Lumbar Puncture for the Injection of Intrathecal Fluorescein: Should It Be Avoided in a Subset of Patients Undergoing Endoscopic Endonasal Resection of Sellar and Parasellar Lesions?

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Abstract

Objectives The use of intrathecal fluorescein (ITF) has become an increasingly adopted practice for the identification of cerebrospinal fluid (CSF) leaks during endoscopic skull base surgery for pituitary adenomas. Administration through lumbar puncture can result in postoperative positional headaches, increasing morbidity, cost, and length of stay. We sought to identify the incidence of and variables associated with postoperative headaches to determine if there was a subgroup of patients in whom this procedure should be avoided.

Methods We conducted a retrospective single-institution review of 148 patients who underwent endoscopic resection with ITF for pituitary adenoma between December 2003 and February 2016. We excluded patients who had lumbar drains and with intraoperative CSF leak, as these patients may have other headache etiologies. Patient demographics, comorbidities, tumor features, surgical approach, surgical closure, and histology were recorded. Primary outcomes included the presence of postoperative and positional headaches.

Results We identified 62 patients with postoperative headaches (41.9%) and 10 with positional headaches (6.8%), of whom 6 underwent blood patch with complete resolution. Following univariate analysis, there was a significant positive association with prolactin-secreting tumors ($p = 0.008$). There was a negative association with a history of hypertension ($p = 0.0001$) and age ($p = 0.01$). Following multivariate modeling, the significance for hypertension ($p = 0.01$) was preserved.

Conclusions Positional headaches in patients who receive ITF are uncommon and should not limit its use in the preparations for endoscopic resection of pituitary adenomas. Avoiding ITF in younger patients without hypertension with prolactinomas might decrease the risk of post-ITF positional headaches.

Keywords

- adverse outcome
- endoscopic
- fluorescein
- lumbar puncture

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Introduction

Intraoperative detection of cerebrospinal fluid (CSF) leaks is critical in preventing postoperative CSF leaks following endoscopic skull base surgery.^{1,2} An important intraoperative diagnostic tool is intrathecal fluorescein (ITF).²⁻⁶ Our group recently assessed the utility of ITF in a cohort of 419 patients and found it to be highly sensitive (92.9%) and specific (100%) for the detection of intraoperative CSF leaks.⁷

While the utility of ITF appears promising, development of postoperative headache after performing preoperative lumbar puncture (LP) is a potentially unfavorable outcome. Post-LP headache is defined as a positional headache arising within 7 days of the procedure.⁸ Reported rates of headache following LP vary; however, a recent study reported an incidence of 21.9% for immediate postprocedural headaches and 17.5% at 24-hour follow-up.⁹

The aim of this study was to determine the incidence and preoperative predictors of postoperative positional headaches following administration of ITF for pituitary adenoma surgery.

Methods

Study Design

The primary objective of this study was to determine the incidence of postoperative positional headaches following delivery of ITF through LP for pituitary adenoma surgery. LP for ITF administration introduces the possibility of leakage from the puncture site, possibly leading to postoperative positional headaches.

Patient Selection

We queried a prospectively acquired database of all endoscopic skull base surgeries performed by the senior authors (T. H. S, V. K. A.) at NewYork-Presbyterian/Weill Cornell Medical Center to find patients with pituitary adenomas who underwent preoperative LP for injection of ITF. This maneuver was performed with a 20-gauge needle to identify any intraoperative CSF leaks that might require repair using an autologous fat graft. Under general anesthesia, 10 mL of CSF is withdrawn and 0.5 mL of 10% fluorescein is injected.^{2,3,10} Patients in whom a lumbar drain was placed were excluded, as were patients in whom an intraoperative CSF leak was identified.

Retrospective Review

A retrospective cohort review was conducted, which included documentation of patient demographics, comorbidities (weight, body mass index [BMI], smoking, diabetes mellitus (DM), hypertension, cardiovascular risk, and a history of cardiac events), tumor size, long-term steroid use, and BMI), tumor size and involvement (suprasellar extension, optic compression, and cavernous sinus involvement), treatment approaches (transsphenoidal–transsellar, transplanum, transcavernous, and others), treatment closures (with dead-space closure, multilayer packing, buttressing, vascularized flap, and sealant), and histology (staining for

adrenocorticotrophic hormone [ACTH], growth hormone [GH], or prolactin). Cardiovascular events including a history of myocardial infarction, deep venous thrombosis, pulmonary embolism (PE), stroke, congestive, and heart failure were identified. Extent of resection was determined by examining the neuroradiologist's report of postoperative films obtained on postoperative day 2.

Patients were further stratified based on a history of headache: preoperative headaches, postoperative headaches, and positional headaches. These were determined based on retrospective chart review. Patients requiring blood patch for severe positional postoperative headache were also identified.

Statistical Analysis

Tests of significance were performed on all primary and secondary outcomes using two-tailed tests with an α of 0.05. Categorical variables were analyzed using Fisher's exact test, and continuous variables were analyzed using Student's *t*-test. Logistic regressions were performed on variables with subsequent multivariate modeling. Data preparation and analysis were performed using Stata software (StataCorp).

Results

Cohort Overview

Of the 191 adenomas operated, we eliminated five with lumbar drain, 12 with intraoperative CSF leaks, and 26 missing annotations for postoperative headache development for a total of 148 patients (52% female, mean age of 49.4 years) who met the inclusion criteria for this study. Mean baseline body mass index (BMI) was 29.7 (standard deviation [SD]: 6.7), 7.4% had a history of smoking, 18.2% had DM, 39.9% had hypertension, and 4.7% had a past medical history of a cardiovascular event (defined as myocardial infarction, deep vein thrombosis, PE, stroke, or congestive heart failure) (►Table 1).

Mean tumor size was 1.8 cm (SD: 0.96), and the most common histological types were nonhormone-producing adenoma (41.9%), prolactinoma (25.7%), GH-secreting adenoma (14.9%), and ACTH-secreting adenoma (15.5%). Gross total resection was achieved in 83.8% of patients. Mean length of stay was 4.3 days (SD: 1.8), and mean follow-up was 65.9 months (SD: 41.1) (►Table 1).

Univariate Predictors of Postoperative and Positional Headaches

There were five patients with preoperative headaches, 62 with postoperative headaches (41.9%), and 10 with positional headaches (6.8%), of whom 6 underwent blood patch with complete resolution. Univariate analyses were conducted to identify associations between baseline demographics, surgical factors, and development of any postoperative versus positional headaches. We found significant associations between postoperative headache, and comorbid hypertension (odds ratio [OR]: 0.23; $p < 0.001$), prolactinoma histology (OR: 2.8; $p < 0.01$), and age (OR 0.98, $p < 0.05$). (►Table 2). The relatively rare development of positional postoperative headache ($n = 10$) impaired our ability to identify statistically significant predictors of positional headache development. However, we did

Table 1 Cohort demographics and overview

	N or mean	Percentage or SD
Total cohort	148	100
Demographics		
Age	49.4	17.5
Female	77	52
BMI	29.7	6.7
Preoperative		
Smoking history	11	7.4
Diabetes mellitus	27	18.2
Hypertension	59	39.9
CV event	7	4.7
Preoperative headache	5	3.4
Tumor characteristics		
Adenoma (other)	62	41.9
Prolactinoma	38	25.7
Adenoma (GH +)	22	14.9
Adenoma (ACTH +)	23	15.5
Adenoma (mixed)	3	2
Size (centimeters)	1.75	0.96
Clinical		
GTR	119	83.8
LOS (days)	4.3	1.75
Follow-up (months)	65.9	41.1
Closure		
Dead space	136	91.9
Seal	134	90.5
Buttress	45	30.4
Flap	40	27
Layer	1	0.7
Outcomes of interest		
Postoperative headache	62	41.9
Positional postoperative headache	10	6.8

Abbreviations: ACTH, adrenocorticotrophic hormone; BMI, body mass index; CV, cardiovascular; GTR, gross total resection; GH, growth hormone; LOS, length of stay; SD, standard deviation.

observe a trend toward significance for comorbid hypertension (OR: 0.14; $p = 0.07$).

Multivariate Analysis of Postoperative Headache Development

Multivariate analysis was performed using binomial logistic regression with the development of postoperative headache as the response variable. Model parameters were selected based on a p -value ≤ 0.1 in univariate analysis and included comorbid hypertension, prolactinoma histology, age, comor-

bid DM, and ACTH-secreting adenoma. Only hypertension (OR: 0.32; $p < 0.05$) demonstrated a significant independent association ($\rightarrow$ Table 3).

Discussion

We routinely perform preoperative LP to deliver ITF before endoscopic surgery to aid in the detection of intraoperative CSF leaks,^{1–3,7,10} and sought to evaluate the incidence of postoperative headaches in our patient population. Post-LP headache is the most common adverse outcome associated with this procedure.¹¹ Notably, incidence of positional postoperative headaches (6.8%) was markedly lower than recently reported rates, 21.6% immediate post-LP headaches and 17.5% at 24-hour follow-up.⁹ The genesis of this study, and an important point of discussion, is that the benefits of ITF for endonasal endoscopic resection of sellar pathology must be weighed against potential risks. While positional postoperative headaches were uncommon in our study, six patients did require blood patch—an intervention which would have been avoided in the absence of LP for ITF. Given the utility of ITF for the detection of intraoperative CSF leak detection, we sought to identify patient and disease characteristics that would optimize the risk–benefit tradeoff.

Univariate analysis revealed significant positive association with prolactin-secreting tumors ($p < 0.01$) and the development of postoperative headache. Significant negative associations for postoperative headache development were identified between patients with a history of hypertension ($p < 0.001$) and increasing age ($p < 0.05$). Multivariate modeling revealed that only a history of hypertension ($p < 0.05$) was an independent predictor of postoperative headache development. The rationale for the protective relationship with hypertension is not evident. One possible explanation may be that hypertensive patients receive more mindful and stricter control of blood pressure following surgery, possibly explaining this observation. We posit that the positive association with prolactinomas and the negative association with age may reflect a subpopulation of young female patients. Indeed, this demographic is the same group with classically higher rates of pseudotumor cerebri. While the pathophysiology of this association remains poorly understood, evidence to date suggests that female sex hormones may increase resistance to CSF outflow.¹² Overall, avoiding LP in younger patients without hypertension and with prolactinomas might reduce the overall incidence of post-procedure positional headaches.

This study is subject to the limitations of single-institution reports, namely, being retrospective in nature, lacking randomization, and reporting results based on a relatively limited patient sample size. Moreover, headaches were documented based on patient self-reporting, introducing potential subjectivity. A final limitation is that the incidence of positional headaches was relatively rare ($n = 10$), which restricts our statistical power to conclude that we did not identify treatment-level predictors of developing this complication. The elimination of patients with lumbar drains was required since the size of the dural defect needed to place a

Table 2 Univariate analysis of postoperative and postoperative positional headache development

Variable	Postoperative headache			Postoperative positional headache		
	OR	95% CI	p-Value	OR	95% CI	p-Value
Hypertension	0.23	0.11–0.48	0.0001	0.14	0.01–0.8	0.07
Prolactinoma	2.79	1.32–6.06	0.01	2.08	0.51–7.73	0.28
Age	0.98	0.96–0.99	0.01	0.97	0.93–1.01	0.11
Diabetes mellitus	0.42	0.16–1.03	0.07	0.48	0.03–2.71	0.49
Adenoma (ACTH +)	0.43	0.15–1.12	0.10	0.58	0.03–3.3	0.61
Tumor size	0.70	0.44–1.06	0.11	0.47	0.17–1.11	0.11
Suprasellar location	0.58	0.29–1.14	0.12	0.52	0.11–1.94	0.35
Adenoma (GH +)	0.47	0.16–1.22	0.14	–	–	–
Buttress closure	0.63	0.29–1.3	0.22	0.96	0.2–3.66	0.96
Transcavernous approach	0.61	0.22–1.56	0.32	0.68	0.04–4.02	0.73
Seal closure	2.15	0.48–15.07	0.36	–	–	–
Flap closure	0.71	0.33–1.5	0.38	1.08	0.22–4.1	0.92
Other approach	1.94	0.41–10.17	0.40	–	–	–
Mixed histology	2.83	0.27–61.79	0.40	7.44	0.33–85.36	0.11
Blood on pathology	0.57	0.12–2.16	0.43	–	–	–
Cavernous sinus location	0.75	0.34–1.64	0.48	0.31	0.02–1.76	0.28
GTR	0.74	0.3–1.83	0.51	1.83	0.32–34.67	0.57
CV risk	0.82	0.42–1.59	0.56	0.76	0.19–2.79	0.69
Sex	0.82	0.43–1.58	0.56	0.71	0.17–2.59	0.60
Dead-space closure	0.68	0.12–3.78	0.64	0.36	0.05–7.28	0.37
Weight	1	0.98–1.01	0.65	0.98	0.94–1.01	0.22
Transplanum approach	1.43	0.26–7.97	0.67	3.27	0.16–23.84	0.30
Transsphenoidal–transsellar approach	1.18	0.5–2.9	0.71	1.82	0.31–34.51	0.58
Optics	0.87	0.42–1.78	0.71	0.54	0.08–2.28	0.45
Other histology	0.89	0.46–1.73	0.74	0.92	0.23–3.38	0.91
Smoker	1.20	0.33–4.17	0.78	3.44	0.47–16.51	0.15
BMI	1	0.95–1.05	0.94	0.95	0.83–1.05	0.35
CV event	1.05	0.2–4.95	0.95	–	–	–

Abbreviations: ACTH, adrenocorticotrophic hormone; BMI, body mass index; CI, confidence interval; CV, cardiovascular; GH, growth hormone; GTR, gross total resection; OR, odds ratio.

Note: In the positional headache analysis, dashes (–) indicate perfect separation and were thus not reported (i.e., no patients with positional headache had adenoma [GH +]). Significant associations are indicated in bold.

Table 3 Multivariable analysis of postoperative headache development

Variable	Postoperative headache		
	OR	95% CI	p-Value
Hypertension	0.32	0.13–0.77	0.01
Prolactinoma	1.55	0.64–3.82	0.33
Age	0.99	0.97–1.02	0.50
Diabetes mellitus	0.83	0.28–2.35	0.73
Adenoma (ACTH +)	0.77	0.24–2.33	0.65

Abbreviations: ACTH, adrenocorticotrophic hormone; CI, confidence interval; OR, odds ratio.

Note: Value in bold indicates statistical significance.

drain is larger, and the drain is left in longer. Hence, the incidence of positional headache after lumbar drains would be expected to be much higher. Likewise, we eliminated patients with intraoperative CSF leaks. These patients might have a higher risk of postoperative headache from their intraoperative loss of CSF and might bias the results of this study.

To our knowledge, this is the first study to assess the development of postoperative headaches in patients who receive ITF prior to endoscopic skull base surgery. We found that younger age, prolactinoma histology, and normal blood pressure were associated with higher incidence of postprocedure positional headache. The use of ITF in these patients should be used only when necessary, and the possibility of

positional headaches should be discussed with the patients before surgery.

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Conflict of Interest

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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