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ORIGINAL ARTICLE

Incidence and Significance of Intraoperative Cerebrospinal Fluid Leak in Endoscopic Pituitary Adenoma Surgery Using Intrathecal Fluorescein

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Background: Cerebrospinal Fluid (CSF) leak during endonasal endoscopic pituitary adenoma surgery is an important factor that affects the way of sellar floor closure, postoperative CSF leak rate and postoperative outcome. Our objective is to determine the rate and significance of intraoperative cerebrospinal fluid leak in endoscopic pituitary Adenoma surgery with intrathecal fluorescein administration. **Methods:** The study focused on 18 patients diagnosed with pituitary adenoma. These patients underwent resection through endonasal transsphenoidal approach with the use of intrathecal fluorescein injection. The rate of intraoperative CSF leak was noted and correlated with tumor size, consistency, extension, extent of resection, postoperative CSF leak and the way of closure of the sellar floor. **Results:** With the use of intrathecal fluorescein, intraoperative CSF leak appeared to be higher than usual. Intraoperative CSF leak occurred in 15 patients (83.3%). As regard grades of CSF leak, 11 patients had grade 1(61.1%), 3 patients had grade 2(16.7%) and only one patient had grade 3 (5.6 %). Fluorescein injection was done for patients with no CSF leak or suspicion of CSF leak but not done for grade 2 and 3, hence, it was done for 14 patients (77.8%) and in 7 of them (50%), CSF leak appeared only with Fluorescein, in 4 of them (28.5%) suspicious leak was confirmed with Fluorescein and 3 of them (21.5%) had no CSF leak confirmed with no Fluorescein appearance after injection. Postoperative CSF leak occurred in 3 of 18 patients (16.7%) and relieved in all patients after few days with lumbar drain kept in place till CSF leak stopped. **Conclusion:** The use of intrathecal fluorescein during endoscopic transsphenoidal pituitary surgery is very helpful in identifying intraoperative CSF leak especially G1 leak, resulting in better sellar closure and less postoperative CSF leak.

Keywords: Cerebrospinal Fluid Leak; Fluorescein; Intrathecal; pituitary adenoma

INTRODUCTION

A common brain lesion that is becoming more and more diagnosed is pituitary adenomas. It is estimated that 15% of the general population has pituitary adenomas based on radiologic and postmortem investigations [1]. After meningiomas and gliomas, pituitary adenomas are the third most prevalent neoplasms of the central nervous system [2]. Because it offers many benefits over the transcranial approach such as being the least traumatic route to the sella turcica, avoiding the need for brain retraction, and providing excellent visualization of the pituitary gland and related lesions the endoscopic transsphenoidal approach has become the standard procedure for the removal of pituitary tumors [3].

Cerebrospinal fluid (CSF) leaks remain the most common complication during endonasal endoscopic transsphenoidal approach (EETSA) procedures, and are reported to occur in approximately 50% of pituitary tumor cases, despite the fact that the rates of morbidity and mortality associated with these procedures have significantly decreased [4]. More severe side effects such pneumocephalus, meningitis, and ventriculitis could happen if intraoperative CSF leaks are not entirely stopped. These conditions could result in neurological impairments or even

death. In order to reduce morbidity, mortality, and hospital length of stay and to ensure successful pituitary surgery, it is crucial to prevent postoperative CSF leaks [5]. Because a little volume of clear fluid mixed with blood in the surgical field is difficult to perceive, it is hypothesized that small CSF leaks may go unnoticed. They are thought to be the consequence of tiny, unnoticed interruptions in the arachnoid [6]. In theory, a greater number of intraoperative CSF leak detections could result in more careful and comprehensive sella closure and a decreased incidence of postoperative CSF leaks[6].

Fearing a postoperative CSF leak, surgeons may become less aggressive in some circumstances to limit the chance of intraoperative CSF leakage; nevertheless, this would result in a lower rate of postoperative leaks at the expense of attaining a Gross total resection (GTR). Therefore, higher rates of GTR and surgical confidence may result from a safe method for guaranteeing the detection and repair of CSF leaks [7]. It was first described more than 40 years ago to highlight CSF using intrathecal fluorescein (ITF) injection. With endoscopic white light illumination, the green fluorescence (peak emission wave length 519 nm) may be seen. It is believed to be able to distinguish CSF from the surrounding liquids in the operating field, which could make it more difficult to locate and diagnose an intraoperative leak [8].

This study aimed to determine the rate and significance of intraoperative cerebrospinal fluid leak in endoscopic pituitary Adenoma surgery with intrathecal fluorescein administration, to ensure tight closure of the sellar floor and to determine the predictive factors of intraoperative CSF leak.

METHODS

This was randomized clinical trial that was conducted at the Neurosurgery Department, Faculty of Medicine, Zagazig University during the period between October 2023 and June 2024 after receiving approval from the Institutional Review Board (IRB # 11104-17-9-2023) at Zagazig University. The study included 18 patients with an age range of 22 to 65 years with a mean age of 40.83 years and 77.8% of patients were females. Prior to surgery, all patients consented to get a fluorescein injection and have a lumbar drain placed. All patients had endoscopic endonasal technique for pituitary adenoma removal.

Records were kept of the patients' demographics, co-morbidities, clinical and radiological information, surgical specifics, and postoperative problems. To determine the size, type, location, and extent of the tumors in each patient, preoperative hormonal profiles, CT scans, and MRIs were performed.

Surgical technique

A neurosurgeon subspecializing in endoscopic pituitary and anterior skull base surgery with the cooperation of an otolaryngologist carried out all endoscopic transsphenoidal surgical procedures. In summary, the procedure consists of a binostril endoscopic transsphenoidal approach.

CSF identification and closure

After tumor removal, a careful examination for CSF leakage is undertaken, aided by the Valsalva maneuver. If any suspicion about CSF leak or the surgeon cannot be certain about no leak or minor grade 1 leak, here comes the role of injection of intrathecal fluorescein through the lumbar drain which was inserted preoperatively by an anaesthesiologist to ensure there is no leak or identify minor leaks. The standard lumbar drain is performed using a large-bore Tuohy needle (14- to 16-gauge). Ten milliliters of CSF were withdrawn (or ten millimeters of normal saline if unable to withdraw enough CSF) and dissolved in 0.25 milliliters of 10% fluorescein solution. The injection was done slowly by an anaesthesiologist. The Over the course of many minutes, the fluid was gradually pumped into the intrathecal region. The CSF took the green color of the fluorescein after about 30 minutes and any CSF leak intraoperatively was observed. We graded closure techniques according to grades of CSF leak. G0, we filled the sellar floor with gelfoam only. G1, we used both gelfoam and bone graft and in higher grades we used all of fat, bone graft, fascia lata graft and NS flap. We used both intrathecal fluorescein and valsalva maneuvers for better assurance of tight sellar closure.

Postoperative management

All patients postoperatively were transferred to the intensive care unit with monitoring for postoperarive complications especially CSF leak. If no CSF leak, lumbar drain was removed after 24 h, and if CSF leak appeared, then the lumbar drain was kept in place till the leak stopped with good coverage with antibiotics. Postoperative hormonal profile was done for assessment of hormonal balance and patients receiving preoperative hormone supplementations were continued on them postoperatively. An input and output chart were documented, and the output of urine was noted. Serum electrolyte levels were regularly checked. Every patient underwent an immediate postoperative CT scan. Third-month postoperative MRI was performed to evaluate the degree of resection.

STATISTICAL ANALYSIS

Data analysis was performed using the software SPSS (Statistical Package for the Social Sciences) version 26. Categorical variables were described using their absolute frequencies and were compared using chi square test, Fisher exact test and Monte Carlo test when appropriate. Shapiro-Wilk test was used to verify assumptions for use in parametric tests. Quantitative variables were described using their means and standard deviations. The level statistical significance was set at $P<0.05$. Highly significant difference was present if $p\leq0.001$.

RESULTS

Cerebrospinal Fluid Leak Grading System table 1 [9].

Intraoperative CSF leak occurred in 15 patients (83.3%). As regard grades of CSF leak, 61.1% had grade 1, 16.7% ha grade 2 and only one patient had grade 3 (Table 2).

Fluorescein injection was done for patients with no CSF leak or suspicion of CSF leak but not done for grade 2 and 3, hence, it was done for 14 patients and 7 patients had CSF leak that appeared only with Fluorescein, 5 patients had suspicious G1 CSF leak confirmed with Fluorescein and 3 patients had no CSF leak confirmed with no Fluorescein appearance after injection as shown in (Table 3).

Table 4 showed that there is statistically non-significant relation between intraoperative CSF leak and different hormonal typing of tumor, tumor size or extent of tumor resection. ACTH- secreting tumor, prolactinoma, and non-functioning tumor non-significantly associated with leak.

Table 5 showed that there was no post operative CSF leak appeared with no intraoperative Leak, only 1 patient (9%) of G1 CSF leak developed post op CSF leak, half of high-grade leaks developed post op CSF leak. There was statistically significant relation between grades of CSF leak with type of closure and post operative CSF leak. The incidence of post operative CSF leaks increases with higher grades of post operative CSF leaks.

Figure 1 showed that 26y old female patient presented with headache, diminution of vision and amenorrhea. Complete resection of adenoma was done endoscopically through endonasal transsphenoidal approach with G1 CSF leak identified after intrathecal Fluorescein injection with postoperative relief of symptoms with no.

Table (1): Cerebrospinal Fluid Leak Grading System.

Grade of Leak	Description of Leak
0	No leak observed
1	Small cerebrospinal fluid leak without a visible diaphragmatic defect
2	Moderate leak with diaphragmatic definite defect
3	Large diaphragmatic defect with or without a third ventricular cerebrospinal fluid leak

Table (2): Distribution of the studied patients according to intraoperative CSF leak.

	n=18	%
Intraoperative CSF leak	15	83.3%
Grade		
No leak	3	16.7%
Grade 1	11	61.1%
Grade 2	3	16.7%
Grade 3	1	5.6%

Table (3): Distribution of the studied patients according to fluorescein injection.

	n=18
Fluorescein injection No Yes	 4 14
G1 CSF Leak Appeared only with fluorescein	7/11
G1 CSF leak confirmed with fluorescein	4/11
No CSF leak confirmed with fluorescein	3/14

Table (4): Relation between intraoperative CSF leak and tumor- specific characteristics.

	Total Number	No leak N=3 (16.7%)	Leak N=15 (83.3%)
Hormonal Typing			
ACTH-secreting adenoma	1	0 (0%)	1 (6.7%)
GH-secreting adenoma	5	1 (33.3%)	2 (13.3%)
Prolactinoma	5	1 (33.3%)	5 (33.3%)
Non-functioning adenoma	7	1 (33.3%)	6 (40%)
Tumor Consistency			
Soft	12	3 (100%)	9(60%)
Hard	6	0 (0%)	6(40%)
Tumor Extension			
Sellar	2	2 (66.7%)	0(0%)
Supra or Parasellar	16	1(33.3%)	15(100%)
Tumor Resection			
Gross Total Resection	13	1 (33.3%)	12 (80%)
Partial	5	2 (66.7%)	3 (20%)
Tumor Size			
Group 1 (0 to 1.5 cm^3)	2	2 (66.7%)	0 (0%)
Group 2 (1.6 to 2.5 cm^3)	9	1(33.3%)	8 (53.3%)
Group 3 (more than 2.6 cm^3)	7	0 (0%)	7 (46.7%)
Median (range)	18	1.2(0.7 – 1.9)	2.4(1.6 – 14.8)

Table (5): Relation between sellar floor closure according to intraoperative CSF leak grade and incidence of postoperative CSF leak.

	No leak N=3 (%)	Leak N=15 (%)
Postoperative CSF leak		
Gelfoam (G0)	3 (20%)	0 (0%)
Gelfoam ,bone graft (G1)	10 (66.7%)	1 (33.3%)
Fat, bone graft, fascia lata graft,NS flap (G2,3)	2 (13.3%)	2 (66.7%)

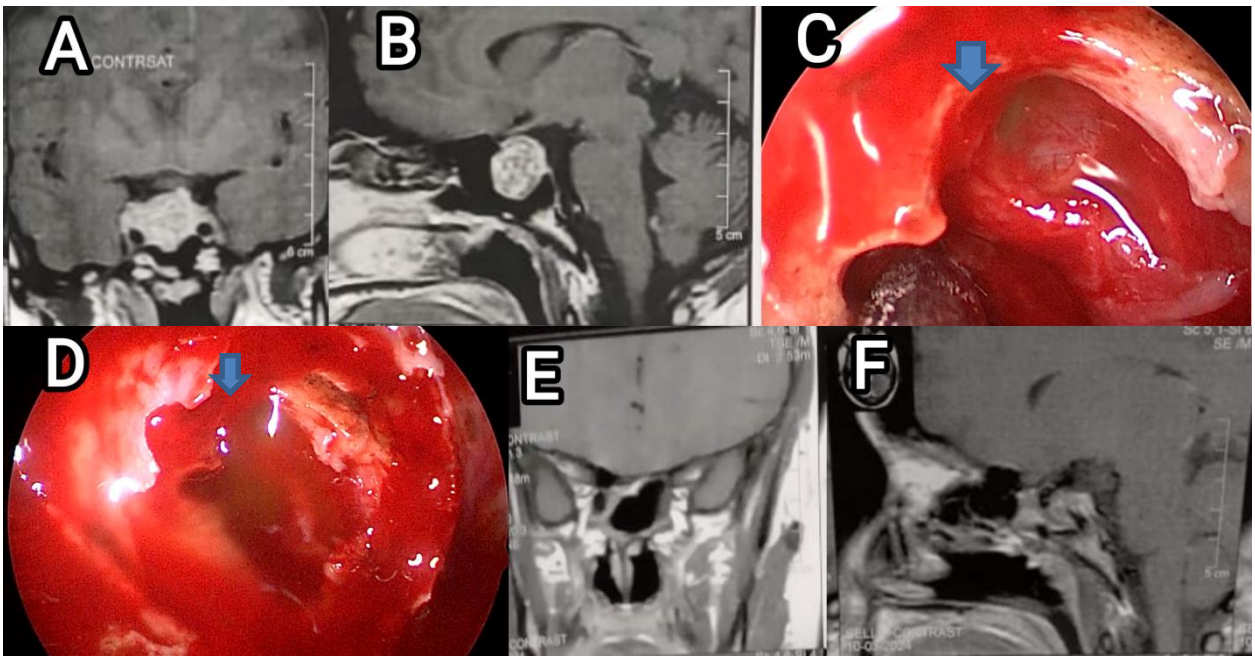

Figure 1: (A) and (B): preoperative MRI sella with contrast, coronal & sagittal views showing hemorrhagic pituitary macroadenoma**. (C) and (D):** intraoperative CSF leak appeared after fluorescein intrathecal injection and took the green colour of fluorescein**. (E) and (F):** postoperative MRI sella with contrast showing complete excision of the adenoma.

DISCUSSION

The rates of intraoperative CSF leak have received less attention than the rates of postoperative leak after transsphenoidal pituitary surgery. It would seem sense that locating leaks during surgery is essential to improving closure methods and reducing postoperative CSF leakage [1]. Our study showed that with the use of intrathecal fluorescein, the rates of intraoperative CSF leaks appeared to be much higher. Among 18 patients, intraoperative CSF leak occurred in 15 patients (83.3%). As regard grades of CSF leak, 61.1% had grade 1 (11 patient), 16.7% had grade 2 (3 patients) and only 5.5% had grade 3 (one patient). Jakimovski *et al*. [6] demonstrated that the rate of iCSF leak with intrathecal fluorescein was 61%, and that the rates of iCSF leak with both intrathecal fluorescein and endoscopic inspection were significantly greater than previously thought [6].

In our study we arranged patients into 3 groups according to the tumor size to study the relation between iCSF and tumor size. Group (1) for tumors 1.5 cm^3 or less, group (2) for tumors ranging from 1.6 to 2.5 cm^3 and group (3) for tumors more than 2.5 cm^3. We found that there is a significant relationship between the size of the tumor and intraoperative CSF leak. Group 1 developed no leak (0%), while group 2 (88,9%) of patients developed CSF leak and all patients in group 3 (100%) had CSF leak. Jakimovski *et al*. [6] showed that by dividing patients into eight groups according to tumor volume and using the approximate volume cutoff of 1.5 cm^3, for each of the eight volume groups, the rate of iCSF leak grew steadily. In the first two groups, the overall leak was 35%, while in the following six groups, it was 68%. The amount of iCSF leak increased from 35% (0-1.487 cm^3) to 55% (1.553-4.941 cm^3) to 70% (4.950-10.450 cm^3) to 77% (10.482-115.897 cm^3) after the volumetric values were divided into quartiles to improve statistical power [6].

AS regard extent of tumor resection, tumor extension and consistency, our study showed higher incidence of iCSF with gross total resection of the tumors, tumor extension outside the sella and hard tumors. With gross total resection, CSF leak occurred in 12 of 13 patients (92,3%), but with partial resection and residuals remaining, CSF leak occurred in 2 of 5 patients (60%) which shows that intraoperative CSF leak increases with the extent of resection. While regarding tumor extension, tumors confined to the sella developed no leak, while tumors with either supra or parasellar extension had more adhesions and developed leak in 14 of 16 patients (87.5%). Regarding consistency, soft tumors developed iCSF leak in 9 of 12 patients (75%) while all hard tumors developed iCSF leak (100%). Cetinalp *et al*. shown that increased CSF leakage and tumor volume connection may be explained by larger tumors that extend through the arachnoid and diaphragma sella. Furthermore, CSF leakage rates may rise as a

result of surgeons' aggressive efforts to achieve GTR in larger tumors [10]. While Zhao *et al*. demonstrated the critical significance that tumor invasion, size, and texture play in influencing postoperative CSF leakage. Following pituitary adenoma removal, the macroadenoma has a variety of wounds, and there is a significant change in intracranial pressure. The arachnoid is more likely to collapse due to the remaining space, which can cause arachnoid damage and CSF leaking. Aggressive tumors, on the other hand, have a significant eroding effect on the dura and skull base bone as well as a huge adhesion region with the arachnoid membrane. When removing hard-textured tumors, surgeons must perform more forceful and intrusive anatomical procedures, which increases the risk of dura and arachnoid membrane rupture [11].

As regard closure of the sellar floor, we graded closure techniques according to grades of CSF leak. In G0, we fill the sellar floor with gelfoam only. In G1, we use both Gelfoam and bone graft, and in higher grades we used fat, bone graft, fascia lata graft and NS flap. We used both intrathecal fluorescein and valsalva maneuvers for better assurance of tight sellar closure. We found that postoperative CSF leak correlated with higher grades; no postoperative CSF leak appeared with G0 Leak, only 1 patient (9%) of G1 CSF leak developed postoperative CSF leak, half of high-grade leaks developed postoperative CSF leak with overall postoperative CSF leak of 16.7% and CSF leak in all patients relieved after few days with lumbar drain kept in place till CSF leak stopped. Esposito *et al*. have put out grading schemes for intraoperative leaks and advocated for a graded sella repair based on the extent of the leak. This rational conclusion assumed that intrathecal fluorescein gives more data to support any closure technique, making it more effective, and that all leaks can be properly located [12]. Some authors as by Couldwell *et al*. suggested using the Valsalva movement to verify the closure's integrity [13]. Zhao *et al*. demonstrated that CSF leakage should be graded. A single-layer collagen sponge should be used to repair a grade 0 leak; a double-layer collagen sponge should be used for a grade 1 leak; fat tissue should be used to fill the sphenoid sinus for a grade 2 leak; and a multi-layer method using collagen sponge, muscle, fat, and fascia lata or a free pedicled nasal septum should be used for a grade 3 leak [11].

As regard side effects of intrathecal fluorescein injection, our study didn’t show any side effects of fluorescein injection in lower doses (25 mg) in the intrathecal space. Jakimovski *et al*. revealed that there were no instances of aseptic meningitis, radiculopathy, or postoperative seizures related to fluorescein side effects. Other studies using lumbar puncture injections of lower fluorescein concentrations showed little problems [6]. Keerl *et al*. a set of 420 applications revealed the incidence of two generalized tonic-clonic seizures [14]. Whereas Felisati *et al*. and Seth *et al*. did not observe any complications [15,16]. While Jolly *et al*. demonstrated that low-dose intrathecal fluorescein was a safe and effective way to detect CSF leaks. No significant side effects, including seizures, limb paralysis, or mortality, were recorded, and complications were unlikely to be directly related to the use of intrathecal fluorescein [16].

As regard the efficacy of fluorescein in identifying CSF leak, intraoperative Fluorescein test was positive in all of eleven patients with confirmed CSF leakage with a sensitivity 100%, and it was negative in the three patients with confirmed no leak with a specificity of 100%. With an overall diagnosis accuracy of 100%, positive and negative predictive values were 100% and 100%, respectively. Raza *et al*. revealed that the sensitivity and specificity with 25 mg intrathecal fluorescein were 92.9% and 100%, respectively, while the NPV and PPV were 88.8% and 100%, respectively [8]. While Seth *et al*. conducted a retrospective analysis using 10 mg intrathecal fluorescein, reporting 73.8% and 100% of the data for sensitivity and specificity, respectively [16].
Patients who may be at risk of CSF leaking during surgery may benefit from lumbar drainage. Within 48 hours, the drain can be withdrawn if there was no CSF leak. If CSF leaks, they should be stored for three to seven days. If lumbar leakage lasts longer than two weeks, repair surgery should be done [18]. In our study postoperative CSF leak occurred in 3 of 18 patients (16.7%) and CSF leak in all patients stopped after few days with lumbar drain kept in place till CSF leak stopped with no need for repair surgery.

Declaration of interest:

The authors report no conflicts of interest.

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CONCLUSION

The use of intrathecal fluorescein during endosopic transsphenoidal pituitary adenoma surgery is very helpful in identifying intraoperative CSF leaks especially G1 leaks, resulting in both better sellar closure and less postoperative CSF leak. Tumor

size, consistency, extension and extent of resection are all factors the affect the rate of intraoperative CSF leaks. With better closure of the sellar floor and the use of lumbar drain, the management of postoperative CSF leak becomes much easier.

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