sciendo

DOI: 10.2478/rjr-2025-0010

Romanian Journal of Rhinology, Volume 15, No. 58, April - June 2025

LITERATURE REVIEW

# Safety of intrathecal fluorescein in the repair of anterior skull base fluid fistulas: An umbrella review

**Juan Antonio Lugo-Machado[1], Diana Isabel Espinoza-Morales[2], Jeaneth Serrano Armenta[2], Araceli Zazueta Cardenas[2]**

[1]Mexican Social Security Institute, Ciudad Obregón, Sonora, Mexico

[2]University of Sonora Cajeme Campus, Ciudad Obregón, Sonora, Mexico

## ABSTRACT

**BACKGROUND.** The use of intrathecal fluorescein to detect cerebrospinal fluid (CSF) fistulas remains controversial, as it is employed empirically and not authorized for intrathecal administration due to concerns about its safety via this route.

**OBJECTIVE.** This study evaluates the available evidence on the safety of intrathecal fluorescein for diagnosing and localising nasal cerebrospinal fluid leaks.

**MATERIAL AND METHODS.** An umbrella review was independently conducted by two researchers, following the appropriate methodology and PRISMA guidelines, to evaluate the available evidence on the safety of intrathecal fluorescein for diagnosing and localising cerebrospinal fluid leakage. Articles were searched in databases including Scopus, PUBMED, Google Scholar, Mendeley, and ScienceDirect ("intrathecal fluorescein" AND ("CSF fistula" OR "cerebrospinal fluid leak") AND ("repair" OR "diagnosis")) from January 2015 to January 2025. Selected articles were evaluated using the ASMTAR Scale 2 rating.

**RESULTS.** Of 446 studies reviewed, only 3 met the inclusion criteria. The results suggest that intrathecal fluorescein is safe when used with proper dosing and protocols, although concerns remain regarding its long-term safety. The need for standardization in dosing and further studies to evaluate chronic effects is emphasized.

**CONCLUSION.** Its use at low doses (10-25 mg) is generally safe, though standardization and long-term data on adverse effects are lacking. Despite its advantages, further research is essential to establish uniform protocols and enhance its safety in clinical practice.

**KEYWORDS:** fluorescein, subarachnoid space, fistula, cerebrospinal fluid, safety.

## INTRODUCTION

Cranial-base cerebrospinal fluid fistulas (CSF leaks) involve a leakage of cerebrospinal fluid (CSF) from the subarachnoid space into an extracranial compartment, either of acquired or spontaneous origin. Among CSF leaks, nasal fistulas are the most frequent forms of leakage and manifest themselves with headache and rhinorrhea, characterized by the discharge of a clear and watery fluid from one or both nostrils[1,2,3] and can originate from tumors at the base of the skull, trauma, surgeries or arise spontaneously. They are generally linked to intracranial hypertension[4].

Cerebrospinal fluid fistulas appear when the protective barrier that separates the nasal cavities from the subarachnoid space is broken. The presence of CSF leaks is determined by positive biochemical results for β-2 transferrin or tau protein, followed by radiological and endoscopic evaluation to locate the exact area of the defect or leak at the skull base. Initial cranio-facial computed tomography (CT), supplemented by cranio-facial magnetic resonance imaging (MRI), may be useful in identifying the site of confirmed CSF fistulas in up to 90% of cases.

In cases of biochemically confirmed CSF leaks, where imaging does not detect a defect at the base

**Corresponding author:** Juan Antonio Lugo-Machado, Specialist Physician, "Lic. Luis Donaldo Colosio Murrieta" Specialty Hospital No. 2, Mexican Social Security, Institute, Ciudad Obregon, Sonora, Mexico. **Address:** Prolongación Blvd. Bordo Nuevo S/N, Ejido Providencia, 85199, Ciudad Obregon, Sonora, Mexico
**ORCID:** https://orcid.org/0000-0003-4864-8546
**e-mail:** otorrinox@gmail.com
**Received for publication:** March 3, 2025 / **Accepted:** March 27, 2025

of the skull, or in situations of intermittent low-flow CSF leakage, surgical repair can be complicated. Treatment consists of closure of the fistula, the most common intervention being endonasal endoscopy. Advances in skull base surgery have enabled successful endoscopic repair of CSF fistulas with success rates in excess of 90%[5-11].

When locating the fistula site is difficult, intrathecal fluorescein (IF) is a valuable tool during surgery to successfully locate the CSF fistula site[5]. Its use was first recorded in 1960[12,13]. The localisation rates of CSF leakage range between 88.7%[14] and 88.1%[15]. It was first used by physicians in ophthalmology in 1882 for diagnostic imaging, and has since gained popularity, extending its application to angiography. In 1960, Kirchner and Proud demonstrated the effectiveness of intrathecal fluorescein in locating the site of CSF fistulas, and its use has been widely adopted, despite not being approved by the U.S. Food and Drug Administration (FDA) or the U.K. Medicines and Healthcare products Regulatory Agency. The method of administration of IF usually involves performing a lumbar puncture and removing 10 mL of CSF. It is then diluted with the required dose of IF, before a slow injection of the solution into the intrathecal space over 1 to 10 minutes. Despite these factors, previous publications have indicated that IF is an excellent adjunct to identify the location of CSF leaks, especially in anterior cranial fossa defects, where they tend to be smaller and have low flow. Previous research on the use of intrathecal fluorescein has shown remarkable variability in doses, ranging from 10 mg to 1250 mg, resulting in varying degrees of side effects, complications, and localisation rates[16,17]. The administration of higher doses of intrathecal fluorescein (IF) has been linked to serious health risks, such as significant morbidity and neurological issues, including seizures, muscle weakness in the limbs, and, in severe cases, fatalities. More recent use has shown that lower doses of IF are safer; however, to date, an internationally accepted dose of IF has not been agreed[16,18-20]. A study by Seth et al.[17] indicates that the sensitivity and specificity for the detection of CSF leaks with intrathecal fluorescein were 73.8% (95% CI between 57.7% and 85.6%) and 100% (95% CI between 46.3% and 100%), respectively. There was a false negative rate of 26.2% (95% CI between 15.8% and 43.5%). The location of the leak area was more accurate when examining CSF leaks with intrathecal fluorescein. Reported complications following intrathecal fluorescein (IF) administration showed a wide variability, with rates ranging from 0% to 20%. While some studies indicate a complication rate of 2.4%, others found no adverse effects directly attributable to the use of IF[14,17,21].

At present, there are still doubts regarding the use of IF and its risk of complications in the surgical localisation of CSF leaks. Therefore, we set out to review the literature in order to try to clarify the uncertainty regarding the safety and published side effects of IF during surgery for CSF leaks.

## MATERIAL AND METHODS

An umbrella review was independently conducted by two investigators, following the appropriate methodology, to evaluate the available evidence on the safety of intrathecal fluorescein in diagnosing and locating cerebrospinal fluid leakage. The systematic review methodology following the PRISMA guidelines was used to guide the search for relevant documents in the electronic databases[22,23].

Literature search

We searched in Scopus, PUBMED, Science Direct, Mendeley and Google Scholar databases for relevant articles published in the English language, with the following keywords: "Intrathecal fluorescein" AND ("CSF fistula" OR "cerebrospinal fluid leak") AND ("repair" OR "complications"), in the period from January 2015 to January 2025.

For the quality and risk of bias of the studies, we used the AMSTAR Scale 2 rating. The AMSTAR 2 scale (A Measurement Tool to Assess systematic Reviews) is a tool designed to evaluate the methodological quality of systematic reviews, including those that incorporate meta-analyses. Its use allows for the identification of strengths and weaknesses in the conduct of systematic reviews, focusing on key aspects such as study selection, risk of bias assessment, and interpretation of results. The tool classifies confidence in the review findings into four levels: high, moderate, low, or critically low, depending on how many critical and non-critical items are met. Its application is widely recommended to ensure rigor and transparency in the development of systematic reviews[24,25].

The following selection criteria were established:

- Inclusion criteria:
  - → English language articles
  - → Systematic review articles with or without meta-analysis
  - → Articles that include the variables of interest in the title
  - → Articles that evaluate children and adults are included.
- Exclusion Criteria
  - → Non-English language articles

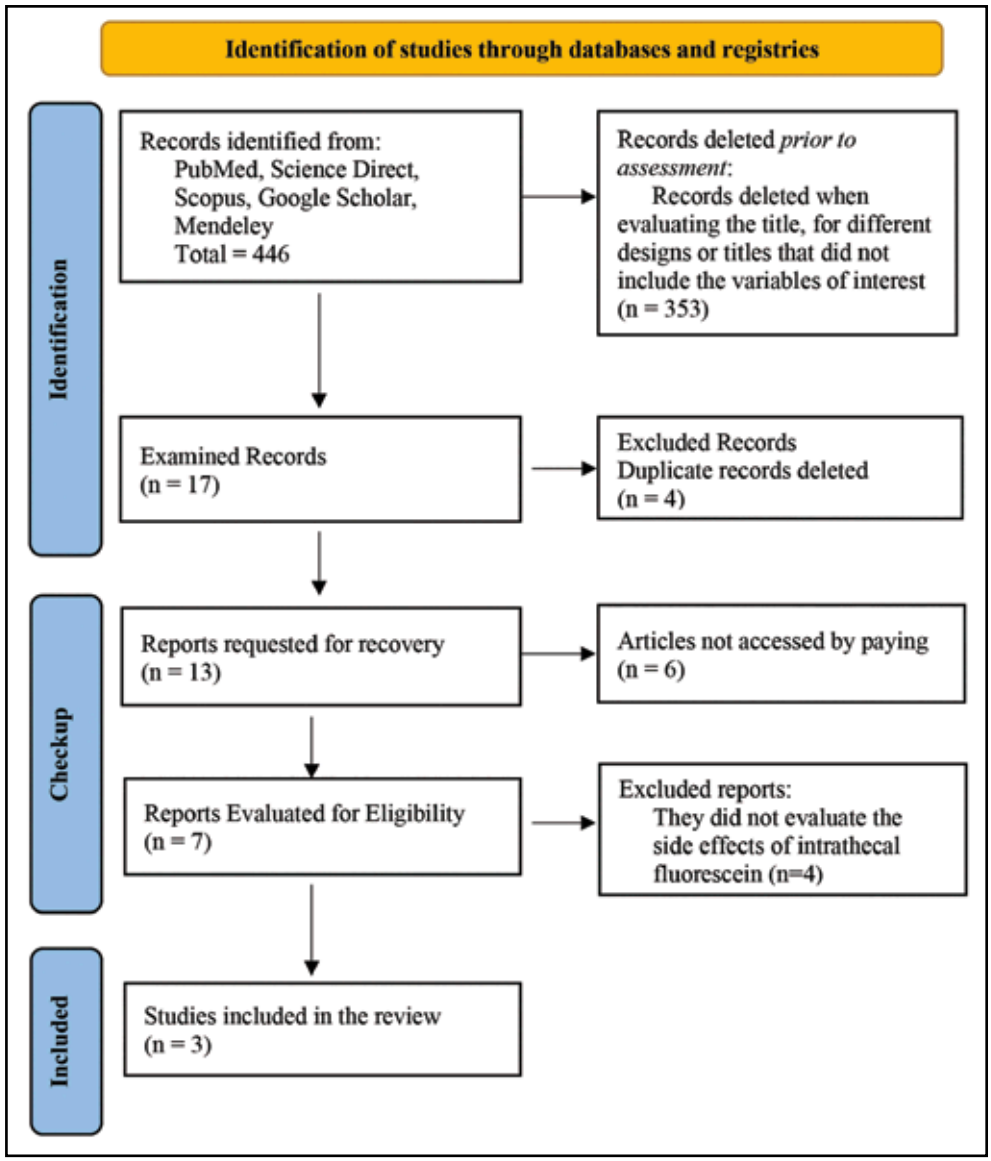


**Figure 1.** PRISMA flowchart. Safety of Intrathecal Fluorescein in the Repair of Anterior Skull Base Fluid Fistulas: Umbrella Review.

→ Original Studies, Case Series, Case Presentation, Narrative Reviews, Scoping Reviews
→ Systematic reviews that did not address the intrathecal fluorescein variable

Data collection process

The Rayyan system was used to evaluate abstracts and remove duplicates. The Rayyan system is an online tool and mobile application designed to streamline systematic literature reviews by assisting researchers in managing and filtering large volumes of studies. It automatically removes duplicates, enables real-time collaboration among reviewers, and facilitates the classification of studies using labels such as "included", "excluded", or "pending". Additionally, it offers advanced search functions to efficiently locate studies. Its use enhances efficiency, transparency, and accuracy in the article selection process, making it a key tool for conducting rigorous systematic reviews. The abstracts were read and evaluated, according to the eligibility criteria by pair of reviewers, as well as the full texts, after the first stage of abstracts[26,27].

## RESULTS

446 writings were identified in the databases. Of these, 353 did not meet the criteria, 17 met the selection criteria, 6 were not accessed, 4 were eliminated due to duplication, 7 were accessed. After evaluating their objectives related to the analysis of the safety of IF in patients with CSF leaks, only 3 met the criteria (Figure 1, Table 1).

The study performed by Romeo et al.[28], pub-

**Table 1. The chosen articles are summarized.**

| Author(s) | Year | Country | Study design | Objective of the study | Total number of participants | Study Environment | Strengths and limitations | AMSTAR 2 Rating |
|---|---|---|---|---|---|---|---|---|
| AlSharhan et al.[29] | 2024 | Saudi Arabia | Systematic review and meta-analysis | To assess the diagnostic accuracy of intrathecal fluorescein (IF) compared to other radiological tests for detecting acquired defects of the skull base. | 2101 patients from 14 included studies, 1898 with IF | Endoscopic skull base surgery | Strengths: Rigorous quantitative synthesis with meta-analysis, use of PRISMA. Limitations: High heterogeneity between studies, lack of randomised controlled trials. | Low |
| de Laurentis et al.[30] | 2022 | France | Systematic review | To assess the usefulness of sodium fluorescein in paediatric oncological neurosurgery to improve the resection of brain and spinal tumours. | 19 studies, 119 patients (11 months - 17.9 years) | Pediatric Neuro-Oncology Surgery | Strengths: First extensive pediatric series on this topic, with no serious adverse events. Limitations: Small sample size, lack of control group, subjective evaluation of the surgeon. | Moderate |
| Romeo et al.[28] | 2022 | USA | Systematic review | To assess the efficacy and safety of intrathecal fluorescein for localising CSF rhinorrhea in endoscopic surgery. | 25 studies with 3801 cases of ITF administration | Endoscopic CSF fistula repair surgery | Strengths: Evaluation of multiple studies with a large number of cases. Limitations: Lack of randomised trials, heterogeneity in dosage and methods of administration. | Moderate |

lished in 2022, evaluates the efficacy and safety of intrathecal fluorescein (IF) in detecting cerebrospinal fluid leaks in patients with CSF rhinorrhea, a condition resulting from skull base defects. This technique is crucial for optimizing endoscopic surgical repair. Through a systematic review of 25 studies involving 3801 cases of IF administration, both diagnostic accuracy (sensitivity and specificity) and safety aspects, as well as different application techniques, were analyzed. The results showed that a 25 mg dose exhibited higher sensitivity (92.36%) in identifying the leakage site compared to a 10 mg dose (71.88%), without increasing risks. Additionally, slow fluorescein administration (<50 mg over 30 minutes) reduced the incidence of complications. It was also found that diluting fluorescein in double-distilled water, rather than in CSF or saline solution, enhances safety and reduces waiting times[28].

AlSharhan et al.[29], in a study published in 2024, reviewed the efficacy and safety of intrathecal fluorescein (ITF) in the localisation of cerebrospinal fluid (CSF) leaks in non-congenital skull base defects. The overall detection rate of ITF was 88.1%, with similar results between concentrations of 5% (91.1%) and 10% (88.8%). No significant differences were found compared to other radiological tests (CT or MRI). Complications were low (2.4%), primarily neurological (seizures, headaches) and endocrinopathies. The recurrence rate of leaks was 4%, reaching up to 9.9% in some cases. ITF is effective, but its use should be selective[29].

On the other hand, de Laurentis et al.[30] (2023) review the use of fluorescein sodium in pediatric neurosurgery. The review included data from 119 pediatric patients (11 months - 17.9 years) across 19 studies, all of whom underwent surgery for different brain tumors with the use of sodium fluorescein. Fluorescein was administered at low doses (2-5mg/kg) at the end of anaesthetic induction, and it proved to be useful in identifying biopsy targets or maximizing resection.

We acknowledged that most of the studies reviewed were small-scale and lacked evidence on the long-term impact of their use. It appears that the safety of fluorescein, both in its intrathecal use and in neurosurgery, appears to be generally positive when an appropriate dosage and method of administration protocol is followed. However, the lack of comprehensive studies on long-term effects and variability in doses and delivery techniques highlight the need for further research to ensure its safety in various clinical contexts.

## DISCUSSIONS

Fluorescein traces its origins back to the 19th century and, since its discovery, has evolved into an essential tool in fields such as chemistry, biology and medicine. It was first synthesized in 1871 by the German chemist Adolf von Baeyer, who achieved its creation through the condensation of phthalic anhydride and resorcinol, using zinc chloride ($ZnCl_2$) as a catalyst. This method, known as the Friedel-Crafts reaction, led to the formation of fluorescein, a compound renowned for its unique fluorescent properties[31].

Fluorescein is characterized by its xanthene structure, which grants it the ability to emit fluorescence when exposed to ultraviolet light. In the early 20th century, it began to be used in analytical

chemistry as a pH indicator, thanks to its capacity to change colour depending on the acidity or alkalinity of the medium. Later, in the 1930s, it was discovered that fluorescein could be utilized as a fluorescent marker in biological studies, paving the way for its application in the visualization of tissues and cells under the microscope. This advancement marked the beginning of its use in biological and medical research[31].

The administration of intrathecal fluorescein (IF) for the analysis of cerebrospinal fluid (CSF) fistulas and leaks has been the subject of multiple studies in recent years, focusing mainly on its safety. However, systematic reviews as an evidence base to support its safety and universal use are very limited, most research points to a lack of standardization in intrathecal application doses. Authors, such as Romeo et al.[28] indicated that administration of 25 mg of fluorescein slowly reduces complications and suggested the use of distilled water instead of saline or cerebrospinal fluid to improve safety. AlSharhan et al.[29] agreed that no serious adverse effects were reported but stressed that the absence of standardized dosing protocols could pose a risk, also highlighting the need to assess their long-term safety. De Laurentis et al.[30] reported that the use of low-dose fluorescein in pediatric neurosurgery minimizes side effects.

Jolly et al.[8] evaluated the safety and efficacy of intrathecal fluorescein (IF) in the repair of cerebrospinal fluid (CSF) fistulas. The study was conducted at a skull base referral centre in the United Kingdom and included 55 patients (60 procedures) between 2010 and 2019. Below is a synthesis focusing on the side effects of IF, supported by key statistics.

In terms of side effects and complications, the overall perioperative complication rate was 8.3% (5/60 procedures). These complications are divided into two main categories. First, intraoperative complications, which occurred in 3.3% of cases (2/60 procedures). Among these, one case of intraoperative hypotension was reported, which was not attributed to the use of IF but rather to anesthetic agents, and one case of bradycardia and cardiac arrest, which was also not related to IF, as the patient did not experience adverse effects in a second surgery where the same dose of IF was used. Second, postoperative complications, which accounted for 5.0% of cases (3/60 procedures). Here, 3 cases of bacterial meningitis were diagnosed, confirmed by positive cultures. Although not directly attributed to IF, it was considered that these cases could be related to the lumbar puncture or the surgery itself. Additionally, complications potentially related to IF were identified in 5.0% of cases (3/60 procedures), mainly due to the meningitis cases, although a definitive causal relationship was not established. Regarding other postoperative symptoms, headache was the most frequent, affecting 28.3% of patients (17/60 procedures). These episodes were transient and resolved within 72 hours, considered multifactorial, i.e., related to the surgery, anesthesia, or lumbar puncture. Olfactory disturbances were also reported in 3.3% of cases (2/60 procedures), and epistaxis in 1.7% of patients (1/60 procedures). It is important to highlight that no serious complications such as seizures, muscle weakness, altered mental status, or death were reported, which have been described in the literature with higher doses of IF (500-1250 mg). In this study, a low dose of 30 mg was used, supporting its safety profile.

Santos Guimarães et al.[32] studied changes in cerebrospinal fluid (CSF) following intrathecal injection of hypodense fluorescein in 24 patients with CSF fistulas. CSF samples were analyzed at the time of lumbar puncture, as well as 24- and 48-hours post-injection. After the injection, the CSF acquired a yellow-greenish colour in 80% of patients at 24 hours, and in 36%, this colour persisted up to 48 hours, indicating the presence of fluorescein. Regarding cellularity, there was a significant increase in cell count, particularly in patients with more than 5 cells/mL initially (Group 2), between 24 and 48 hours ($p$=0.019). Additionally, an increase in the percentage of neutrophils was observed at 24 hours ($p$=0.048), followed by a decrease at 48 hours ($p$=0.05). In relation to protein and glucose levels, there were no significant changes in glucose levels. However, in Group 1 (patients with less than 5 cells/mL initially), protein levels increased significantly at 48 hours ($p$=0.032). Despite these changes, no patient experienced clinical symptoms such as meningitis, seizures, muscle weakness, or altered mental status, effects that have been reported with higher doses of fluorescein[32].

Although fluorescein in high doses can be neurotoxic, Javadi et al.[20] study suggests that in low doses it is safe and effective. In 20 patients, fluorescein identified the CSF leak in 90% of cases (18/20). Definitive closure was achieved in 80% (16/20) after the initial surgery, with recurrences in 4 cases, which were resolved with a second intervention. There were no serious complications attributed to fluorescein, such as seizures or pulmonary edema, effects reported in other studies (the FDA recorded 136 severe cases, including 13 deaths, between 1969 and 2003). In this study, postoperative adverse effects (20%, 4 patients) included meningitis (2 cases), pneumocephalus (1

case) and pseudoaneurysm (1 case), but these were not directly linked to fluorescein. The authors suggest that the lower rate of side effects could be due to the use of lower doses and the variability in patient characteristics. They conclude that low-dose fluorescein is safe and useful, although further studies are needed to confirm its safety[20].

The use of fluorescein proved to be safe also in oncological neurosurgery. De Laurentin et al.[33] performed a retrospective study on the use of sodium fluorescein (SF) as an intraoperative tool in pediatric oncological neurosurgery. Fifty children, aged between 2 months and 17.6 years, who underwent surgery for brain or spinal tumors in the Pediatric Neurosurgery Unit of Hôpital Femme Mère Enfant, Lyon, between September 2021 and July 2022, were analyzed. Most lesions were located in the supratentorial region (27 cases), followed by the infratentorial (15 cases) and spinal regions (8 cases). In all cases where total tumor resection (GTR) was planned (34/50), it was successfully achieved, while subtotal resection (STR) was performed in 12 cases and biopsy in 4 cases. 80% of the lesions (40/50) showed sodium fluorescein (SF) uptake during surgery. Of these, 97% of the lesions that exhibited gadolinium uptake on preoperative MRI also showed intraoperative fluorescence. However, in 45% of the lesions that did not show gadolinium uptake on MRI, some degree of fluorescence with SF was observed, suggesting that SF may be more sensitive in certain cases. Regarding the utility of SF, in 66% of cases (33/50), it allowed for good differentiation between tumor and healthy tissue. In 14% of cases, although SF uptake was observed, differentiation between tumor and healthy tissue was not possible because both showed fluorescence. In the remaining 20%, no intraoperative fluorescence was observed. Quantitative analysis of the images using ImageJ software confirmed that, in cases where the surgeon reported good differentiation, there was a significant difference in green brightness between healthy and tumor tissue ($p < 0.001$). SF was considered useful in 67% of cases where it allowed differentiation. In the subgroup of low-grade gliomas (LGG), SF showed even greater utility, with 75% of cases where it was deemed very useful for guiding resection. In terms of safety, no serious adverse effects related to SF were reported. All patients exhibited a self-limiting yellowish discoloration of urine during the first 24 postoperative hours, an expected and transient effect.

Raza at al.[34] explained the use of intrathecal fluorescein as a diagnostic and therapeutic tool in the management of cerebrospinal fluid (CSF) fistulas during the skull base surgery. All patients included in their study (n=419) received 25 mg of intrathecal fluorescein diluted in 10 ml cerebrospinal fluid. The IF showed a sensitivity of 92.9% and a specificity of 100% in detecting CSF leaks.

Although fluorescein has proven useful in identifying and repairing these fistulas, its intrathecal administration is not approved by the U.S. Food and Drug Administration (FDA). The FDA does not explicitly prohibit the intrathecal use of fluorescein, but it also does not authorize it, meaning its use via this route is considered "off-label" (outside of approved indications). This "off-label" status raises legal and safety concerns, as there is no formal authorization for its intrathecal use in any country, despite its widespread use in clinical practice.

The literature highlights that, although intrathecal fluorescein has been shown to be clinically useful, its use is limited by reports of complications, which are often related to dosing errors. The FDA has not granted authorization for this route of administration, leading to debates about its safety and legality. Despite this, many studies and clinical experiences support its use when administered in low doses (up to 50 mg) and properly diluted in CSF[34].

Fluorescein metabolism is rapid, with predominant renal clearance within 48-72 hours. In cases where intraoperative fluorescence is not observed, manoeuvres such as Valsalva can improve the visualization of the dye[34,35].

Despite the potential risks, fluorescein remains a valuable tool for the identification and management of CSF fistulas, contributing to a better hermetic closure rate of skull base defects. Topical application has emerged as an alternative to avoid adverse effects of intrathecal administration, with diagnostic success rates of 100% in some studies[34,36-39].

## CONCLUSIONS

The studies reviewed indicate that fluorescein is a useful tool in the diagnosis and localisation of cerebrospinal fluid fistulas, as well as in pediatric neurosurgery. Its use in the evaluation of non-congenital defects of the skull base shows a high detection rate, comparable to other radiological modalities. In the localisation of cerebrospinal fluid fistulas, its use is generally safe with low doses between 10 and 25 mg, although concerns persist about the lack of standardization and the absence of long-term studies on its adverse effects, while in pediatric neurosurgery its application at low doses has improved the identification of surgical targets and tumor resection without serious adverse effects. It has been suggested that its dissolution in distilled water could improve

the safety of the procedure. However, since it does not have the approval of agencies such as the FDA, its application requires informed consent and strict monitoring. The implementation of standardized protocols, including preoperative evaluation and prevention measures, could optimize their safety in clinical practice.

Limitations remain related to the lack of standardization in dosages and administration techniques, as well as the paucity of data on long-term safety. Despite its advantages, further research is needed to establish uniform protocols that maximize its efficacy and minimize risks in different clinical contexts.

**Study limitations:** The main limitations lie in not including some databases such as Web of Science, Dialnet and Science.gov; not having access to all the articles also limits our results. Not accessing all the articles also greatly limits our conclusions and veracity.

**Funding:** None.

**Conflicts of interest:** The authors declare that they have no conflict of interest.

**Ethical aspects:** This work adheres to ethical and transparency standards for access to information. AI was used for corrections of writing, spelling, syntax and paraphrasing.

**Acknowledgements:** We thank the University of Sonora Campus Cajeme for the support to access the different databases.

**Contribution of author**: Diana Isabel Espinoza Morales and Janeth Serrano Armenta – systematic review of the literature and writing of the final manuscript. Araceli Zazueta Cárdenas and Juan Antonio Lugo Machado – systematic review of the literature, selection of articles, synthesis and final draft of the manuscript.

**Financial discloser:** The authors fully funded the article.

**Authors' information**

Juan Antonio Lugo Machado, Specialist Physician, "Lic. Luis Donaldo Colosio Murrieta" Specialty Hospital No. 2, Mexican Institute of Social Security, Ciudad Obregón, Sonora. E-mail: otorrinox@gmail.com. ORCID: https://orcid.org/0000-0003-4864-8546.

Diana Isabel Espinoza Morales, Medical student, University of Sonora, Cajeme campus, Ciudad Obregón, Sonora, Mexico. E-mail: otorrinox@gmail.com. ORCID: https://orcid.org/0009-0002-2629-1734.

Janeth Serrano Armenta, Medical Student, University of Sonora, Cajeme campus, Ciudad Obregón, Sonora, Mexico. E-mail: otorrinox@gmail.com. ORCID: https://orcid.org/0009-0006-6012-9801.

Araceli Zazueta Cárdenas, Medical Student, University of Sonora, Cajeme campus, Ciudad Obregón, Sonora, Mexico. E-mail: otorrinox@gmail.com. ORCID: https://orcid.org/0009-0006-4690-1412.

## REFERENCES

1. Cardona SADR, Andrade Lozano P, Salas Galicia JE. Fístula de líquido cefalorraquídeo espontánea: meningocele de pared lateral de esfenoides. Lux Médica. 2020;15(44):49-55. DOI: 10.33064/44lm20202797.
2. Arshad M, Faisal MJ, Ashfaq AH, Riaz N, Maqbool S. Trans-nasal endoscopic repair of CSF rhinorrhea: an institutional experience. Indian J Otolaryngol Head Neck Surg. 2024;76(1):748-52. DOI: 10.1007/s12070-023-04267-2.
3. Mishra SK, Mathew GA, Paul RR, Asif SK, John M, Varghese AM, et al. Endoscopic repair of CSF rhinorrhea: An institutional experience. Iran J Otorhinolaryngol. 2016;28(84):39-43.
4. Bernal-Sprekelsen M, Alobid I, Mullol J, Trobat F, Tomás-Barberán M. Closure of cerebrospinal fluid leaks prevents ascending bacterial meningitis. Rhinology. 2005;43(4):277-81.
5. Rodríguez-Navarro MA, Díaz-Alejo C, Padilla-del Rey ML, Alcaraz AB, González-Pérez P, Benítez M. Safe intrathecal fluorescein use for identification of cerebrospinal fluid leaks: Case-report and perioperative algorithm description Rev Esp Anestesiol Reanim. 2017;64(9):533-6. DOI: 10.1016/j.redar.2017.03.003.
6. Alobid I, Enseñat J, Rioja E, Enriquez K, Viscovich L, de Notaris M, et al. Manejo de las fístulas nasales de líquido cefalorraquídeo según su tamaño. Nuestra experiencia. Acta Otorrinolaringol Esp. 2014;65(3):162-9. DOI: 10.1016/j.otorri.2013.12.003.
7. Roschina DV, Godkov IM, Grin AA, Tovmasyan AS, Garov EV. Endonasal repair of spontaneous CSF fistulas of the lateral recess of the sphenoid sinus. Vestn Otorinolaringol. 2023;88(5):97-103. DOI: 10.17116/otorino20238805197.
8. Jolly K, Gupta KK, Banota A, Ahmed SK. The effectiveness and safety of intrathecal fluorescein in the management of cerebrospinal fluid leaks. Am J Rhinol Allergy. 2021;35(6):879-84. DOI: 10.1177/19458924211020564.
9. Kreatsoulas DC, Shah VS, Otto BA, Carrau RL, Prevedello DM, Hardesty DA. Surgical outcomes of the endonasal endoscopic approach within a standardized management protocol for repair of spontaneous cerebrospinal fluid rhinorrhea. J Neurosurg. 2021;134(3):780-6. DOI: 10.3171/2019.12.JNS192891.
10. Lee ES, Ng BHK, Tang IP. Endoscopic endonasal orbital and optic nerve decompression for traumatic orbital injuries: A review of outcome. Polish Annals of Medicine. 2022;29(1):1-5.
11. Fan J, Liu Y, Pan J, Peng Y, Peng J, Bao Y, et al. Endoscopic endonasal versus transcranial surgery for primary resection of craniopharyngiomas based on a new QST classification system: a comparative series of 315 patients. J Neurosurg. 2021;135(5):1298-1309. DOI: 10.3171/2020.7.JNS.20257.
12. Jolly K, Gupta KK, Muzaffar J, Ahmed SK. The efficacy and safety of intrathecal fluorescein in endoscopic cerebrospinal fluid leak repair –a systematic review. Auris Nasus Larynx. 2022;49(6):912-20. DOI: 10.1016/j.anl.2022.03.014.
13. Kirchner FR, Proud GO. Method for the identification and localization of cerebrospinal fluid, rhinorrhea and otorrhea. Laryngoscope. 1960;70:921-31. DOI: 10.1288/00005537-196007000-00004.
14. Flynn JP, Pavelonis A, Ledbetter L, Bhalla V, Alvi SA, Chiu AG, et al. The utility of computed tomography and intrathecal fluorescein in the management of cerebrospinal fluid leak. Am J Rhinol Allergy. 2020;34(3):342-7. DOI: 10.1177/1945892419896243.
15. Xie M, Zhou K, Kachra S, McHugh T, Sommer DD. Diagnosis and local-

ization of cerebrospinal fluid rhinorrhea: a systematic review. Am J Rhinol Allergy. 2022;36(3):397-406. DOI: 10.1177/19458924211060918.
16. Felisati G, Bianchi A, Lozza P, Portaleone S. Italian multicentre study on intrathecal fluorescein for craniosinusal fistulae. Acta Otorhinolaryngol Italica. 2008;28(4):159-63.
17. Seth R, Rajasekaran K, Benninger MS, Batra PS. The utility of intrathecal fluorescein in cerebrospinal fluid leak repair. Otolaryngol Head Neck Surg. 2010;143(5):626-32. DOI: 10.1016/j.otohns.2010.07.011.
18. 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(2):266-72. DOI: 10.1097/00005537-200402000-00016.
19. Laufer I, Anand VK, Schwartz TH. Endoscopic, endonasal extended transsphenoidal, transplanum transtuberculum approach for resection of suprasellar lesions. J Neurosurg. 2007;106(3):400-6. DOI: 10.3171/jns.2007.106.3.400.
20. Javadi SAH, Samimi H, Naderi F, Shirani M. The use of low-dose intrathecal fluorescein in endoscopic repair of cerebrospinal fluid rhinorrhea. Arch Iran Med. 2013;16(5):264-6.
21. Jakimovski D, Bonci G, Attia M, Shao H, Hofstetter C, Tsiouris AJ, et al. Incidence and significance of intraoperative cerebrospinal fluid leak in endoscopic pituitary surgery using intrathecal fluorescein. World Neurosurg. 2014;82(3-4):e513-23. DOI: 10.1016/j.wneu.2013.06.005.
22. Hutton B, Catalá-López F, Moher D. The PRISMA statement extension for systematic reviews incorporating network meta-analysis: PRISMA-NMA. Med Clín (Barc). 2016;147(6):262-6. DOI: 10.1016/j.medcli.2016.02.025.
23. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group T. Ítems de referencia para publicar Revisiones Sistemáticas y Metaanálisis: La Declaración PRISMA. Rev Esp Nutr Hum Diet. 2014;18(3):172-81.
24. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic review that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. DOI: 10.1136/bmj.j.4008.
25. Li L, Asemota I, Liu B, Gomez-Valencia J, Lin L, Arif AW, et al. AMSTAR 2 appraisal of systematic reviews and meta-analyses in the field of heart failure from high-impact journals. Syst Rev. 2022;11(1):147. DOI: 10.1186/s13643-022-02029-9.
26. Yu F, Liu C, Sharmin S. Performance, usability, and user experience of Rayyan for systematic reviews. Proc Assoc Inf Sci Technol. 2022;59(1):843-4. DOI: 10.1002/pra2.745.
27. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016;5:210. DOI: 10.1186/s13643-016-0384-4.
28. Romeo D, Go BC, Ng JJ, Barrette LX, Rhodes IJ, Rajasekaran K. Systematic review: evaluating the efficacy of intrathecal fluorescein for localizing cerebrospinal fluid rhinorrhea. J Craniofac Surg. 2022;33(8):2581-5. DOI: 10.1097/SCS.0000000000008849.
29. AlSharhan SS, Aljubran HJ, Alrusayyis DF, AlGhuneem AA, AlMarzouq WF, Al Bar MH, et al. Diagnostic accuracy of intrathecal fluorescein versus other radiological modalities in evaluating non-congenital skull base defects: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2024;281(9):4435-54. DOI: 10.1007/s00405-024-08603-2.
30. de Laurentis C, Bteich F, Beuriat PA, Mottolese C, Giussani C, Szathmari A, et al. Sodium fluorescein in pediatric neurosurgery: a systematic review with technical considerations and future perspectives. Child Nerv Syst. 2023;39(6):1451-62. DOI: 10.1007/s00381-022-05772-5.
31. Rajasekar M. Recent development in fluorescein derivatives. J Mol Struct. 2021;1224:129085. DOI: 10.1016/j.molstruc.2020.129085.
32. Guimarães RES, Stamm AEC, Giannetti AV, Crosara PFTB, Becker CG, Becker HMG. Chemical and cytological analysis of cerebral spinal fluid after intrathecal injection of hypodense fluorescein. Braz J Otorhinolaryngol. 2015;81(5):549-53. DOI: 10.1016/j.bjorl.2015.07.016.
33. de Laurentis C, Bteich F, Beuriat PA, Almeida LCA, Combet S, Mottolese C, et al. Sodium fluorescein in pediatric oncological neurosurgery: a pilot study on 50 children. Childs Nerv Syst. 2023;39(6):1473-84. DOI: 10.1007/s00381-022-05765-4.
34. Raza S, Banu MA, Donaldson A, Patel KS, Anand VK, Schwartz TH. Sensitivity and specificity of intrathecal fluorescein and white light excitation for detecting intraoperative cerebrospinal fluid leak in endoscopic skull base surgery: a prospective study. J Neurosurg. 2016;124(3):621-6. DOI: 10.3171/2014.12.JNS14995.
35. Guimarães R, Becker H. A new technique for the use of intrathecal fluorescein in the repair of cerebrospinal fluid rinorrhea using a hypodense diluent. Rev Laryngol Otol Rhinol (Bord). 2001;122(3):191-3.
36. Banu MA, Kim JH, Shin BJ, Woodworth GF, Anand VK, Schwartz TH. Low-dose intrathecal fluorescein and etiology-based graft choice in endoscopic endonasal closure of CSF leaks. Clin Neurol Neurosurg. 2014;116:28-34. DOI: 10.1016/j.clineuro.2013.11.006.
37. Ozturk K, Karabagli H, Bulut S, Egilmez M, Duran M. Is the use of topical fluorescein helpful for management of CSF leakage? Laryngoscope. 2012;122(6):1215-8. DOI: 10.1002/lary.23277.
38. Liu HS, Chen YT, Wang D, Liang H, Wang Y, Wang SJ, et al. The use of topical intranasal fluorescein in endoscopic endonasal repair of cerebrospinal fluid rhinorrhea. Surg Neurol. 2009;72(4):341-5; discussion 346. DOI: 10.1016/j.surneu.2009.03.034.
39. Albaharna H, Alshareef M, Alromaih S, Aloulah M, Alsaleh S, Alroqi A. Topical intranasal fluorescein to diagnose and localize cerebrospinal fluid leak: a systematic review. Turk Arch Otorhinolaryngol. 2021;59(3):223-9. DOI: 10.4174/tao.2021.2021-3.12.