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ORIGINAL RESEARCH

Usefulness of topical intranasal fluorescein for localization of anterior skull base fluid fistulas: a systematic review

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ABSTRACT

OBJECTIVE. This study evaluates the available evidence on the usefulness of topical intranasal fluorescein in diagnosing and localizing nasal cerebrospinal fluid (CSF) leakage.

MATERIAL AND METHODS. A systematic review of the literature was conducted to investigate the usefulness and safety of intranasal topical fluorescein for locating nasal cerebrospinal fluid fistulas, following PRISMA guidelines. Articles were searched in databases including Scopus, PubMed, and ScienceDirect, ("Intranasal Fluorescein" AND "Cerebrospinal Fluid Fistula") OR ("Intranasal Fluorescein" AND "CSF Fistula") in the publications with no time restriction, in the English language. The chosen articles were evaluated with the Newcastle-Ottawa Scale. A table was used to summarize the results.

RESULTS. The 6 included studies on topical intranasal fluorescein to locate CSF fistulas show high effectiveness and safety, with success rates close to 100%. However, limitations include small samples, lack of control groups, and the need for more comparative studies. The methodological quality of the studies is mostly moderate.

CONCLUSION. Intranasal topical fluorescein is an effective and safe method to locate intranasal cerebrospinal fluid leaks, with high diagnostic accuracy. It is a less invasive and more economical option compared to techniques such as intrathecal fluorescein. More controlled research is needed to confirm its effectiveness.

KEYWORDS: fluorescein, intranasal administration, fistula, cerebrospinal fluid, efficiency.

INTRODUCTION

Cerebrospinal fluid fistulas (CSF) of the skull base occur when cerebrospinal fluid leaks from the subarachnoid space into an extracranial region. These can have a spontaneous or acquired origin[1-3]. Among these, nasal fistulas are the most common and usually manifest with headache and rhinorrhea, characterized by the outflow of a clear, watery fluid through one or both nostrils[4-6]. Their etiology is diverse, including skull base tumors, trauma, surgical interventions or spontaneous causes, usually related to intracranial hypertension[7].

These fistulas arise when the barrier separating the nasal cavities from the subarachnoid space is broken, increasing the risk of infection and other complications[8,9]. To confirm their presence, biochemical analyses such as detection of β-2 transferrin or tau protein are used[10-12]. Subsequently, radiological and endoscopic studies are employed to identify the exact anatomical site of the defect. In this regard, the initial computed tomography (CT) scan[13,14], together with magnetic resonance imaging (MRI), can locate the leak site in up to 90% of confirmed cases[15-18]. However, in patients with positive biochemical tests but no clear radiological evidence, or in cases of intermittent low-flow leakage, surgical intervention can become particularly complex.

The treatment of choice is surgical closure of the fistula,

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with the endonasal endoscopic technique being the most common. Advances in skull base surgery have significantly improved outcomes, with success rates exceeding 90%[19-21]. However, when the location of the defect cannot be accurately determined by conventional imaging, intrathecal fluorescein becomes a key intraoperative tool[22,23]. Its use was first reported in 1960 and has demonstrated a localization ability of between 88.1% and 88.7%[24].

Despite its effectiveness, the intrathecal use of fluorescein has not been approved by the U.S. Food and Drug Administration or the UK Medicines and Healthcare products Regulatory Agency[25] due to its potential neurological risks. In this context, the intranasal topical administration of fluorescein has emerged as a less invasive alternative for localizing CSF leaks. However, the scientific literature presents contradictory positions regarding its effectiveness. For example, Albaharna et al.[26] conducted a systematic review to evaluate the efficacy of topical intranasal fluorescein (TINF) in diagnosing and localizing CSF leaks. After searching multiple databases, they identified five case series studies, which together included 94 patients. The authors concluded that the available evidence is limited and of low methodological quality (grade C recommendation), as all studies were observational and without control groups. Therefore, they do not recommend the routine use of TINF in clinical practice, and insist on the need for randomized clinical trials to strengthen the evidence. In contrast, a more recent systematic review by Romeo et al.[27] analysed the diagnostic efficacy of topical intranasal fluorescein in the localization of nasal CSF leaks. To do this, they reviewed six databases, including studies that addressed the use of intranasal fluorescein in the diagnosis and surgical management of these leaks. The results were more encouraging: all included studies reported diagnostic accuracy rates greater than 96%, with no major complications reported in the 99 patients analysed. The fluorescein used was 5% or 10%, and the methodological quality of the studies was rated as moderate, with a mean score of 7.29 out of 24 according to the MINORS instrument. This review concluded that TINF represents an easy-to-apply, safe, inexpensive, and effective diagnostic technique for sinonasal CSF leaks, making it a useful option particularly in resource-limited settings. Despite these positive results, uncertainty persists regarding its actual effectiveness, especially compared to invasive methods such as intrathecal fluorescein. Some studies show important limitations, such as small sample sizes, lack of comparative groups, and heterogeneity in the surgical techniques used. In addition, the localization of multiple defects remains a challenge for topical fluorescein, restricting its applicability in certain clinical scenarios.

Given this panorama, the objective of this study was to carry out a systematic review of the available literature to clarify the degree of usefulness and accuracy of TINF in the localization of CSF leaks at the anterior skull base. This need responds to the growing clinical interest in adopting less invasive and safer techniques that allow optimising the surgical approach to these lesions without compromising diagnostic accuracy or patient safety.

MATERIAL AND METHODS

A systematic review of the literature was carried out independently by two researchers, following a methodology appropriate to the objectives proposed in this research, because the usefulness of topical intranasal fluorescein for the localization of cerebrospinal fluid fistula at the anterior skull base is sought. The systematic review methodology, following the PRISMA guidelines, was used to guide the search for relevant documents in the following electronic databases[28,29]: Scopus, PubMed and ScienceDirect in the English language, with the keywords for PubMed ("Intranasal Fluorescein" AND "Cerebrospinal Fluid Fistula") OR ("Intranasal Fluorescein" AND "CSF Fistula") OR ("Fluorescein Nasal" AND "Cerebrospinal Fluid Leak"), ScienceDirect ("intranasal fluorescein" AND "cerebrospinal fluid fistula"), OR ("intranasal fluorescein" AND "CSF fistula"), OR ("intranasal fluorescein" AND "cerebrospinal fluid leak"), and Scopus TITLE-ABS-KEY ("intranasal fluorescein" AND "cerebrospinal fluid fistula"), OR ("intranasal fluorescein" AND "CSF fistula"), OR ("intranasal fluorescein" AND "cerebrospinal fluid leak"), with no time restriction.

For the quality and risk of bias of the studies, we used the Newcastle-Ottawa Scale rating[30].

The following selection criteria were established:

Inclusion criteria

→ English-language articles
→ Original items
→ Articles that include the variables of interest in the title. Original writing, observational, cross-sectional and case series were included.

Exclusion criteria

→ Non-English-language articles
→ Original writing that does not include the variables of interest

Data collection process

The Rayyan system was used to evaluate abstracts and remove duplicates. 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[31,32].

RESULTS

The databases reviewed yielded a total of 474 writings. Of these, 24 were selected for review, 8 were eliminated because they involved the pediatric population and 4 could not be accessed. 12 met the eligibility criteria, 6 were eliminated because they presented systematic review designs, letters to the editor, narrative reviews and single case reports. A total of 6 articles were included for analysis and synthesis[33-38] (Figure 1).

The reviewed studies show a variety of approaches and

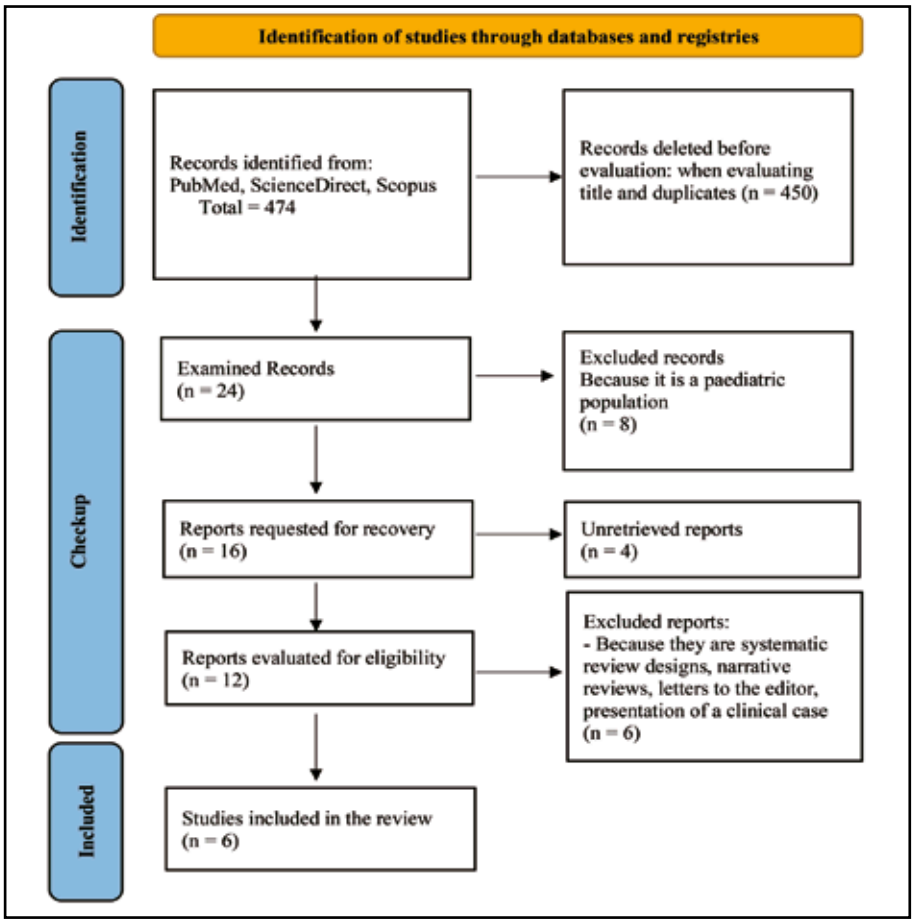

Figure 1. PRISMA flowchart presenting the data selection for the study

results on the efficacy of TINF in diagnosing and localizing cerebrospinal fluid (CSF) leaks (Table 1).

In the study by Eren et al.[33], the effectiveness of TINF in the endoscopic closure of CSF leaks was evaluated. In a series of 27 patients, the retrospective study showed a success rate of 88% on the first attempt and 96% after reoperation. Strengths included the safety of topical fluorescein compared to intrathecal use, although it was recognised that it did not always allow the exact defect to be located. This study received a "good" rating on the Newcastle-Ottawa scale.

Jeremy Barr et al.[34] reported a single case of a male patient with benign intracranial hypertension and rhinorrhea for two months. This case report demonstrated that topical intranasal fluorescein was effective in locating the CSF leak, with clinical follow-up showing no signs of rhinorrhea at 1 and 3 months. While the study highlighted the lower invasiveness and effectiveness of this technique, the main limitation was its single-case design, making it difficult to generalize the results. It was rated as "low" on the Newcastle-Ottawa scale.

In the work of Ozturk et al.[35], TINF was used for both preoperative diagnosis and intraoperative localization of CSF leaks in 24 patients with endoscopic endonasal surgery. The descriptive study showed that topical fluorescein was effective in both respects, but it was highlighted that it could not detect multiple defects in some cases, which represented an important limitation. This study was given a "moderate" rating.

The study by Liu et al.[36] investigated TINF in 15 patients with CSF rhinorrhea and found 100% accuracy in preoperative diagnosis and a recurrence-free repair success rate over a follow-up period of 2 to 24 months. However, due to the small sample size and lack of a control group, the rating of this study was "low".

In a study conducted on 32 patients suspected of CSF leaks, Hashemi Jazi et al.[37] showed a 100% preoperative diagnosis rate using topical intranasal fluorescein, compared to only 58.3% accuracy with conventional imaging studies. No recurrences or complications were reported. Limitations included the lack of a control group and variability in the patient sample. The study was rated as "moderate."

Finally, Saafan et al.[38] reported that 5% topical intranasal fluorescein was 100% effective for the localization and closure of CSF leaks in a group of 25 patients, with no recurrences or postoperative complications. Despite the strengths of high accuracy and safety, the study did not compare topical fluorescein with other methods in a controlled trial, limiting its comparative validity. This study was also rated as "moderate."

Overall, studies show that topical fluorescein is a promis-

Table 1. Results of the included articles.

Author(s)	Year	Objective of the study	Study setting, participant details	Included method: study design	Results	Strengths and limitations	Newcastle-Ottawa Rating
Eren et al.[33]	2020	To assess the effectiveness of topical fluorescein in closing CSF leaks endoscopically	27 patients (19 women, 8 men) operated on between 2011 and 2017	Retrospective study	Success rate of 88% on the first attempt, 96% after reoperation	Strengths: safe alternative to intrathecal fluorescein Limitations: it does not always allow you to locate the exact defect	Good
Barr et al.[34]	2020	To demonstrate the use of intranasal fluorescein as a less invasive alternative to locate CSF leaks	A 45-year-old male patient with benign intracranial hypertension and 2-month rhinorrhea	Case report with video demonstration	No signs of rhinorrhea at 1- and 3-month follow-up	Strengths: less invasive and efficient Limitations: study of a single case, more research is required	Low
Ozturk et al.[35]	2012	To evaluate the efficacy of topical fluorescein for the diagnosis and intraoperative localization of CSF leaks	24 patients underwent endoscopic endonasal surgery for CSF leak repair	Descriptive study	Topical fluorescein was effective for preoperative diagnosis and intraoperative localization	Strengths: high specificity and sensitivity Limitations: failed to detect multiple defects in one case	Moderate
Liu et al.[36]	2009	To assess the effectiveness of intranasal topical fluorescein in the preoperative and intraoperative localization of CSF fistulas	15 patients with CSF rhinorrhea; Mean age: 34.5 years (19-50 years); 10 males and 5 females	Observational study	Preoperative diagnosis with 100% accuracy in fistula localization. Successful repair in all cases, with no recurrences during follow-up (2-24 months). No reported complications	Strengths: high diagnostic accuracy, safe and non-invasive procedure Limitations: small sample size, observational study without control group	Low
Hashemi Jazi et al.[37]	2018	To assess the efficacy of topical intranasal fluorescein (TIN) in the preoperative diagnosis of cerebrospinal fluid (CSF) rhinorrhea and the intraoperative localization of CSF fistulas	32 patients (11 women and 21 men) with suspected CSF rhinorrhea were included	Cross-sectional study	The preoperative diagnosis rate with INRT was 100%, compared to 58.3% accuracy with available imaging studies. No recurrences or complications were reported	Strengths: TINF is a fast, safe, sensitive and non-invasive technique Limitations: uncontrolled study, heterogeneous sample, lack of comparison with intrathecal fluorescein in a double-blind clinical trial.	Moderate
Saafan et al.[38]	2006	To develop and validate the use of topical fluorescein in the intraoperative localization of CSF fistulas and to evaluate its usefulness in the preoperative and postoperative diagnosis of CSF rhinorrhea	25 patients (14 men and 11 women) with CSF rhinorrhea were included.	Observational study	A 100% success rate was achieved in the localization and closure of CSF fistulas. No recurrences or complications were detected.	Strengths: high sensitivity and precision of topical fluorescein, safe and non-invasive method Limitations: not compared with other methods in a controlled trial, lack of randomized clinical trials	Moderate

ing tool for locating CSF leaks, although there are limitations, such as sample sizes and lack of comparisons with other standard methods. Intranasal topical fluorescein is considered a safe, non-invasive and effective technique, but more controlled research is needed to validate its effectiveness in different contexts.

DISCUSSIONS

Several studies have shown that topical intranasal fluorescein is effective for locating cerebrospinal fluid leaks, with high sensitivity in most cases. For example, Hashemi Jazi et al.[37] reported a 100% preoperative diagnosis rate when using TINF to identify CSF leaks, while Ozturk et al.[35] also pointed out an effectiveness in intraoperative localization with topical fluorescein, highlighting a high specificity and sensitivity. These results are consistent with the systematic review by Albaharna et al.[26] which found a sensitivity of 100% for preoperative diagnosis of CSF fistulas and 97% for intraoperative localization, reinforcing the reliability of TINF.

Despite the promising results, some studies highlight that TINF is not the only useful tool for locating CSF leaks. In the study conducted by Liu et al.[36], topical fluorescein had a diagnostic accuracy of 100%; however, it was an observational study with a small sample size and no control group, which limits the generalizability of these results. In contrast, larger controlled studies such as that by Eren et al.[33] showed that topical intranasal fluorescein could be a less invasive alternative to intrathecal fluorescein, although with limitations in the precise localization of the defect in some cases. In addition, the use of intrathecal fluorescein has been shown to be a more accurate option for identifying CSF leaks, indicating that although topical fluorescein has good effectiveness, intrathecal fluorescein remains the preferred option in more complex cases[27].

The strengths of TINF include its low cost, ease of use, and being less invasive than other techniques such as intrathecal fluorescein or computed tomography (CT). These benefits are reflected in studies such as that by Barr et al.[34] which highlighted the efficiency and lower invasiveness of intranasal fluorescein in locating CSF leaks. However, some limitations have been identified. In particular, the technique does not always succeed in locating multiple defects, as observed in the

study by Eren et al.[33] and results may vary depending on the skill of the surgeon or the clinical presentation of the patient. Additionally, although topical intranasal fluorescein appears to be effective, its accuracy may not be as high as that of more invasive or advanced methods such as intrathecal fluorescein, as noted in several of the articles reviewed.

In terms of complications, Saafan et al.[38] and Hashemi Jazi et al.[37] reported no significant complications in patients treated with topical intranasal fluorescein, indicating that this technique is safe. However, even if Liu et al.[36] reported no complications in all 15 patients included in their study, they suggested that the safety of topical intranasal fluorescein should be evaluated more thoroughly in controlled studies with more participants and control groups.

The research we performed explores the effectiveness of TINF in identifying cerebrospinal fluid (CSF) leaks in various clinical contexts. Overall, studies show high diagnostic accuracy, reaching a 100% success rate in preoperative and intraoperative detection of these fistulas when compared to reference methods such as the β2-transferrin test and surgical findings.

In clinical practice, TINF represents a promising tool for the localization of CSF leaks, with a high success rate in both preoperative and intraoperative settings. Its main advantage lies in being a less invasive and low-cost technique, making it accessible and convenient in clinical settings with limited resources. In addition, its ease of use, especially when compared to more complex methods such as intrathecal fluorescein or computed tomography (CT), makes it an attractive option for many professionals.

However, there are limitations that need to be taken into account. Although TINF has proven to be effective in many cases, its ability to detect multiple defects is limited and results may vary depending on the surgeon's skill and the patient's clinical presentation. In complex situations, intrathecal fluorescein remains the preferred choice due to its higher accuracy, reinforcing the importance of choosing the appropriate technique based on the patient's context and the complexity of the CSF leak.

Moreover, although studies report a high success rate and absence of major complications, some articles suggest that more controlled research with larger participant groups is needed to fully evaluate the safety and efficacy of topical fluorescein. This is especially relevant in contexts where patient safety is a priority and clinical decisions must be based on solid evidence.

CONCLUSIONS

Current data indicate that topical intranasal fluorescein is an effective, safe, and minimally invasive method for locating CSF leaks. However, the quality of the evidence remains moderate, as there are not enough controlled studies or comparative clinical trials. To confirm its effectiveness as a replacement for intrathecal fluorescein with certainty, more rigorous research with randomized and controlled methodologies is required.

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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. Most of the included articles were rated as moderate quality according to the Newcastle-Ottawa Scale.

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.

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