ORIGINAL ARTICLE

Use of Tissue Glues in Endoscopic Pituitary Surgery: A Cost Comparison

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ABSTRACT: ***Background:*** Post-operative cerebrospinal fluid (CSF) leaks are a common complication of endoscopic pituitary surgery and account for a significant proportion of hospital costs associated with this procedure. Tisseel® is a tissue glue commonly used as an adjunct in dural repair but is not optimal for this purpose. DuraSeal® has several properties advantageous for dural repair but is not widely accepted in Canada partly due to its increased cost. ***Objective:*** A cost analysis of DuraSeal® versus Tisseel® in endoscopic pituitary surgery. ***Methods:*** A cost analysis was performed based on typical endoscopic pituitary surgery cases performed at our tertiary care institution. Operating room, hospital admission, and surgical sealant costs were obtained directly while estimates of patient recovery time and post-operative CSF leak rates were based on consensus values reported in the literature. Outcomes were reported for various possible clinical scenarios of sealant use. ***Results:*** In a model where surgical sealant is employed only in high-risk cases, use of DuraSeal® allows for a yearly cost savings of at least $4486.72. If surgical sealant is used in all cases, regular use of DuraSeal® versus Tisseel® either marginally reduces yearly costs or increases them by a maximum of $7619.25, depending on the case volume and estimated post-operative CSF leak rate. ***Conclusion:*** In most clinical scenarios, use of DuraSeal® in endoscopic pituitary surgery may reduce overall yearly hospital costs compared to Tisseel®.

RÉSUMÉ: Comparaison du coût d'utilisation de colles à tissus dans la chirurgie pituitaire endoscopique. ***Contexte :*** Les fuites postchirurgicales de liquide céphalo-rachidien sont une complication fréquente de la chirurgie pituitaire endoscopique et génèrent une portion importante des coûts hospitaliers associés à cette intervention. Tisseel est une colle à tissus qui est utilisée fréquemment comme traitement d'appoint pour la réparation durale, mais ne constitue pas une solution optimale dans cette situation. La colle DuraSeal possède plusieurs propriétés avantageuse pour la réparation durale, mais elle n'est pas largement utilisée au Canada, en partie parce que son coût est plus élevé. ***Objectif :*** Le but de l'étude était de comparer le coût de la colle DuraSeal et de la colle Tisseel lors de la chirurgie pituitaire endoscopique. ***Méthodes :*** Une analyse des coûts a été effectuée basée sur des cas de chirurgie pituitaire endoscopique opérés dans notre institution de soins tertiaires. Nous avons déterminé directement les coûts pour la salle d'opération, l'hospitalisation et le scellant chirurgical et nous avons estimé le temps de guérison et le taux de fuites postopératoires de LCR à partir de valeurs consensus rapportées dans la littérature. Nous rapportons les résultats pour différents scénarios cliniques possibles d'utilisation du scellant. ***Résultats :*** Dans un modèle où le scellent chirurgical est utilisé uniquement chez les cas à haut risque, l'utilisation du DuraSeal permet d'épargner au moins $4486,72. Si le scellent chirurgical est utilisé chez tous les cas, l'utilisation régulière de DuraSeal plutôt que de Tisseel réduit peu les coûts annuels ou les augmente de $7619,25 au maximum, selon le volume de cas et le taux estimé de fuites postopératoires de LCR. ***Conclusion :*** Dans la plupart des scénarios cliniques, l'utilisation de DuraSeal pour la chirurgie pituitaire endoscopique peut réduire les coûts hospitaliers annuels totaux par rapport au Tisseel.

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Endoscopic pituitary surgery is an evolving field in which safety and efficacy are continually being improved[1]. A particular focus of research efforts has been the management and prevention of post-operative cerebrospinal fluid (CSF) leaks. While the majority of sellar and parasellar lesions can be excised without violating the subarachnoid space, the tenuous anatomy in this region still puts the arachnoid membrane at risk for disruption, and hence post-operative CSF leaks are one of the most common complications of endoscopic pituitary surgery[2,3]. Post-operative CSF leaks can predispose patients to subsequent severe complications such as meningitis and tension pneumo-cephalus and often require additional surgery and longer hospitalization[3,4]. A review of the literature suggests an overall post-operative CSF leak incidence rate of 0.3-15%, with the majority of authors reporting an incidence between 0.5% and 6%[4,5].

Post-operative CSF leaks can be prevented with careful surgical technique and proper sealing of the dural defect created during surgery. The latter, however, is a point of controversy, as various authors have described different methods and materials for dural repair[2-12]. One commonality amongst almost all

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techniques is the deployment of some form of tissue glue to form a final sealant layer buttressing the dural repair site. The most commonly used sealant glues are Tisseel® (Baxter Healthcare Corporation, Deerfield, IL) and DuraSeal® (Covidien, Mansfield, MA)[13-17]. Tisseel® is a two-component fibrin glue made from pooled human plasma[18]. Its off-label use in dural repair has been described in several reports[18-23] but it is recognized to be sub-optimal in this regard because it is designed for use on a dry surface[18]. Tisseel® mimics the final steps of the blood coagulation cascade. Upon mixing of its fibrinogen and thrombin components, a rubber-like mass forms which adheres to wound surfaces and achieves hemostasis and sealing or gluing of tissues, while additional aprotinin prevents premature degradation of the fibrin clot[18]. In contrast, DuraSeal® (Confluent Surgical, Inc., Waltham, MA) is a synthetic polyethylene glycol (PEG)-based hydrogel recently approved for watertight closure of the dura in cranial surgery[24]. It is absorbable, self-polymerizes within seconds of application, and is specifically designed for use on wet surfaces[14-17,24]. Importantly, reports from the scientific literature have suggested that DuraSeal® use reduces the rate of post-operative CSF leaks in a variety of open neurosurgical procedures[13,25].

Despite its technical advantages and theoretical potential for reducing the overall rate of post-operative CSF leaks in endoscopic pituitary surgery, reports on the usage of DuraSeal® in this field are absent from the scientific literature. One barrier to acceptance of DuraSeal® by Canadian skull base surgeons may be its relatively increased cost per product. Therefore, the purpose of this study was to conduct an overall cost comparison of DuraSeal® versus Tisseel® in managing post-operative CSF leaks following endoscopic pituitary surgery.

Methods

This study was approved by the Ethics and Research Board at the University of Western Ontario. Models for cost analyses were based on typical cases operated on by the study's senior authors (B.W.R. and N.D.), working out of London Health Sciences Centre (LHSC), a tertiary referral centre in London, Ontario, Canada. The authors perform approximately 40 endoscopic pituitary surgeries at LHSC yearly.

The authors' approach for a large intra-operative CSF leak is to use a standard inlay repair using thigh fat and fascia. A vascularized septal flap is used in most cases as a final layer, after which the composite repair site is covered in the tissue glue of choice to form a final watertight seal. Post-operative CSF leaks are repaired in much the same way after site re-exploration confirms the location of the leak.

Costs used for calculations (Table 1) were based on 2009 prices and were obtained from LHSC Case Costing and directly from the suppliers of DuraSeal® and Tisseel®. All values are in Canadian dollars. DuraSeal® and Tisseel® costs include applicators and any other materials required for sealant use. The factors used to calculate medical costs were days of hospital stay, costs of surgical repair of CSF leaks, and costs of surgical sealant use. Average per diem costs for hospital stay on a neurosurgical ward, where all post-operative patients are admitted to, include the full cost of nursing labour, meals, and materials. Operating room costs represent the average hourly costs for nursing labour, materials, and surgical equipment required for endoscopic pituitary surgery procedures. Assumptions used to estimate costs of post-operative CSF leaks were based on consensus values

Table 1: Cost elements included in models for comparison purposes

Item	Cost ($)
DuraSeal®	
1 unit (5mL) DuraSeal®	510.00
Endoscopic applicator	175.00
Total per surgery	685.00
Tisseel®	
2 units (2mL) Tisseel®	304.00
Metal applicator	40.00
Trimmable plastic catheter	40.00
Total per surgery	384.00
Operating room for CSF leak repair	
Full cost per hour	616.80
Total per surgery	1233.60
Hospital stay (neurosurgery ward)	
Average daily cost	894.53
Total per CSF leak	4472.65

Table 2: Systematic review of literature for post-operative CSF leak rates in transsphenoidal surgery

Study	Study design	Patients	Cases	CSF leak rate (%)
Shiley et al. (2003)	Retrospective chart review	202	217	6
Seiler & Mariani (2000)	Retrospective chart review	376	376	0.53
Ciric et al. (1997)	Neurosurgeon questionnaire	>958*	>958*	3.9
Black et al. (1987)	Retrospective chart review	255	255	2.7
Koltai et al. (1994)	Retrospective chart review	111	111	4.5
Jho (2001)	Retrospective chart review	160	160	6
Han et al. (2008)	Retrospective chart review	592	592	4.4
Sudhakar et al. (2004)	Retrospective chart review	108	126	13
Sanai et al. (2007)	Prospective case series	64	64	0
Nishioka et al. (2009)	Retrospective chart review	324	324	2.2
Senior et al. (2008)	Retrospective chart review	176	193	10.3
Tamasauskas et al. (2008)	Retrospective chart review	313	356	0.84
Sherman et al. (2008)	Prospective alternate case trial	60	60	5
Charalampaki et al. (2006)	Prospective case series	9	9	11
Cappabianca et al. (2006)	Prospective case series	15	15	6.7
Rudnik et al. (2005)	Prospective case series	70	70	0
Sonnenburg et al. (2003)	Retrospective chart review	45	45	2.2
Kelly et al. (2001)	Prospective case series	62	62	0
Chee et al. (2001)	Retrospective chart review	61	61	0
Citardi et al. (2000)	Prospective case series	13	13	7.7
Kelley et al. (1999)	Prospective case series	7	7	0

*958 neurosurgeons were grouped by number of procedures performed (<200, 200-500, >500), precise case volumes for each surgeon were not reported.

reported in the literature and on average values based on the authors' surgical experience. Surgeon and anaesthetic fees were intentionally omitted from the cost analysis because these are variable across different Canadian institutions, which may employ fee-for-service or salary payment methods.

Several assumptions were made in order to calculate the costs. In our models, all post-operative CSF leaks were treated surgically by re-exploration of the surgical site. The average duration of a post-operative CSF leak repair surgery was two hours (local data) and the same sealant (Tisseel® or DuraSeal®) was used for leak repair as was used in the initial surgery. On average, 1 unit (5mL) of DuraSeal® or 2 units (2mL) of Tisseel® were used in each surgery (local data). Patients with post-operative CSF leaks require on average five additional days of hospitalization compared to patients who had uncomplicated surgery (local data).

To determine an appropriate baseline post-operative CSF leak rate for our model, we performed a systematic review of the literature. The PubMed database was queried using the search terms "transsphenoidal surgery" and "CSF leak". The inclusion criteria were reports written in English for studies that involved any transsphenoidal procedure on human patients for any indication. Any type of study design was accepted if post-operative CSF leak rates were reported as a primary or secondary outcome. Technical notes, case reports, and studies with pediatric patients were excluded. Fifty-seven abstracts were reviewed and 21 studies met the inclusion criteria[2,4,26-44] (Table 2). Post-operative CSF leak rates in these studies ranged from 0% to 13%. The majority of studies reported rates of 6% or less. Five studies reported rates higher than 6%, however three of these studies had 15 or fewer patients. Based on these results, we felt that a post-operative CSF leak rate of 6% was a conservative estimate that would reflect the upper end of incidence rates reported by most authors.

Cost comparisons were performed based on models where 30, 50, or 100 endoscopic pituitary surgeries are performed yearly. Cost analyses were calculated by subtracting the extra cost of DuraSeal® from the costs of additional surgery and hospitalization associated with post-operative CSF leaks (Table 1). Use of DuraSeal® in place of Tisseel® is purported to reduce the rate of post-operative CSF leaks, thus we assumed an overall reduction from 6% to either 1% or 2.2%. The 1% rate is meant to represent an ideal "best-case" scenario while the 2.2% rate is extrapolated from evidence found in the literature[4,13].

Results

Two scenarios for usage of sealants were included in the cost analysis in order to account for varying surgical practices (Table 3). In the first scenario, it was assumed that Tisseel® is used in all endoscopic skull base surgeries and would simply be replaced by DuraSeal®. In a best-case scenario where one were to assume a reduction in the post-operative CSF leak rate from 6% to 1% with DuraSeal®, total yearly hospital cost savings would amount to $15.07, $25.12, or $50.25 for case volumes of 30, 50, or 100 patients per year, respectively (Table 3). If one were to extrapolate from evidence found in the literature, which suggests a 63% reduction in post-operative CSF leaks from DuraSeal® use[13], a new 2.2% leak rate would be possible. Given a reduction of the leak rate to 2.2% using DuraSeal® in this scenario, one would expect yearly costs to increase by $2285.78, $3809.63, or $7619.25 for case volumes of 30, 50, or 100 patients, respectively (Table 3).

Table 3: Cost analysis results for DuraSeal® use in various clinical scenarios

Scenario	Cost savings/year ($)		
	30 cases	50 cases	100 cases
Prophylactic DuraSeal® use in all surgeries			
1% post-operative CSF leak rate	15.07	25.12	50.25
2.2% post-operative CSF leak rate	-2285.78*	-3809.63*	-7619.25*
Prophylactic DuraSeal® use only in high-risk surgeries			
1% post-operative CSF leak rate	6787.57	11,312.62	22,625.25
2.2% post-operative CSF leak rate	4486.72	7477.87	14,955.75

*Negative values indicate a total increase in costs with DuraSeal® use.

In the second scenario, it was assumed that Tisseel® is only used in 25% of endoscopic pituitary surgery cases, specifically those deemed to be at high risk for a post-operative CSF leak due to an intra-operative CSF leak or another risk factor. DuraSeal® would replace Tisseel® in these high-risk cases. Assuming that DuraSeal® use would reduce the post-operative CSF leak rate to 1%, yearly cost savings in this scenario would be $6787.57, $11,312.62, or $22,625.25 for case volumes of 30, 50, or 100 patients, respectively (Table 3). Similarly, if we assumed that DuraSeal® were to reduce the leak rate to 2.2%, there would be yearly cost savings of $4486.72 for 30 patients, $7477.87 for 50 patients, and $14,955.75 for 100 patients (Table 3).

Discussion

Post-operative CSF leaks are one of the most common complications of endoscopic pituitary surgery[2,3] and have a reported incidence of 0.3-15%[4,5]. To address this problem, a number of different surgical sealant products have been developed which facilitate and enhance dural repair. Among these, fibrin glues such as Tisseel® are commonly used but are sub-optimal because they are designed for use on a dry tissue surface[18] and because they carry risks of infection and anaphylaxis[13-17]. DuraSeal® is a synthetic PEG-based hydrogel which has recently been approved for cranial surgery and has many features which make it an effective dural sealant[14-17,24]. Despite its potential benefits, however, DuraSeal's® higher cost in relation to other surgical sealants represent a barrier to acceptance by Canadian skull base surgeons. The goal of our study was thus to perform a cost analysis that compares the cost of DuraSeal® use to that of Tisseel® in endoscopic pituitary surgery.

The use of fibrin glues for dural repair has been documented extensively in the literature, with Tisseel® the most commonly used substance[19-23,45]. Despite reports of its successful use in dural repair, Tisseel® is sub-optimal for this purpose. Individual

components of the fibrin glue are stored as a freeze-dried powder that must be reconstituted or a frozen solution that requires external heating sources for thawing, both of which take operative time and nursing resource to do[18]. Furthermore, Tisseel® is recommended for use on dry tissue surfaces[18], which can be difficult to achieve in the context of a CSF leak; in fact, its common application in CSF leak repair is actually an off-label use of the substance. Fibrin glue is made from pooled human plasma and thus carries a theoretical risk of transmission of blood-borne viruses and prions[18,46], although Tisseel® is reported to have an excellent safety profile with a negligible disease transmission risk[46]. Anaphylaxis to Tisseel® and other fibrin glues has been reported[18,47,48]. The aprotinin component in Tisseel® may also delay wound healing in CSF leak repairs[49].

DuraSeal® possesses several properties which make it useful in CSF leak repair. The hydrogel requires no preparation time, self-polymerizes within seconds of application, is stored at room temperature, contains a translucent blue dye for easy visualization, is absorbed and renally excreted within several weeks of application, and is intended for use on wet surfaces[24,50]. The synthetic nature of this sealant eliminates the risk of disease transmission associated with biologically-derived tissue glues and provides an acceptable alternative for patients with religious or other objections against the use of products derived from human blood.

A review of the literature shows DuraSeal® to be safe and effective and a number of authors have described its use in dural repairs[12,51,52]. A prospective, non-randomized, single-center preliminary clinical trial for DuraSeal® was conducted on 46 patients scheduled for elective cranial or intradural spinal surgery[17]. After application of DuraSeal® there were no spontaneous CSF leaks or CSF leaks after a Valsalva maneuver. Follow-up after three months revealed that only 2 of 46 patients (4.3%) had experienced a post-operative CSF leak and no adverse outcomes were reported. Another clinical trial involved 111 patients who underwent elective cranial surgery where DuraSeal® was used in dural repair[16]. In this prospective, multicentre, single-arm trial DuraSeal® was again found to be 100% effective in achieving watertight dural closure after a Valsalva maneuver. There were no signs of post-operative CSF leaks in 106 (95.5%) of the patients after three months and no sealant-related adverse events. A retrospective cohort study of posterior fossa surgery patients matched 100 subjects in whom DuraSeal® was employed for dural repair with an equal number of subjects treated with fibrin glue[25]. A statistically significant difference in post-operative CSF leaks was found between the groups, with DuraSeal® patients experiencing a 2% rate compared to 10% for the fibrin glue group.

The results of our cost analysis suggest that DuraSeal® may be cost-effective for endoscopic pituitary surgery in certain situations. Assuming a reduction in post-operative CSF leak rates from 6% to 1% with DuraSeal® use, centres where Tisseel® is employed in all surgeries could expect a yearly hospital cost savings of $15.07, $25.12, or $50.25 for yearly case volumes of 30, 50, or 100 patients, respectively. Using a more conservative 2.2% leak rate in this scenario, DuraSeal® use could increase yearly costs by $2285.78, $3809.63, or $7619.25 for case volumes of 30, 50, or 100 patients, respectively. In centres where Tisseel® is currently used in only 25% of cases, those deemed to be high-risk for post-operative CSF leaks, replacing Tisseel® with DuraSeal® could lead to yearly savings of $6787.57, $11,312.62, or $22,625.25 for case volumes of 30, 50, or 100 patients, respectively, if one assumes a post-operative CSF leak rate reduction from 6% to 1%. Assuming a reduction to 2.2% in this scenario, DuraSeal® use could give a yearly cost savings of $4486.72 for 30 patients, $7477.87 for 50 patients, or $14,955.75 for 100 patients.

Our findings are consistent with those of a recent retrospective study which examined the costs associated with CSF leaks in 412 consecutive elective neurosurgical procedures in a Dutch tertiary care hospital[13]. The authors found that post-operative CSF leaks in 44 (10.7%) patients accounted for 21.7% of the total costs of all 412 procedures. Comparing these results to those from another study at the same institution where a 4% post-operative CSF leak rate had been achieved with DuraSeal®, the authors extrapolated that prophylactic DuraSeal® use in the series of 412 patients would have allowed for a total cost savings of €226,600.

Our study design was intended to be as externally valid as possible. By employing multiple scenarios in the cost analysis, we hoped to account for the varying practices of different Canadian surgical centres. A number of assumptions were also made to simplify calculations, but these may be a source of bias. In one scenario, we state that fibrin glue or hydrogel would be used only in high-risk cases, which we estimated to occur in 25% of surgeries. A number of factors are known to predispose patients to post-operative CSF leaks, including intra-operative CSF leak, non-adenomatous pituitary disease, radiotherapy, and revision surgery[4,53]. The most important of these risk factors is thought to be intra-operative CSF leak, which occurs in 18-53.2% of endoscopic skull base surgeries[3]. Our estimate of the rate of high-risk cases was meant to reflect these figures. Estimates of reasonably achievable reductions in post-operative CSF leak rates with DuraSeal® use were based on data reported in the literature. A study of posterior fossa surgery patients compared 100 cases in which DuraSeal® was employed to a similar cohort of 100 patients using fibrin glue[25]. The DuraSeal® group experienced a 2% post-operative CSF leak rate compared to 10% in the fibrin glue group, a reduction of 80%. A more conservative estimate was derived from a study in which DuraSeal® was estimated to decrease the overall post-operative CSF leak rate across multiple neurosurgical procedures by 63%[13]. Applying this reported reduction to an initial 6.0% leak rate, we extrapolated that a 2.2% rate could be achieved with DuraSeal®. The 1% rate with DuraSeal® that we assumed in one of our cost estimates can be considered as a "best-case" scenario. This scenario approximates what would be expected based on the results of another study[25] in which DuraSeal® was found to decrease the post-operative CSF leak rate in posterior fossa surgery by 80% over fibrin glues.

Our cost calculations are hypothetical estimates based on rational assumptions and data found in the literature. They represent an indirect measure of actual costs. Case loads and distribution of costs for materials, hospital admissions, and other items may vary among Canadian centres. Nevertheless, we have provided an objective description of costs associated with DuraSeal® and Tisseel® use in the context of endoscopic pituitary surgery and these can generally be extrapolated to

reflect the practices and costs at other centres. Importantly, we have not included the costs of physicians' fees, namely those of surgeons and anaesthetists. These were omitted to account for varying payment systems across Canadian hospitals, which include both salaried and fee-for-service remuneration. The inclusion of physicians' fees would likely alter the results of our analysis. Moreover, our analysis did not take into account costs of diagnostic procedures such as CT or MRI imaging or costs associated with secondary complications of CSF leaks, including antibiotics and prolonged hospitalization. As a result, our cost analysis is a conservative estimate and likely underestimates the cost savings associated with DuraSeal® use.

Several directions for future research exist. There as yet exists no prospective evidence of DuraSeal's® superiority over Tisseel® with respect to clinical benefits or cost-effectiveness. Thus, future research with DuraSeal® must involve head-to-head comparisons that include Tisseel® and other commonly used dural sealants, with no conflicting interest or industry support. Studies using animal models and *in vitro* systems as well as trials in humans would be effective for determining how these different sealants compare in the prevention of post-operative CSF leaks.

Conclusion

To our knowledge, our study is the first to assess the cost effectiveness of DuraSeal® specifically in the setting of endoscopic pituitary surgery. Our results suggest that the prophylactic use of DuraSeal® may be cost-effective due to a reduction in expenditures associated with post-operative CSF leaks.

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