Sensitivity and specificity of intrathecal fluorescein and white light excitation for detecting intraoperative cerebrospinal fluid leak in endoscopic skull base surgery: a prospective study

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OBJECTIVE The intraoperative detection of CSF leaks during endonasal endoscopic skull base surgery is critical to preventing postoperative CSF leaks. Intrathecal fluorescein (ITF) has been used at varying doses to aid in the detection of intraoperative CSF leaks. However, the sensitivity and specificity of ITF at certain dosages is unknown.

METHODS A prospective database of all endoscopic endonasal procedures was reviewed. All patients received 25 mg ITF diluted in 10 ml CSF and were pretreated with dexamethasone and Benadryl. Immediately after surgery, the operating surgeon prospectively noted if there was an intraoperative CSF leak and fluorescein was identified. The sensitivity, specificity, and positive and negative predictive power of ITF for detecting intraoperative CSF leak were calculated. Factors correlating with postoperative CSF leak were determined.

RESULTS Of 419 patients, 35.8% of patients did not show a CSF leak. Fluorescein-tinted CSF (true positive) was noted in 59.7% of patients and 0 false positives were encountered. CSF without fluorescein staining (false negative) was noted in 4.5% of patients. The sensitivity and specificity of ITF were 92.9% and 100%, respectively. The negative and positive predictive values were 88.8% and 100%, respectively. Postoperative CSF leaks only occurred in true positives at a rate of 2.8%.

CONCLUSIONS ITF is extremely specific and very sensitive for detecting intraoperative CSF leaks. Although false negatives can occur, these patients do not appear to be at risk for postoperative CSF leak. The use of ITF may help surgeons prevent postoperative CSF leaks by intraoperatively detecting and confirming a watertight repair.


KEY WORDS cerebrospinal fluid leak; cranial base; endoscopy; fluorescein; intrathecal; minimally invasive; skull base; surgery

Endoscopic endonasal approaches provide a minimal access corridor to the ventral skull base. Although anatomically appealing, the success and applicability of these approaches has hinged upon the surgeon’s ability to successfully close the resulting defects in the skull base in order to prevent a postoperative CSF leak. The complications of an inadequate closure can also include meningitis and tension pneumocephalus. As such, a variety of closure methods have been developed, ranging from free tissue grafts and rigid buttresses to vascularized pedicled flaps and gasket seal closure; however, these techniques are not without morbidity and hence are used in a tailored fashion. The primary indication for utilizing a closure technique is the successful identification of intraoperative CSF leaks.16 Hence, any method that increases the surgeon’s ability to detect intraoperative CSF leaks would be potentially advantageous. Because CSF is translucent and the surgical cavity can contain small pools of blood and irrigation, it may be difficult to recognize small, low-flow CSF leaks. Using intrathecal fluorescein (ITF) injection to highlight CSF was described over 40 years ago.10,11,15 The green fluorescence (peak emission wavelength 519 nm) can be detected with endoscopic white light illumination and is thought to eas-
ily differentiate CSF from the surrounding liquids in the operative field, which may obscure the detection and localization of an intraoperative leak. Prior reports have described the utility and safety of fluorescein at variable doses, ranging from 10 to 250 mg. Higher dosages run risks of hypersensitivity reactions, and lower dosages may be inadequately sensitive and specific. At very low dosages (e.g., 10 mg), the sensitivity can be as low as 73.8% with a false-negative rate of 26.2%.21 We routinely use a slightly higher dose (25 mg) and have previously reported the safety of this technique.1,8,16,17,22 Although safe, there are no data on the sensitivity and specificity of using 25 mg ITF to detect intraoperative CSF leaks. Thus, a prospective study was initiated to address this issue.

**Methods**

**Study Design**

After obtaining appropriate institutional review board approval for this study, we queried a prospectively acquired database of 648 endonasal endoscopic skull base surgeries that were performed by the senior authors (T.H.S. and V.K.A.) at Weill Cornell Medical College, Sackler Brain and Spine Center, NewYork-Presbyterian Hospital. Only patients undergoing pure endonasal endoscopic approaches who received ITF were selected for this study. To avoid biases and errors that stem from retrospective analyses, we only included the most recent series of consecutive patients for whom complete data regarding intraoperative fluorescein detection had been prospectively collected. In total, 419 consecutive patients were ultimately enrolled in this study. Once patients were selected based on these criteria, we performed a retrospective chart review of the hospital and office records for the remaining pre-, intra-, and postoperative treatment-related parameters; of note, data regarding if fluorescein was intraoperatively visualized and if a postoperative CSF leak occurred were prospectively collected. The presence or absence of CSF leaks and the color of the CSF were prospectively noted. The presence or absence of visible fluorescein was noted in a prospective fashion during the Valsalva maneuver after repair of the skull base defect.

**ITF Administration and Intraoperative Protocol**

We have described our low-dose ITF protocol for endonasal endoscopic skull base procedures in detail elsewhere.4,5,7,12,14–20 Of note, this is an off-label use of fluorescein; all patients were informed about the off-label use and potential complications prior to surgery. Briefly, after intravenous premedication with dexamethasone (10 mg) and diphenhydramine (50 mg), patients received 0.25 ml of 10% ITF (AK-Fluor, Akorn). Of note, patients with Cushing’s disease were not pretreated with dexamethasone, as this would interfere with the postoperative assessment of adrenal insufficiency and Cushing’s disease remission. Furthermore, most patients were not sent home on a regimen of hydrocortisone therapy. We checked morning fasting cortisol on postoperative Day 2 and only undertook replacement therapy in those patients with low cortisol levels or those with Cushing’s disease in remission. Fluorescein was diluted with 10 ml of withdrawn CSF and administered over several minutes, either through a lumbar puncture or lumbar drain. Lumbar drains were generally used for patients in whom a high-flow CSF leak was expected, such as intradural tumors (meningiomas, cranio-pharyngiomas, intradural chordomas) and pituitary macroadenomas > 2.5 cm in diameter with > 1 cm suprasellar extension.16 Given that the endonasal approach exposure typically requires 1 hour, the approximate time from administration to visualization of CSF was the same.

Our endoscopic endonasal techniques have been described elsewhere.4,5,7,12,14–20 Visualization was provided using 0°, 30°, and 45° rigid 4-mm endoscopes (Karl Storz GmbH & Co.), a digital camera (Karl Storz GmbH & Co.), and a 21-inch color monitor (Karl Storz GmbH & Co.). Inspection for fluorescein was performed throughout the procedure using white light. White light illumination allowed for visualization of fluorescein’s emission in the yellow-green spectrum (Fig. 1). Although we used specific filters at times in the beginning of our series, we found that white light visualization was adequate for observing fluorescein and that the filters did not offer additional sensiti-

[FIG. 1. Intraoperative image of fluorescein-stained CSF under white light illumination. Upper: Stained CSF is noted during the endoscopic resection of a tuberculum sella meningioma. Lower: View at the end of a “gasket seal” closure where no CSF fistula is noted. Figure is available in color online only.]
ty. At the end of the procedure, closure was achieved using a variety of techniques based on the severity of the intraoperative leak, as well as the location and size of the cranial base defect. For all procedures performed after January 2010, a single case-specific protocol has been used for reconstruction. For extradural pathology, Gelfoam (Pfizer) and DuraSeal (Integra LifeSciences) were used when no leak is encountered, or a fat graft with DuraSeal when a small leak occurred. For intradural, intrasellar pathology where a small leak was encountered, closure consisted of a fat graft with Medpor (Stryker Inc.) and DuraSeal. When a large leak was encountered with such pathology, a fat graft with Medpor and a nasoseptal flap followed by 24 hours of postoperative CSF diversion via a lumbar drain was used. For intradural, nonsellar pathology, the reconstruction was composed of a “gasket seal” (fascia lata, Medpor), nasoseptal flap followed by 24–48 hours of postoperative CSF diversion. The integrity of the closure was tested intraoperatively by the Valsalva maneuver with close inspection for fluorescein. Large pituitary tumors received lumbar drainage at a rate of 5 ml/hour for 1 day. Spontaneous CSF leaks or encephaloceles received lumbar drainage at a rate of 5 ml/hour for 3 days. Intradural tumors received lumbar drainage at a rate of 5 ml/hour for 1 day.

Statistical Analysis

Statistical analysis was performed using the SPSS software package for Macintosh (version 20.0). We report the continuous variables, age, and follow-up time as the mean ± SEM of the mean and range (minimum–maximum). Categorical variables are given as frequencies and percentages. A p value < 0.01 was considered statistically significant. Sensitivity was calculated as true positives/(true positives + false negatives); specificity was calculated as true negatives/(true negatives + false positives); the positive predictive value (PPV) was calculated as true positives/(true positives + false positives); and the negative predictive value (NPV) was calculated as true negatives/(true negatives + false negatives). We used univariate ANOVA or 2-tailed t-tests to compare continuous variables, false negatives, and true positives, as well as between patients with and without postoperative CSF leaks. We used the Pearson chi-square or Fisher exact test, as appropriate, to compare false negatives, true negatives, true positives, and patients with and without postoperative CSF leaks based on sex, pathology, surgical approach, placement of lumbar drain, and extent of resection.

Results

General Cohort Characteristics

Between May 2005 and January 2014, there were 419 patients who underwent endonasal endoscopic procedures at our institution and were selected for this study based on the inclusion criteria described in Methods. The general cohort characteristics are shown in Table 1. The average follow-up time was 34.6 ± 1 months (range 2–106 months). Based on pathology type and location, patients were divided into 7 distinct groups: Group 1, sellar lesions (adenomas, hyperplasia, hemorrhage/apoplexy, metastases); Group 2, CSF leaks/encephaloceles; Group 3, suprasellar lesions (craniopharyngiomas, xanthogranulomas, epidermoids, Rathke cleft cysts); Group 4, anterior skull base lesions (olfactory groove meningiomas, tuberculum sellae/planum meningiomas, esthesioneuroblastomas, chondrosarcomas); Group 5, posterior skull base lesions (cavernous sinus meningioma/lymphoma/hemangioma/hemangiopericytoma metastases, ependymoma, trigeminal schwannoma, sphenoid wing meningioma, chordoma); Group 6, intranasal lesions with/without skull base invasion (juvenile nasopharyngeal angiofibroma, lymphoma, fibrous dysplasia); and Group 7, odontoid lesions. The patient distribution by pathology was as follows: Group 1, n = 227 (54.2%); Group 2, n = 47 (11.2%); Group 3, n = 46 (11%); Group 4, n = 39 (9.3%); Group 5, n = 40 (9.5%); Group 6, n = 14 (3.3%); and Group 7, n = 6 (1.4%).

Patients were further divided into 7 operative groups depending on the endoscopic corridor and approach used to access the skull base lesion: pure transsphenoidal (n = 124; 29.6%); transcavernous/transclival (n = 70; 16.7%); transethmoidal/transplanum/transstuberculum (n = 165; 39.4%); transodontoid (n = 6; 1.4%); combined anterior and posterior corridors and approaches (n = 36; 8.6%); transmaxillary/transpterygoid (n = 14; 3.3%); and intranasal with no intracranial component (n = 4; 1%). A total of 86 patients (20.5%) underwent closure with the fascia lata, while 204 patients (48.7%) and 227 patients (54.2%) underwent closure of the skull base defect with a gasket seal or a gasket seal with a nasoseptal flap, respectively. For those patients at high risk of an intraoperative CSF leak,
we decided to place an intraoperative lumbar drain at the start of surgery in 227 patients (54.2%).

**Diagnostic Value of Low-Dose ITF for Detecting Intraoperative CSF Leak**

Of the 419 patients who underwent endoscopic procedures with ITF, extensive dissection with dural violation occurred in 269 patients (64.2%). Fluorescein-tinted CSF was visualized in 250 (59.7%) patients. All patients with visible fluorescein during the surgery had actual intraoperative CSF leaks and are, therefore, considered true-positive cases. Given that fluorescein was intrathecally injected and, therefore, solely disseminated through the CSF, there were no false-positive cases, i.e., visualizing fluorescein without a real intraoperative CSF leak (Table 2). In 19 patients there was an intraoperative leak of clear unstained CSF without visible fluorescein; these were considered the false-negative cases (4.5%). In total, 150 patients did not have either visible fluorescein or discernible intraoperative CSF leaks, and were therefore labeled as true-negative cases (35.8%). The sensitivity and specificity of low-dose ITF for detecting intraoperative CSF leaks were 92.9% (250 of 269 patients) and 100% (150 of 150 patients), respectively (Table 3). The NPV and PPV were 88.8% (150 of 169 patients) and 100% (250 of 250 patients), respectively. In other words, there is an 88.8% chance that a patient undergoing an endoscopic procedure in conjunction with ITF who does not have visible fluorescein during the procedure actually does not have an intraoperative CSF leak. Fluorescein may reach the suprasellar cistern in varying periods of time. We, therefore, wanted to verify if the false-negative results had shorter operative times. The operative times were as follows: true positives, 201.8 ± 98.3 minutes; true negatives, 177.6 ± 80.1 minutes; and false negatives, 204.2 ± 55.6 minutes. These differences were not statistically significant (p = 0.681; ANOVA).

**Incidence and Management of Postoperative CSF Leaks**

Of the 419 endoscopic patients included in this study, 7 patients developed postoperative CSF leaks (1.7%). All 7 postoperative CSF leaks developed in the first 30 days after the initial endoscopic procedure. Only true positives developed postoperative CSF leaks in this cohort, and thus in all 7 patients there was an intraoperative CSF leak that was identified as ITF (p = 0.045). In other words, if fluorescein was not seen intraoperatively, there was a 0% chance of a postoperative CSF leak. Likewise, if an intraoperative CSF leak occurred but the CSF was not stained with fluorescein (false negative), then the risk of a postoperative CSF leak was also 0%. Of the 250 true-positive cases, 7 patients later developed postoperative CSF leaks (2.8%). Five of these 7 patients were part of the first half of this series who were treated before 2009. After 2009, we settled on a closure algorithm that led to a significant reduction in our CSF leak rates.1,16

A subanalysis was performed to assess the risk factors predictive of a postoperative CSF leak. The type of reconstruction was not a risk factor: the gasket seal was used in 4 of 7 patients (p = 0.471), the nasoseptal flap was also used in 4 of 7 patients (p = 0.591), and fascia lata alone was only used in 1 of 7 patients (p = 0.562). In 4 patients, a lumbar drain was used during the endoscopic procedure (p = 0.591). Pathology was not shown to be a risk factor. Two patients had pituitary adenomas, 2 patients had craniopharyngiomas, 1 patient had a chordoma, 1 patient had an epidermoid, and 1 patient had a spontaneous CSF leak (p = 0.356). Similarly, the type of approach was not correlated with the risk of postoperative leak. Patients who developed postoperative CSF leaks underwent the following endoscopic procedures (p = 0.957): 2 of 7 underwent the pure transsphenoidal approach; 2 of 7 underwent the transsphenoidal/transclival approach; 2 of 7 underwent the transethmoidal/transplanum approach; and 1 of 7 underwent the combined anterior and posterior approach. In most patients with postoperative CSF leaks (5 of 7), we achieved gross-total resection, with subtotal resection achieved in one case and near-total resection in the other (p = 0.897). Since the majority of leaks occurred early in our series, the only factor correlated with postoperative CSF leaks was intraoperative visualization of the fluorescein-tinted CSF and lack of experience.

Three of 7 patients with postoperative CSF leaks required an intervention to repair the skull base defect. Endoscopic re-interventions were performed at 6 days, 9 days, and 6 days after the initial endoscopic procedures. One of these 3 patients underwent a second endoscopic procedure at 7 days for a recalcitrant leak that posteriorly extended the endonasal CSF leak. This was considered a separate postoperative CSF leak. In the remaining 4 patients, conservative measures were sufficient for the complete cessation of the CSF leak.

**Discussion**

To adequately control an intraoperative CSF leak, one

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**Table 2. Definitions of true and false negatives and positives**

<table>
<thead>
<tr>
<th>(+) CSF Leak</th>
<th>(-) CSF Leak</th>
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</thead>
<tbody>
<tr>
<td>(+) Fluorescein</td>
<td>True positive</td>
</tr>
<tr>
<td>(-) Fluorescein</td>
<td>False negative</td>
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</tbody>
</table>

* (+) CSF leak indicates that an intraoperative CSF was identified either with or without fluorescein. (-) CSF leak indicates that no intraoperative CSF leak was identified. (+) Fluorescein indicates that fluorescein-stained CSF was identified. (-) Fluorescein indicates that no fluorescein was identified.

**Table 3. Diagnostic utility of ITF**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>False positive</td>
<td>0</td>
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<tr>
<td>True positive</td>
<td>59.7</td>
</tr>
<tr>
<td>False negative</td>
<td>4.5</td>
</tr>
<tr>
<td>True negative</td>
<td>35.8</td>
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<tr>
<td>Sensitivity</td>
<td>92.9</td>
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<tr>
<td>Specificity</td>
<td>100</td>
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<tr>
<td>NPV</td>
<td>88.8</td>
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<td>PPV</td>
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must first be able to identify it. Likewise, the ability to assess if a skull base closure is indeed watertight requires an assessment of the persistence of an intraoperative CSF leak after the closure has been performed. Although a Val-salva maneuver can be useful for eliciting leaks, CSF is translucent and the operative field is often blurred with small pools of blood or mucosal secretions, making it difficult to recognize small leaks. For this reason, some surgeons employ ITF to help visualize potentially small, unappreciated leaks that may require additional layers of closure of increasing complexity. In this prospective study, we define the sensitivity, specificity, NPV, and PPV of using 25 mg ITF with white light excitation to detect CSF leaks, which we have already shown in prior studies to be safe. In contrast to lower dosages of ITF, the 25-mg dose is much more specific and has a lower false-negative rate. Seth et al. performed a retrospective study of 10 mg ITF and reported sensitivity and specificity values of 73.8% and 100%, respectively, and a false-negative rate of 26.2%. In our prospective study, using a dose of 25 mg, the sensitivity was markedly higher at 92.9% and the false-negative rate was lower at 4.5%.

The false-negative rate of 4.5% warrants a discussion on the possible reasons why clear CSF was detected without the visual presence of fluorescein at the site of surgery. While our retrospective review did not identify any risk factors, several possibilities exist. Factors such as arachnoid scarring (i.e., prior meningitis), severe lumbar stenosis, or inadequate time from intrathecal injection could account for why the injected fluorescein did not circulate to the skull base. Another possibility is that an uneven distribution of fluorescein occurred within the subarachnoid space. While it is possible that lower doses of fluorescein may only be detected with a blue light filter (465–495 nm) or blocking filter (515–555 nm), we have not found this to be the case in our anecdotal observations using these filters. Blue filters have been advocated for cases in which the diagnosis is equivocal or the intensity of the yellow-green fluorescein is difficult to visualize. It is also interesting to note that among those patients with a CSF leak in whom ITF was not appreciated, there were no postoperative CSF leaks. It is possible that whatever physiological process limits the diffusion of ITF into the operative field also decreases the rate of CSF flow into the basal cisterns and minimizes the risk of postoperative CSF leak. However, this is mere speculation. Nevertheless, the fact that the risk of postoperative CSF leak was 0% in patients in whom there was no appreciation of fluorescein in the operative field, regardless of whether a non-fluorescein CSF leak was identified (i.e., the combination of true- and false-negative groups), demonstrates the power of using 25 mg ITF to predict postoperative CSF leak.

Safety concerns have historically limited the use of fluorescein. Previously, the administration of higher doses of ITF was associated with infrequent, but severe, and transient side effects, including lower extremity paresis and auras, seizures, and cranial nerve palsies. Consequently, the cautious and limited use of this agent prohibited large-scale studies to determine if the observed events were dose-dependent or idiosyncratic. Additional, recently published, larger series indicate an improved safety profile for ITF doses less than 50 mg. In an effort to establish the safety of the 25 mg dose, we retrospectively reviewed our experience in a cohort of 54 patients. In this study, most observed side effects were nonspecific, transient, and likely not caused by fluorescein, including malaise (57.4%), headaches (51.9%), dizziness (31.5%), and nausea/vomiting (24.1%); there were no seizures. Likewise, in a larger study of 203 pituitary patients, we also did not find any evidence of side effects related to the ITF.

Limitations

Although prospective, there are still limitations to this study. Patients were not randomized in this study; therefore, it is difficult to ascertain the true benefit of ITF injection over general evaluation. For instance, other institutions that do not use ITF also report low rates of postoperative CSF leak, so it is unclear if our technique offers any advantage. Ideally, a randomized trial would be performed with identical closures so that the rates of postoperative CSF leaks could be compared. Such a study would be extremely difficult to do since the surgeons could not be blinded and the rates of CSF leak are so low that it would require potentially thousands of patients to reach significance. Another challenge with this study is that theoretically patients could have a small postoperative leak that is asymptomatic and resolves spontaneously, but based on current practices we have no way of detecting them. There are several methodological and design limitations of this study. Although the data were prospectively collected, the analysis was retrospectively performed. Furthermore, the data are largely descriptive, as there is no objective measurement tool for intraoperative CSF leaks. Therefore, due to the lack of a true gold standard for assessing the presence of intraoperative CSF leaks, certain cases may have been incorrectly classified as true negatives. This may have led to an overestimation of specificity.

Conclusions

The intraoperative detection of CSF during endoscopic endonasal procedures is critical for guiding skull base reconstruction and preventing postoperative CSF leaks and associated complications. ITF is a technique that can help identify an intraoperative CSF leak. At 25 mg, the sensitivity is 92.9% and the specificity is 100%. Although there is a 4.5% rate of false negatives, postoperative CSF leaks only occur in true-positive patients. Further studies may be necessary to determine the relative efficacy in comparison with procedures where ITF is not used.

References

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Disclosure
Dr. Schwartz reports that he is a consultant for VioSense and Karl Storz and that he receives non–study-related support from NIH.

Author Contributions
Conception and design: Schwartz, Raza. Acquisition of data: Raza, Banu, Patel. Analysis and interpretation of data: Schwartz, Raza, Banu, Anand. Drafting the article: all authors. Critically revising the article: Schwartz, Raza, Donaldson, Anand. Reviewed submitted version of manuscript: Schwartz, Raza, Banu, Donaldson, Anand. Approved the final version of the manuscript on behalf of all authors: Schwartz. Statistical analysis: Banu. Study supervision: Schwartz.

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