**Title:**

**Cerebrospinal fluid leaks after transsphenoidal surgery - effect of a polyethylene glycol hydrogel dural sealant.**

**Authors:**

Erlick A.C. Pereira 1, Carly A. Grandidge 2, Victoria A. Nowak 2, Simon A. Cudlip 2

Affiliations:

1 Academic Neurosurgery Unit, St George’s, University of London, London, UK.

2 Department of Neurological Surgery, John Radcliffe Hospital, Oxford University Hospitals, Oxford, UK.

Corresponding Author:

Mr. E.A.C. Pereira, Atkinson Morley Neurosciences Unit, St George’s Hospital, London SW17 0QT, UK.

Phone: +44 208 725 4173

Fax:+44 208 725 1724

Email: eacp@eacp.co.uk

Running Title: CSF leaks after pituitary surgery

Words:

2167

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**Abstract**

To investigate cerebrospinal fluid (CSF) leak rates after mainly endoscopic endonasal transsphenoidal surgery with and without polyethylene glycol hydrogel dural sealant (DuraSeal**®**), we prospectively collected data from a single-centre consecutive case series over four years from January 2007 to December 2010 inclusive.

250 patients were identified (135 male, 115 female; median age 52 years, range 14-83). 180 patients received DuraSeal**®** (72%). 85 (34%) had intra-operative dural breach and 13 (5.2%) developed post-operative CSF leaks (3 without intra-operative dural breach) requiring lumbar drainage or formal repair. Of this group 5/251 (2.0%) patients required a formal repair. Post-operative CSF leak was seen in 5/189 (2.7%) of patients with pituitary adenoma, of which 2/5 (40%) were in cases undergoing revision surgery. 5/13 (38.4%) patients who developed a CSF leak presented with either Rathke's cleft cyst or craniopharyngioma. 3/71 patients not receiving DuraSeal**®** leaked (4.2%) and 10/180 patients receiving DuraSeal**®** leaked (5.6%). 11/234 patients without Tisseel (4.7%) and 2/16 receiving Tisseel (12.5%) leaked. 54 patients (22%) received intra-operative lumbar drains, one of whom developed subsequent CSF leak (1.9%), in contrast to 12/197 (6.1%) of patients without intra-operative lumbar drains who later developed CSF leak.

The rate of post-operative CSF leak requiring re-exploration and nasoseptal flap repair was low (2.0%) in this mainly endoscopic case series without statistically significant benefit from either DuraSeal**®** or Tisseel. Intra-operative and post-operative lumbar drainage appears beneficial in patients at higher risk of post-operative CSF leak.

**Key Words**

Cerebrospinal fluid leak, DuraSeal**®**, Endoscopic, Lumbar drain, Outcomes, Pituitary, Tisseel, Transsphenoidal adenohypophysectomy

**Introduction**

The transsphenoidal approach to the sellar and parasellar region was first described over a century ago [1]. From the 1970s onwards transsphenoidal surgery was predominantly microsurgical[2] but today, with the advanced optics and engineering of clinical endoscopes, the preferred approach to pituitary lesions is the endoscopic endonasal transsphenoidal approach [3], first described in 1992 by Jankowski et al [4, 5]. Owing to increased illumination, magnified, angled and high definition views of intricate sellar anatomy, this approach is considered relatively safe, with low morbidity and mortality [6]. The main complications of pituitary surgery are diabetes insipidus and cerebrospinal fluid (CSF) leak. CSF leak is an important complication, as it can lead to significant complications, including meningitis [7, 8] and even tension pneumocephalus [9]. The endoscopic approach has gained popularity in recent years, as multiple meta-analyses demonstrate shorter lengths of stay and more thorough tumour resection [10]. However, there are concerns regarding increased incidence of CSF leak with the endoscopic technique and long term outcomes have not been fully assessed or compared with a randomised controlled trial.

As such, a variety of techniques have evolved to deal with CSF leak recognised during endoscopic endonasal approaches to the pituitary, since historical techniques such as septal bone and cartilage harvest [11] are not easily available endoscopically. These include abdominal fat grafts and the use of tissue sealants, such as Fibrin glue or DuraSeal**®** (a polyethylene glycol hydrogel dural sealant [12 Covidien, Waltham, MA, USA]) or a combination of approaches. All have advantages and limitations, yet the use of DuraSeal**®** has increased in popularity in recent years, having been approved to protect against CSF leakage during cranial neurosurgery by the Food and Drug Agency (FDA) in 2005 [3]. However, to date there are no controlled trials or studies to support any particular method of repair for CSF leakage. We wished to analyse leak rates with different methods of dural sealant including DuraSeal**®**, using a large cohort within our institution.

**Patients and Methods**

A retrospective analysis was performed on prospectively collected data from consecutive patients undergoing endonasal transsphenoidal surgery at a large tertiary referral centre (Oxford, UK) over 48 months from January 2007 to December 2010 and for up to four years of subsequent follow-up. Endoscopic endonasal procedures were undertaken, occasionally augmented by image guidance from Medtronic (Watford, UK) or BrainlabAG (Feldkirchen, Germany) neuronavigation equipment utilizing CT imaging co-registered to the MRI.

Surgical indications included the presence of neurological symptoms or signs related to the tumour mass at presentation including visual field deficits, a demonstrated trend of lesion growth or hormonal dysfunction. All patients were assessed by a multi-disciplinary team this included endocrinologists and neurosurgeons implementing proactive care. If patients were found to have a giant tumour (typically macroadenoma) or a tumour with large suprasellar extension, a lumbar drain was inserted at the time of surgery.

Neurological and endocrine examinations were performed six weeks before surgery, immediately before and after surgery and six weeks after surgery, then at six months after surgery, then at annual follow-up. Gadolinium enhanced T1-weighted MRI was performed preoperatively and regularly during follow-up according to departmental protocols.

Data from medical case notes, theatre operation notes, histopathology reports and other electronic sources were collected on presenting features, endocrine diagnoses, visual fields, operative procedure including whether the dura was breached and how the sella floor was sealed, post-operative course and complications. Ethical approval was obtained by local institutional review board regarding the clinical study of human subjects. Data analysis was performed on Microsoft Excel (Microsoft Corporation, USA) and IBM SPSS (IBM Corporation, USA).

**Results**

Patient characteristics

A total of 255 transsphenoidal operations were performed on 250 patients over 48 months: 115 (46%) were female and 135 (54%) were male. The median age at time of surgery was 52 years (range 14-83 years). The majority of patients were in their fourth to eighth decades with elderly presentations more commonly being male (figure 1). Patients were followed up clinically for at least four years after surgery. Figure 2 shows presenting symptoms and signs leading to surgery for the whole patient group. The majority (52%) had only visual (usually field) problems, followed by only endocrine abnormalities (37%). Only three patients (1%) presented as emergencies with true apoplexy. Figure 3 shows the endocrine presentation in the 131 patients who had an endocrine abnormality. Hypopoituitarism was most common in 34% of patients, followed by oligo/amenorrhoea in 33% and Cushing’s disease in 13%. Histopathology demonstrated adenoma in 189 patients (74%), other diagnoses including craniopharyngioma and Rathke’s cleft cysts (figure 4). Most adenomas were gonadotrophic (figure 5).

Dural breaches and cerebrospinal fluid leaks

Figure 6 shows the number of patients who had intra-operative dural breaches with subsequent CSF leak and those who had post-operative CSF leaks despite there being no obvious intra-operative dural breach. Post-operative CSF leaks were typically clinically suspected through symptoms of clear-fluid rhinorrhea, or a salty tasting post-nasal drip. 5 patients (2% overall) required formal repair (figure 7), of which two (40%) had previously received revision transsphenoidal surgeries for recurrence. Table 1 shows subgroups with CSF leak by aetiology.

Numerous permutations of abdominal fat, DuraSeal®, Tisseel (Baxter Immuno, Vienna, Austria) and Spongostan™ (Ferrosan Medical Devices A/S, Søborg, Denmark) were used to seal the sella floor in these surgeries, as illustrated in figure 8. There was no significant difference between those patients who had CSF leaks and those who did not in terms of whether DuraSeal**®** or Tisseel were used or not. There were 3 CSF leaks in 70 patients not receiving DuraSeal**®** (4.3%) and 10 CSF leaks in 180 patients with Duraseal (5.6%), p=1.000 (Fisher’s Exact Test). There were 11 CSF leaks out of 234 patients without Tisseel (4.7%) and 2 CSF leaks out of 16 patients with Tisseel (12.5%), p=0.198 (Fisher’s exact test). Similarly, although the proportion of patients with CSF leaks was lower if a lumbar drain was inserted at time of transsphenoidal surgery (1 out of 53 with lumbar drains (1.9%) versus 12 out of 184 (6.1%) without), the results were not statistically significant (p=0.310, Fisher’s exact test).

**Discussion**

CSF rhinorrhea is the most commonly reported complication following transsphenoidal surgery [13] and is a significant risk-factor for meningitis [7] and tension pneumocephalus [14]. Reported rates of CSF leakage with transsphenoidal surgery vary widely in the literature, with previous estimates ranging from 0.5 – 15%. However, our literature search (with studies over a similar timeframe to our own data collection) revealed rates of 13 – 32.7% [2, 13, 15-20] (Table 2), with comparable results from our institution. A recent meta analysis (up to February 2016) including 950 patients undergoing endoscopic resection revealed intraoperative CSF leakage rates of 21.6% [21]. CSF leakage is usually owing to disruption of the diaphragm sellae and may be identified intraoperatively, thus having implications for duration of surgery and increased length of stay. Prior to the advent of endo-nasal endoscopic approaches to the sella, septal bone & cartilage could be used to repair leaks [22]. This method is adapted endoscopically to nasoseptal flap repair and different strategies have been developed to deal with CSF leaks.

Method of dural closure has multiple implications to the patient and institution. These include the use of further surgical operations to perform abdominal fat grafts, lumbar drain insertion, cost of the mechanism of obtaining an adequate dural seal and prolonged length of stay. An abdominal fat graft involves a surgical incision into the abdomen and introduces a material into the sella that is not readily absorbed. This may cause complications at the abdominal incision [20] and also cranially through mass-effect. Fat grafts also make the interpretation of post-operative MRI imaging difficult, by introducing a non-enhancing iso-intense substance into the sella [23]. Fibrin tissue sealants (such as Tisseel) may not be desirable for use, owing to their animal or human derivatives. This may theoretically introduce a risk or virus transmission, or the use of animal derivatives may be against patient wishes [24].

DuraSeal**®** may be advantageous in its properties of being a completely synthetic material and also its property of being reabsorbed [24]. These factors that may have led to its popularisation in preventing CSF leaks in both cranial and spinal procedures. Polyethylene glycol sealant (DuraSeal**®**) has been approved by the Food and Drug Administration (FDA) since 2005, to protect against CSF leakage following cranial surgery. DuraSeal**®** consists of two solutions, which when mixed cross-link to form an absorbable hydrogel. This hydrogel liquefies over 4-8 weeks, being absorbed and cleared by the kidneys [25].

Lumbar drain insertion peri-operatively is accepted as a method for reducing the rate of CSF leakage following transsphenoidal surgery. The drain is thought to reduce intracranial pressure, preventing CSF fistulae and hastening healing of the sellar floor [22]. However, like most interventions in surgery, this too poses risks. These include nerve root irritation or damage, infection at the insertion site or, more concerning, a risk of meningitis, pneumocephalus or brain herniation [26]. They also require increased nursing intensity and specialist knowledge of the care of lumbar drains. In our study we used lumbar drains at the time of surgery for giant tumours (to aid visualisation, by pulling the diaphragma and tumour tissue into the field of view) and in tumours with large suprasellar extension, for which it can be uncertain as to whether there is an intra-operative dural breach. Lumbar drainage is also an important post-operative treatment strategy, when CSF leakage is suspected. However, there have been no randomized studies to fully assess the role of lumbar drainage in transsphenoidal surgery, leading to debate regarding their usage.

This study retrospectively analysed the CSF leakage rate associated with use of DuraSeal**®**. Through our analysis of a consecutive cohort, we were also able to evaluate the effect of lumbar drain usage on CSF leaks. Interestingly, there was not a statistically significant difference in the prevention of CSF leaks when a lumbar drain was inserted. An article by Mehta and Oldfield [27] investigated the role of lumbar drainage in transphenoidal surgery and concluded that they should be used, removing the need for sellar repair and reducing the rate of intraoperative CSF leak. We did not draw the same conclusion, in our study that also retrospectively analysed a consecutive cohort of lumbar drainage patients, in a similar number of patients (53 versus 44 by Mehta). We used lumbar drainage in patients with giant tumour or suprasellar expansion, the majority of Mehta and colleagues patients also had suprasellar expansion (88%). Mehta’s paper demonstrated the decreased incidence of intraoperative CSF leaks, but did not have a significant effect on the rate of post-operative leak. We feel that further investigation needs to occur, before advocating a potentially risky peri-operative procedure, when the rates of important post-operative leakage are not improved. This again supports the need for a randomized-controlled study into the role of peri-operative lumbar drainage.

The use of DuraSeal**®** in this patient population was also not shown to have a significant effect on incidence of CSF leakage. Our rate of CSF leakage was comparable to other institutions. This raises cost implications regarding intraoperative DuraSeal**®** closure, as there may be other methods (or combinations of such) that would provide a statistically significant effect on the rate of post-operative CSF leakage. A 2013 article by Jalessi et al [28] analysing 240 cases had very low post-operative CSF leak outcomes (0.8%), despite higher rates of intraoperative CSF leaks (44%). The authors advocated a sellar reconstruction algorithm using a combination of methods, depending on the stage of CSF leak recognised. This again supports the need for further studies.

The series in table 2 used a variety of reconstruction techniques to repair or prevent CSF leaks. Many of these used the well-known method of graded-repair of leaks as described in Laws & Lanzino’s book [29] involving collagen or gelatin sponge plus fibrin glue or a titanium mesh buttress. These methods have not been demonstrated to have a significant effect on overall incidence CSF leaks, but may cause difficulties with MRI interpretation in the post-operative follow-up period. Wang et al [15] did use DuraSeal® in their closure method. Like our study, they too did not use lumbar drains for low-grade leaks. They found similar rates of low-grade intraoperative leaks (29% versus 34%) and post operative leak rates, following repair (2/74 versus 4/85). Both of these studies compare purely synthetic repairs of the sellar floor, however neither demonstrate statistically significant reductions in leaks.

We recognise the limitations of this study. It is a retrospective study within a single centre with selection and recall bias, particularly in the usage of lumbar drains. It does not shoe a significant learning curve in an already experienced pituitary surgeon. A variety of dural closure and sealant techniques were implemented based upon single surgeon preference, leading to confounding of the effect of just one method. However, as this and other studies have shown, lumbar drains and DuraSeal**®** have significant cost and complication implications. Owing to this, we feel that a randomized-controlled trial is indicated to further clarify the best method of dural closure, in an otherwise low-risk procedure, although we recognize that it would be challenging to implement. We continue to advocate the use of careful pre-operative planning and patient selection, in transsphenoidal surgery.

**Disclosure**

The authors received no external sources of support to undertake this investigation. The authors have no conflicts of interest to declare.

**Acknowledgments**

EP and SC conceived the study. CG and EP wrote the manuscript. EP and VA collated and analysed the data. SC edited the manuscript and is its guarantor. The authors report no conflicts of interest.

# **Tables**

# Table 1: Subgroups of patients who had CSF leaks expressed as a proportion (percentage) of the total number of patients in that group.

|  |  |  |
| --- | --- | --- |
| Aetiology | CSF leak / total | % |
| Rathke’s cleft cyst or craniopharyngioma | 5 / 13 | 39 |
| Revision surgery | 5 / 34 | 15 |
| Adenoma (all types) | 5 / 189 | 3 |
| Corticotroph adenoma (Cushing’s disease) | 2 / 23 | 9 |

Table 2: Summary of large studies of CSF leaks after transsphenoidal pituitary surgery.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Area | Authors | N | Intra-operative  leaks | Formal repair/  lumbar drain | Formal  repair | Approach |
| Oregon | Shiley et al 2003[13] | 217 | 32.7% | 6.0% | 4.6% | Not stated |
| Naples | Cappabianca et al 2004[20] | 242 | 14.5% | 3.7% | 0.8% | Endoscopic |
| Sao Paulo | de Paula Santos et al 2007[19] | 91 | Not stated | 8.4% | 3.3% | Endoscopic |
| California | Fatemi et al 2008[2] | 881 | 13.0% | 2.2% | 1.6% | Mostly microscopic |
| Buenos Aires | Rabadan et al 2009[17] | 63 | 31.7% | 1.5% | 0.0% | Mostly endoscopic |
| Tokyo | Nishioka et al 2009[16] | 324 | 26.2% | 2.2% | 0.6% | Mostly microscopic |
| Manchester | Wang et al 2010[15] | 255 | 29.0% | 2.7% | 1.4% | Endoscopic |
| Stoke-on-Trent | Hobbs et al 2011[18] | 120 | 23.0% | 0.0% | 0.0% | Endoscopic |

**Figures**

Figure 1: Patient demographics

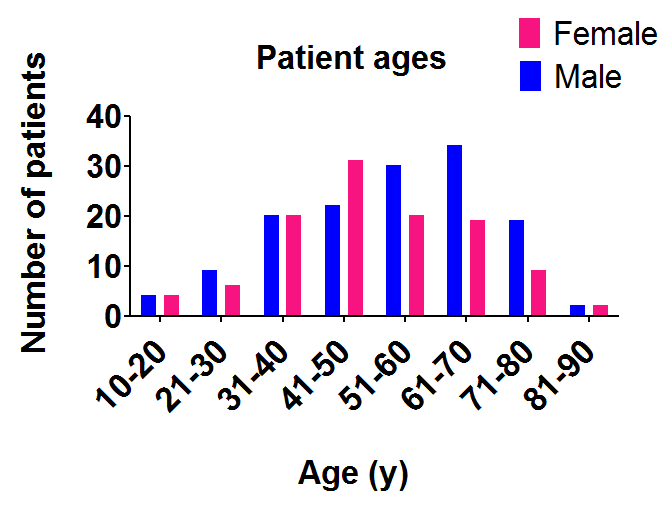


Figure 2: Pie chart showing percentage of patients presenting with different indications for transsphenoidal adenohypophysectomy

Figure 3: Pie chart showing percentage of patients with different manifestations of endocrine presentation for the 131 patients with endocrine symptoms and signs.

Figure 4: Pie chart showing histopathological diagnoses

Figure 5: Graph showing frequency of different adonema subtypes diagnosed

Figure 6: Number of patients with post-operative CSF leaks in groups with and without intra-operative dural breach.

Figure 7: Number of patients requiring formal repair in groups with and without intra-operative dural breach.

Figure 8: Different sealing methods and materials used.

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