management of cerebrospinal fluid rhinorrhea: the Medical College of Wisconsin experience*. Laryngoscope 2004;114:969-74.

26 Silva LR, Santos RP, Zymberg ST. *Endoscopic endonasal approach for cerebrospinal fluid fistulae*. Minim Invasive Neurosurg 2006;49:88-92.

27 Placantonakis DG, Tabaee A, Anand VK, Hiltzik D, Schwartz TH. *Safety of low-dose intrathecal fluorescein in endoscopic cranial base surgery*. Neurosurgery 2007;61(Suppl 3):161-5.

28 Demarco RC, Tamashiro E, Valera FC, Anselmo-Lima WT. *Use of a hypodense sodium fluorescein solution for the endoscopic repair of rhinogenic cerebrospinal fluid fistulae*. Am J Rhinol 2007;21:184-6.

29 Syms CA 3rd, Syms MJ, Murphy TP, Massey SO. *Cerebrospinal fluid fistulae in a canine model*. Otolaryngol Head Neck Surg 1997;117:542-6.

30 Moseley JI, Carton CA, Stern WE. *Spectrum of complications in the use of intrathecal fluorescein*. J Neurosurg 1978;48:765-7.

Received: February 14, 2008 - Accepted: June 14, 2008

Address for correspondence: Prof. G. Felisati, Residenza Faggi 122, 20080 Basiglio (MI), Italy. Fax +39 02 50323166. E-mail: giovanni.felisati@unimi.it

Centres taking part in the investigation: Clinica Otorinolaringoiatrica Polo "San Paolo", University of Milan – Prof. G. Felisati; Clinica Otorinolaringoiatria, Ospedale "San Gerardo", Monza, University of Milan Bicocca – Prof. R. Gaini, Dr. F. Parmigiani; Clinica Otorinolaringoiatrica and Clinica Neurochirurgica, University of Bologna – Dr. E. Pasquini, Dr. G. Frank; Otorinolaringoiatria, Ospedale "Bassini", Cinisello Balsamo – Dr. A. Franzetti; Otorinolaringoiatria, Istituto Clinico "Humanitas", Rozzano – Dr. A. Poletti