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Risk factors and rates of delayed symptomatic hyponatremia after transsphenoidal surgery: a systematic review

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RISK FACTORS AND RATES OF DELAYED SYMPTOMATIC HYponatremia AFTER transspHENOIDAL SURGERY: A SYSTEMATIC REVIEW

by

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ABSTRACT

Background

Delayed symptomatic hyponatremia (DSH) is among the most common reasons for readmission following transsphenoidal surgery. Patients can present with a large range of symptoms, requiring immediate attention and prolonging hospital stay. In rare and severe cases, DSH can result in death. While various risk factors for DSH have been investigated, there is still a need for better understanding in order to identify patients who are at risk. Clinicians can then take preventative measures to improve patient outcomes.

A systematic review was performed to determine both predictors and rates of DSH after both endoscopic (eTSS) and microscopic transsphenoidal surgery (mTSS).

Methods

We conducted a systematic search through databases MEDLINE/PUBMED, MEBASE, and The Cochrane Library. Included studies were selected with the following criteria: (i) case series with at least 10 cases reported, (ii) adult patients who underwent eTSS or mTSS for pituitary adenomas, and (iii) reported occurrence of DSH (hyponatremia defined as blood sodium level <135 mEq/L) three days post-operatively. Data were analyzed using CMA V.3 Statistical Software (2014).
Results

We identified 10 case series that satisfied the inclusion criteria consisting of 2,947 patients with pituitary adenomas. The following were investigated as potential predictors of DSH: age, CSF leak, gender, and tumor size. Rates of DSH were found to be between 4 and 12 percent for both mTSS and eTSS.

Conclusions

Age, gender, tumor size, rate of blood sodium level decline between post-operative day (POD) 4 and 7, and Cushing’s disease are potential predictors of DSH. A better understanding of these predictors can help clinicians identify patients at risk for DSH so preventative measures can be taken to reduce the deleterious effects of hyponatremia after transsphenoidal surgery.
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ADH .................................................................Antidiuretic Hormone
ANP .................................................................Atrial Natriuretic Factor
BMI .................................................................Body Mass Index
BNP .................................................................Brain Natriuretic Factor
CSF .................................................................Cerebrospinal Fluid
CSWS .............................................................Cerebral Salt Wasting Syndrome
DSH .................................................................Delayed Symptomatic Hyponatremia
DI .................................................................Diabetes Insipidus
ETSS ...............................................................Endoscopic Transsphenoidal Surgery
MTSS .............................................................Microscopic Transsphenoidal Surgery
POD ...............................................................Post-operative Day
QOL ...............................................................Quality of Life
SIADH .........................................................Syndrome of Inappropriate Secretion of Antidiuretic Hormone
INTRODUCTION

Diagnoses of pituitary tumors have been significantly increasing over the last two decades as have the number of transsphenoidal surgery resections performed per year. Approximately 90% of these pituitary tumors are classified as adenomas. Pituitary adenoma prevalence has been estimated to be approximately 17%. The pituitary gland comprises of different types of cells, from which these tumors will originate and can cause the over-secretion of hormones resulting in the term “functioning tumors”. The adenomas which are non-hormone-producing are “non-functioning” tumors. Pituitary adenomas mostly grow slowly over time, but can cause significantly harmful symptoms. Typical examples of functioning tumor disorders include Cushing’s Disease, prolactinoma, acromegaly, and gigantism.

Transsphenoidal surgery is recognized as the gold standard for removing pituitary adenomas. While the majority of hyponatremic patients post-surgery are asymptomatic, severe and prolonged hyponatremia is associated with increased mortality. Though a safe and effective procedure, there are several complications that patients are at risk for. Hyponatremia is a known complication that often occurs in a delayed fashion. Patients suffering from delayed hyponatremia will typically experience symptoms between the fourth and seventh day post-operatively, which can be problematic as patients are often discharged by this time and are in their home. Given the severity of delayed symptomatic hyponatremia (DSH) and that it is among the most common causes for readmission within 30 days after transsphenoidal surgery, it is important to better
understand the predictors for this condition to best improve patient outcomes and quality of care.

**Historical Background of Transsphenoidal Surgery**

The origin of transsphenoidal surgery began with the sparked interest in the pituitary, resulting from a paper by Pierre Marie in 1886. In this paper, the author describes two patients with hypertrophic pituitary glands, which was hypothesized by Marie to be a part of the cause of acromegaly. However, the hyper-secreting tumors of the pituitary, which were responsible for acromegaly was not known until 1910. It was only a few years after Marie’s paper when Richard Caton made the first effort to resect a pituitary tumor.

In Caton’s paper in 1893, he discusses a patient in her early thirties that was in significant pain, deaf in both ears, already had lost vision in her right eye, and had impaired vision in her left eye. The patient became very weak, vomiting frequently, and was at the final stages of acromegaly. It became clear to Caton that her life could not be prolonged. He then made the decision to perform surgery in an attempt to remove the tumor. However, this did not turn out to be possible and he decided to create an opening in the skull to relieve intracranial pressure for the patient. The patient’s pain subsided greatly and the remaining three months of her life were relatively comfortable.

Over the next several years there were further attempts in transcranial approaches. Sir Victor Horsley, who had originally recommended the temporal approach taken by Caton, performed 10 operations from 1904 to 1906, which resulted in a mortality rate of
In 1905, it was Fedor Krause who operated using a frontal transcranial approach which laid the groundwork for future variations of the approach by several neurosurgeons: Dandy, Huer, Frazier, and Cushing. Given the high reported mortality rates of transcranial approaches, other routes to the sella turcica, in which the pituitary gland resides, were investigated.

David Giordano, an Italian neurosurgeon, practiced a transglabellar nasal technique to reach the sellar region on cadavers. The procedure consisted of a nasal-glabellar degloving, then ethmoid bone removal, allowing an open sphenoid sinus. Parts of the sella turcica could then be removed. It was because of Giordano’s hard work that Hermann Schloffer was able to perform the first transsphenoidal surgery in 1907.

Schloffer performed the surgery in three stages. First, there was an opening made in the left nasolabial fold and subsequently, the nasal conchae and septum were excised. The next major step was removing the sphenoidal rostrum and vomer. Finally, after removal of the mucosa, an opening was created in the sella turcica. The patient Schloffer operated on, felt significant improvements in his symptoms. He did, however, suffer a few neurological symptoms as minor complications. Although the patient unfortunately died approximately two months after the surgery, Schloffer viewed the operation as a success for the symptomatic relief that it provided. The surgery sparked further interest and several surgeons improved the technique.

In Cushing (1909), the author treated a 38-year-old patient suffering from acromegaly using Schloffer’s approach for the transsphenoidal surgery. The patient, over the course of several years developed photophobia, headaches, enlarged tongue, feet,
hands, and facial features, in addition to severe pain that was so frequent it became constant. The stark contrast of the patient’s condition before and after the onset of symptoms can be seen in Figure 1. The surgery was successful and many of the patient’s severe symptoms lessened or subsided. In his report, Cushing noted that while he foresaw transsphenoidal surgery to become widely accepted, complications such as meningitis would serve as a barrier.\textsuperscript{19} Cushing continued to work on this operation and in 1914 modified his method by using the sublabial approach by Albert Halstead and a submucosal septal resection by Theodore Kocher.\textsuperscript{16,20} For the most part, his modification is the same that is used by neurosurgeons today.\textsuperscript{52}
Figure 1: Patient on whom Cushing performed transsphenoidal surgery. A) The patient years before the onset of symptoms. B) The patient’s condition on admission. (Taken and modified from Cushing et. al 1909).19

Although Cushing switched back to transcranial procedures, which became increasingly popular in the United States, Norman Dott who studied under Cushing, kept the practice alive. He even developed a lighted speculum for improved visualization for transsphenoidal surgery.44 Gerard Guiot, learning the surgical approach from Dott, further improved transsphenoidal surgery by using radiofluoroscopic guidance to better
view the trajectory of the operation.\textsuperscript{32} It is due to both Dott and Guiot’s success that interest in transsphenoidal surgery became re-ignited.\textsuperscript{68}

\textbf{The Microscope and Endoscope}

The next major development came when Hardy in 1967 introduced the operating microscope, which dramatically impacted transsphenoidal surgery through improved illumination, magnification, and visualization.\textsuperscript{44} The use of a microscope significantly improved the transsphenoidal operation for pituitary-related surgeries.\textsuperscript{52} Microscopic transsphenoidal surgery (mTSS) became a well-established, safe, and effective procedure for pituitary lesions.\textsuperscript{35,58,66}

The use of an endoscope was first suggested for use in transsphenoidal surgery by Guiot in 1963,\textsuperscript{33} but did not gain popularity in neurosurgery until later, partly due to optical advancements, and was only used as a complement to the microscope in certain cases.\textsuperscript{9} However, in these endoscopic-assisted surgeries, it was reported that the use of the endoscope was time-saving and reduced trauma.\textsuperscript{26,63} In 1996, Carrau et. al, wrote a paper detailing their experience solely using an endoscope for the technique. The authors praised the endoscope, predicting that endoscopic transsphenoidal surgery (eTSS) would soon become the preferred method for pituitary surgery.

\textbf{Advantages and Disadvantages of mTSS and eTSS}

There are several disadvantages to using the microscope in the transsphenoidal procedure, which is a major reason for the quick acceptance of the endoscope.
Specifically, the microscope used in the operation is restricted by both the lens and the light source, affecting focus and constricting view. Another drawback of mTSS is the bayonet shape of instruments, which are used in order to avoid obstruction of the light from the microscope. With mTSS, there is a reported “tunnel vision” during the operation and limited maneuverability of surgical instruments. The limited operating view provided by the microscope can be seen in an example in Figure 2. With the limitation of line of site, it is difficult for surgeons to see around corners. There are also limited angles of approach in this transsphenoidal technique due to the nasal speculum and transsphenoidal retractor.

Figure 2: A comparison in views using an endoscope versus a microscope. The comparison in views shows the larger area for visualization with the endoscope compared with the microscope. (Taken from Gaillard 2014)
In addition to the limitations of the microscope, the success in using an endoscopic approach has recently lead to its increasing acceptance.\textsuperscript{44,48} The minimally invasive approach is also of appeal to patients.\textsuperscript{49} An advantage of the endoscope that has been reported is the improvement in visualization of the operating field.\textsuperscript{25,28} Specifically, it has been noted by several investigators that the panoramic view provided by the endoscope allows for a better view of structures surrounding the carotid arteries, clivus, and optic nerves.\textsuperscript{1,9,67} In a paper by Cavallo et. al (2007), the authors recount their experience using an endoscope and offer suggestions that may ease the transition from microscope to endoscope. A summary of several of the advantages and disadvantages of eTSS as noted by these researchers is in Table 1.

Table 1: A Summary of advantages and disadvantages in using an endoscope in transsphenoidal surgery. Listed advantages and disadvantages from surgeons with experience using a microscope and endoscope. (Taken from Cavallo et. al 2007).\textsuperscript{13}

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wider view of the surgical field from different orientations</td>
<td>Different hand-eye coordination with respect to the microscope</td>
</tr>
<tr>
<td>Closer look “inside” the anatomy</td>
<td>Minimal spatial distortion</td>
</tr>
<tr>
<td>View in hidden corners</td>
<td>2-Dimensional vision</td>
</tr>
<tr>
<td>Angled view using angled lenses</td>
<td>It is part of a clock-gear mechanism</td>
</tr>
</tbody>
</table>

Some of the listed advantages are thought to potentially help minimize disastrous injuries and reduce complications. The same group had previously reported that using the endoscope resulted in fewer complications post-operatively.\textsuperscript{10} In another study by Jho
and Carrau (1997), the authors report their early experience in eTSS with 50 patients and note visualization advantages in the suprasellar region.\textsuperscript{43} With this endoscopic approach, there is sometimes less pain after surgery, nasal packing is usually not necessary, and there are fewer nasal septal perforations.\textsuperscript{49,11,43}

However, with the use of a “pure” endoscopic approach there is a significant learning curve, which has been reported by many.\textsuperscript{7,11,43,49,28} In a review paper by Laws and Barkhoudarian, who have practiced with both microscope and endoscope, the authors recommended having a microscope ready, as in their early experience they found it appropriate to switch back to the microscopic technique when using the endoscope. However, with greater experience they reported converting back to the microscope less frequently.\textsuperscript{49} The significant limitation of operating using a two-dimensional image is a major reason for the current advancement in eTSS through three-dimensional endoscopy in the past decade.\textsuperscript{5}

**Outcomes and Complications of Transsphenoidal Surgery**

Given the tremendous advancements that have occurred from the first transsphenoidal surgery, it has been important for surgeons to report the outcomes of their patients. In a paper by Ciric et. al (1997), the authors investigate the overall complications following transsphenoidal surgery, which was conducted through a national survey. The authors sent out questionnaires about 14 known complications, to which 952 surgeons responded. In the study, the authors grouped surgeons by their experience from the number of transsphenoidal surgeries performed. The percent of
operations that resulted in a complication is shown in Table 2, which was made from estimates reported by the surgeons from each group.

Table 2: Percent of Operations after Transsphenoidal Surgery resulting in each complication per experience group in the National Survey. There are further reductions in complications in groups with more experienced surgeons. Taken from Ciric et. al 1997.15

<table>
<thead>
<tr>
<th>Complication</th>
<th>% of Operations Resulting in Complication(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;200(^b)</td>
</tr>
<tr>
<td>Anesthetic complications</td>
<td>3.5</td>
</tr>
<tr>
<td>Carotid artery injury</td>
<td>1.4</td>
</tr>
<tr>
<td>Central nervous system injury</td>
<td>1.6</td>
</tr>
<tr>
<td>Hemorrhage into residual tumor bed</td>
<td>2.8</td>
</tr>
<tr>
<td>Loss of vision</td>
<td>2.4</td>
</tr>
<tr>
<td>Ophthalmoplegia</td>
<td>1.9</td>
</tr>
<tr>
<td>Cerebrospinal fluid leak</td>
<td>4.2</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1.9</td>
</tr>
<tr>
<td>Nasal septum perforation</td>
<td>7.6</td>
</tr>
<tr>
<td>Postoperative epistaxis</td>
<td>4.3</td>
</tr>
<tr>
<td>Postoperative sinusitis</td>
<td>9.6</td>
</tr>
<tr>
<td>Anterior pituitary insufficiency</td>
<td>20.6</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
<td>19.0</td>
</tr>
<tr>
<td>Death</td>
<td>1.2</td>
</tr>
</tbody>
</table>

\(^a\) Estimation by participating neurosurgeons.
\(^b\) Number of previous operations.
\(^c\) NA, not applicable.

The authors found that greater experience resulted in fewer complications, which was statistically significant for all but two complications. This study was important for highlighting that experience performing a surgical technique can reduce complications.15
Considering the steep learning curve of the endoscopic technique previously mentioned, it is important to compare outcomes of both visualization methods of transsphenoidal surgery.

In a systematic review by Rotenburg et. al (2010), the authors investigated published literature from 1989 to 2009, where the studies compared mTSS and eTSS for treatment of pituitary adenomas. In terms of operating time, some studies found the endoscopic approach to take slightly longer. However, this is likely due to the newness of the technique. As a whole, operating time using an endoscope was lower than that using a microscope. The differences in tumor resection of the included studies were considered insignificant.\(^6^9\) However, in another systematic review, there seemed to be a trend towards better tumor resection with eTSS when compared with mTSS.\(^7^7\) In Rotenburg et. al, the authors also found that overall, eTSS resulted in a shorter hospital stay for patients when compared with mTSS. The authors found that occurrence of diabetes insipidus (DI), immediately after the surgery was reduced in eTSS; however, long-term morbidity because of DI seemed to be the same between eTSS and mTSS.

The overall comparisons of outcomes in eTSS versus mTSS that have been reported are fairly mixed. In a meta-analysis conducted by Ammirati et. al (2013), the authors did not find any statistical significance between each visualization technique for the following (Table 3): CSF leak, rate of death, DI, visual complication, hypopituitarism, gross total resection, and nerve injury. Interestingly, they found that the endoscopic group experienced greater number of vascular complications.\(^1\) Overall, the
authors concluded that there was not a clear or significant advantage in terms of outcomes for eTSS over mTSS.

Table 3: Estimated proportion with 95% CI of complications after eTSS and mTSS. (Taken and modified from Ammirati et. al 2013)¹

<table>
<thead>
<tr>
<th>Complication</th>
<th>No of studies for eTSS</th>
<th>Proportion (95% CI) for eTSS</th>
<th>No of studies from mTSS</th>
<th>Proportion (95% CI) for mTSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>19</td>
<td>0.49% (0.23% to 0.84%)†</td>
<td>18</td>
<td>0.23% (0.10% to 0.42%)†</td>
</tr>
<tr>
<td>CSF leak</td>
<td>24</td>
<td>7.00% (4.84% to 9.52%)</td>
<td>19</td>
<td>6.34% (3.86% to 9.37%)</td>
</tr>
<tr>
<td>Meningitis</td>
<td>13</td>
<td>1.11% (0.64% to 1.71%)†</td>
<td>14</td>
<td>2.08% (0.83% to 3.86%)</td>
</tr>
<tr>
<td>Vascular complications*</td>
<td>17</td>
<td>1.58% (1.07% to 2.19%)†</td>
<td>12</td>
<td>0.50% (0.28% to 0.78%)†</td>
</tr>
<tr>
<td>Visual loss</td>
<td>13</td>
<td>0.72% (0.37% to 1.19%)†</td>
<td>14</td>
<td>0.60% (0.23% to 1.14%)</td>
</tr>
<tr>
<td>Diabetes insipidus temporary</td>
<td>18</td>
<td>9.10% (6.57% to 11.99%)</td>
<td>14</td>
<td>10.23% (6.50% to 14.69%)</td>
</tr>
<tr>
<td>Diabetes insipidus permanent</td>
<td>21</td>
<td>2.31% (1.41% to 3.41%)</td>
<td>15</td>
<td>4.25% (1.96% to 7.36%)</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>17</td>
<td>8.51% (5.16% to 12.59%)</td>
<td>12</td>
<td>11.64% (5.14% to 20.32%)</td>
</tr>
<tr>
<td>Complete resection</td>
<td>22</td>
<td>68.77% (64.37% to 73.00%)</td>
<td>18</td>
<td>64.44% (57.62% to 70.98%)</td>
</tr>
<tr>
<td>Nerve injury</td>
<td>8</td>
<td>0.28% (0.05% to 0.71%)†</td>
<td>7</td>
<td>0.53% (0.08% to 1.34%)</td>
</tr>
</tbody>
</table>

*Vascular complication rate is higher for eTSS than mTSS (p<0.0001).
†A fixed-effects pooled estimate was used.

However, a more recent meta-analysis by Gao et. al (2014), drew different conclusions. While most complications were relatively similar between groups, there were a few that favored eTSS. They found that gross total resection was greater in the endoscopic group versus the microscopic one. They also found that nasal perforations
occurred significantly less in the endoscopic group. Patients who underwent eTSS also stayed at the hospital for a significantly shorter time in comparison to those who underwent mTSS. There were no reported differences for CSF leak, DI, meningitis, and epistaxis. In another study by DeKlotz et. al (2012), these authors also were able to confirm a statistically significant improvement in gross total resection and a reduction in septal perforations with eTSS. The authors also found lower occurrences of CSF leaks, epistaxis and a shorter hospital stay for patients from the eTSS group when compared to mTSS. They did not find any difference between groups for DI, length of operation, or hospital stay. While the previously discussed studies have not found any significant difference in CSF leak events, a study by Strychowski et. al (2011) did report a higher occurrence in patients treated with eTSS than those with mTSS. This study also found less blood loss, shorter operating times and hospital stay, and fewer nasal complications for eTSS patients.

Overall, the studies show that both mTSS and eTSS are efficacious and safe for treating pituitary adenomas. The inconsistency with clear conclusions regarding outcomes and complications may result from a few issues. One issue is that these meta-analyses have different inclusion criteria as well as search methods, which will result in different, pooled analysis. Another limitation from the literature is that there are no large, prospective, randomized studies to best compare eTSS with mTSS. One final limitation is the new endoscopic technique still requires more experience due to the steeper learning curve. It is thought that after some time, the efficacy of the endoscopic technique will supersede the microscopic one.
An important outcome of surgery is also the comfort or quality of life (QOL) of patients post-operatively. This has not been studied closely for pituitary adenoma patients following transsphenoidal surgery. The first study to investigate both, quality of life and outcomes, for patients operated on through the endoscopic approach was done by Karabatsou et. al (2008). They assessed QOL through Short Form-36 health questionnaire. Although the impact eTSS had on QOL was statistically insignificant, there appeared to be a trend indicating an overall positive effect on QOL. This might be expected as it appears pain following transsphenoidal surgery is less in eTSS patients, which is possibly due to the lack of nasal packing and external incisions in this technique. There is also possibly greater tumor resection, leading to an improved endocrinological outcome. Future studies will need to be conducted in order to properly evaluate transsphenoidal technique impact on QOL.

**Hyponatremia**

One complication quite common with neurosurgical patients is hyponatremia. Hyponatremia is generally classified as having blood sodium levels below 135mEq/L. Mild hyponatremia is considered as sodium levels at 131-134mEq/L, moderate as 125-130mEq/L and severe as <125mEq/L. Given the increased mortality associated with hyponatremia it is an important outcome of interest. In a study by Waiker et. al (2009), the authors investigated hyponatremia and mortality in over 98,000 patients. Hyponatremia, even mild, was found to significantly increase mortality. This effect became pronounced for patients with cardiovascular disease. The association between
increased mortality and hyponatremia was also found in a study of results from the National Health and Nutrition Examination Survey (Figure 2).\textsuperscript{57} Hyponatremia can cause patients to experience dizziness, nausea, and headaches.\textsuperscript{85} It has also been associated with demyelinating disease,\textsuperscript{59} a condition that destroys the myelin sheath surrounding nerve fibers, resulting in neurological problems.\textsuperscript{78} In severe cases, it can cause cardiac dysfunction, seizures, comas, respiratory arrest, and death.\textsuperscript{42,39}

\textbf{Figure 2: Cumulative mortality in hyponatremic and normonatremic subjects.} After adjusting for comorbidities, insurance status, smoking, and ethnicity, risk of mortality remained significant for subjects with hyponatremia. (Taken from Mohan et. al 2013).\textsuperscript{57}
Causes of Hyponatremia

The cause of hyponatremia is most commonly thought to originate from the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and less commonly from cerebral salt wasting syndrome (CSWS).\(^8\) If hyponatremia occurs within the first three days post-operatively, cortisol deficiency or excess fluids could be considered as possible causes.\(^7\) Other potential causes of hyponatremia are an ACTH deficiency, meningitis, over-administration of DDAVP, or hypothyroidism.\(^68\),\(^5\)

Normally, the hypothalamus works in conjunction with the pituitary gland to produce hormones that regulate various processes inside the body, including water regulation. SIADH is a condition where there is an excess production of antidiuretic hormone by the posterior pituitary, which acts on the kidney resulting in an increased retention of water. This will cause the extra cellular fluid to expand with reduction of blood sodium concentration, which as previously discussed, can have seriously deleterious effects on the body.\(^2\)

In a study by Cusick et. al (1984), the authors report on three cases on patients who underwent pituitary tumor resection through transsphenoidal surgery. Due to normal thyroid functioning and proper adherence to steroid replacement therapy of these patients, the authors concluded the cause of hyponatremia was not hypothyroidism or hypoadrenalism. Hyperactivity of the posterior pituitary also did not appear to be responsible. The authors suggested that the cause of the hyponatremia was damage of
posterior pituitary cells containing antidiuretic hormone, causing low serum osmolality despite normal functioning of the neurohypophysis. In a prospective study by Olson et al (1997), investigators sought to determine the pathophysiology of hyponatremia after transsphenoidal surgery. They evaluated posterior pituitary damage through questionnaires to surgeons after each operation and found that greater surgical manipulation and posterior pituitary damage was associated with water balance dysfunction. The association of excess antidiuretic hormone release with posterior pituitary damage has been reported by other studies as well.

The other potential cause of hyponatremia after transsphenoidal surgery is CSWS, which is less frequently reported. CSWS is a condition where excess renal excretion of sodium occurs, resulting in hyponatremia as well as hypovolemia. The first report of the rare condition was by Peter et al (1950) through the description of three patients who were in a volume-contracted state and experiencing hyponatremia. However, following the report by Schwartz et al on SIADH, CSWS was less often reported and only fairly recently has become known to be distinct from SIADH. Although the mechanism of this condition is not well understood, it is hypothesized that sympathetic input to the kidney is reduced, in addition to a release of natriuretic factors (Figure 3). While brain natriuretic peptide (BNP) may possibly be the main contributing factor, atrial natriuretic peptide (ANP) among others are thought to play a role as well.
Figure 3: Proposed Mechanism for CSWS. Reduced renal sympathetic innervation and increased natriuretic factors can result in excess loss of sodium and hypovolemia as seen in CSWS. Abbreviations: AVP = arginine vasopressin; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; EABV = effective arterial blood volume; IMCD = inner medullary collecting duct. (Taken from Palmer et. al 2003).62

While both SIADH and CSWS can result in hyponatremia, their distinction is important regarding treatment. SIADH is a volume-expanded state, where the extracellular volume is increased; CSWS is the opposite, where extracellular volume is decreased. The fluid restriction that serves as a treatment for SIADH would worsen the condition for a patient with CSWS. CSWS is usually treated through intravenous saline
and salt tablets, which would worsen the hyponatremia of a patient with SIADH. The major differentiation between the two regarding diagnosis lies with the assessment of extracellular fluid status.62

**Delayed Symptomatic Hyponatremia**

While hyponatremia has been a known consequence of transsphenoidal surgery, delayed symptomatic hyponatremia (DSH) is not as often reported, but appears to be more common than previously thought.6 In a recent study, delayed hyponatremia was actually found to be the most common cause for readmission within 30 days after transsphenoidal surgery.6 Considering that patients will remain in the hospital post-operatively for only a few days, DSH will often occur once a patient is at their home.86 DSH has been reported to occur somewhere between four and seven days post-operatively.6,36,86

DSH has been described and reported by several investigators.46,50,80 While potential risk factors for postoperative hyponatremia have been investigated, the results are mixed and there is no solid conclusion about which patients are at risk. One study found that patients with preoperative hypopituitarism were at increased risk for hyponatremia.40 However, this study was not focused on pituitary adenomas and also did not differentiate into delayed and symptomatic hyponatremia. Another study, while specifically investigating patients with delayed hyponatremia, only found low body mass index (BMI) as an increased risk factor. But like the previous study mentioned, the
authors included all pituitary tumors.\textsuperscript{39} While one study found that age was a predictor of delayed hyponatremia,\textsuperscript{50} another study reported a contradictory finding.\textsuperscript{80}

Other potential predictors that have been investigated include: gender, tumor type, and tumor size, but a consensus has not been reached. Part of the difficulty in identifying these high-risk patients is the retrospective nature of the studies, in addition to a lack of clear distinction in type of hyponatremic events. It is the goal of this study to evaluate not only predictors, but also rates of DSH for both transsphenoidal techniques (eTSS and mTSS) in patients with pituitary adenomas.
SPECIFIC AIDS

The prevalence of pituitary adenomas has been increasing the last twenty years, as has the number of transsphenoidal surgeries that treat them. The two major developments include the use of the microscope and subsequently the endoscope, which both have significantly impacted tumor resection rates, operating time, recovery time, complications, and hospital stay. There has been much discussion over the benefits of each visualization method. However, the current body of evidence regarding which method is superior to the other is insufficient. One complication of both techniques is delayed symptomatic hyponatremia (DSH), which may be more common than previously thought. While the majority of patients who experience hyponatremia after transsphenoidal surgery are asymptomatic, severe and prolonged hyponatremia can cause significant harm to patients and is associated with increased mortality. Given the short hospital stays following transsphenoidal surgery, patients often experience DSH while at home. Predictors of delayed hyponatremia have been investigated, however, there is not sufficient evidence for a consensus on these risk factors. To our knowledge there is no meta-analysis or systematic review that has compared rates of DSH in patients with pituitary adenomas for mTSS and eTSS nor identified risk factors for DSH.

The specific aims of this study are:

1. To assess rates of DSH in patients after both mTSS and eTSS
2. To identify predictors of DSH in patients after both mTSS and eTSS
3. To elucidate differences in risk factors for DSH in mTSS versus eTSS
Through this study we hope to obtain a better understanding of risk factors and predictors of DSH after transsphenoidal surgery, which could allow clinicians to more accurately identify patients at an increased risk for this potentially catastrophic complication. For these high-risk patients, clinicians will be able to monitor them more closely and apply preventative measures to improve quality of care and patient outcomes. The goal of this study is to pool results from a set of case series so that we can compare DSH rates for the two visualization techniques as well as identify potential predictors.
METHODS

Search strategy

A thorough search of the following databases was conducted:

MEDLINE/PUBMED, EMBASE, and The Cochrane Library (Tables 4 and 5). The last search was performed in September 2015 and there were not limitations to our search strategy.

Table 4: Medline search strategy using MeSH terms and text word keywords.
(Taken from Cote et. al 2016).


Result=576
Table 5: Emtree keywords used in Embase search. (Taken from Cote et al. 2016).\textsuperscript{18}

| exp neuroendoscopy/ OR "neuroendoscop*".tw. OR exp transsphenoidal surgery/ OR "transsphenoid* surger*".tw. OR "endoscop* endonasal".tw. OR "endonasal endoscop*".tw. OR endoscopic surgery/ OR neurosurgery/ OR microsurgery/ OR "microscop*".tw. OR "microsurgery*".tw. OR "micro-surger*".tw. OR "Transsphenoidal microscopic surgery".tw. OR "microscopic transsphenoidal surgery".tw. OR "microscopic endonasal transsphenoidal".tw. AND exp hypophysis tumor/ OR "hypophys*".tw. OR "pituitary adenoma".tw. OR "pituitary gland adenoma".tw. OR "pituitary microadenoma".tw. OR craniopharyngioma/ OR hyperpituitarism/ OR "microsurgery*".tw. OR "microsurgery*".tw. OR "microscop*".tw. OR "Transsphenoidal microscopic surgery".tw. OR "microscopic transsphenoidal surgery".tw. OR "microscopic endonasal transsphenoidal".tw. AND exp hyponatremia/ OR "hyponatremia".tw. OR "hyponatriemia".tw. OR "hyponatraemia".tw. OR "inappropriate vasopressin secretion/ OR "syndrome of inappropriate secretion of antidiuretic hormone".tw. OR "SIADH".tw. OR natriuresis/ OR "natriuresis".tw. OR neurogenic diabetes insipidus/ OR "Neurogenic Diabetes Insipidus".tw. OR "Diabetes Insipidus".tw. Result= 531

\textbf{Eligibility Criteria and Study Selection}

Articles that were animal studies, case reports or were not written in English (n=1) were excluded from the current investigation (Figure 4). The study inclusion criteria consisted of case series with at least 10 patients who were diagnosed with pituitary adenoma and were treated through microscopic or endoscopic transsphenoidal surgery. We were unable to identify any cohort studies or randomized control trials that met the study selection criteria. The primary outcome of the investigation was the incidence of delayed and symptomatic hyponatremia occurring on or after the third day post-operatively. A blood sodium level below 135 mEq/L was defined as hyponatremia. Each investigator evaluated the retrieved articles, using the search strategy and inclusion criteria, independently. Any disagreements on which studies to include were resolved by the senior author (TRS).
Figure 4: Flow chart for systematic search and selection of studies. (Taken from Cote et. al 2016.)

Articles found in Pubmed (n=576)
Articles found in Embase (n=531)
Articles found in Cochrane Library (n=35)

Duplicates (n=275)

Studies included (n=867)

Case Report (n= 251)
Meta-analysis (n= 7)
Systematic Review (n= 5)
Review (n= 95)
Others (n= 83)

Studies included (n=426)

Articles excluded on basis of title and abstract screening (n=389)

Studies included (n=37)

Not founded (n=4)
Short Follow-up (n=2)
Not English (n=1)
Abstract (n=1)
No info. About Delayed Hyponatremia (n=2)
Not clear if it’s Delayed or not (n=9)
Not clear if it’s microscopic or endoscopic (n=1)
Not Systematic delayed hyponatremia

10 Articles included
Data Extraction

The included articles were divided among five researchers. The data was extracted independently by members of the team and then reviewed by a second member. Any differences with data extraction were resolved by the senior author. Extracted data included the following: author, year of the publication, patient demographics, surgical technique (microscopic or endoscopic), tumor size (macroadenoma or microadenoma), post-operative complications, study location, whether or not the surgery was performed by a single surgeon, and whether or not the study included a single center. The mean age of each case series was used as a potential predictor. To standardize the measure for age, the mean for one of the investigated studies was estimated from the median.

Exploratory analysis

A stratified exploratory analysis was performed using descriptive statistics, histograms, and scatterplots once the included studies were identified, in order to explore trends in the data. The exploratory analysis was useful in selecting the appropriate mode of meta-regression for assessing risk factors for DSH post-operatively.

Risk of bias and quality assessments

Due to the non-comparativeness of the available studies, the Newcastle-Ottawa Scale was modified to assess study quality with primary and secondary outcomes. The preferred effect measure was proportional. Egger’s test was conducted to assess possible
publication bias using the trim and fill technique. A sensitivity analysis was also conducted.

**Pooled analysis and heterogeneity**

Initially, the results of the investigated studies were combined statistically and provided a pooled estimate of the average intervention effect. The DerSimonian-Laird random effect model was used to assess the weighted average of the effect estimate due to the unknown variability of risk factors leading to DSH in the included studies. For comparison, fixed-effects models were evaluated. The results were shown as point estimates with CI and p-values. Forest plots were then created to show the individual and pooled effect estimate, as well as CI. Heterogeneity was visually assessed through the forest plots. To evaluate the heterogeneity, the Chi-square test (Cochran Q) and I² were used. Heterogeneity was considered insignificant if I² statistic was below 40%, moderate if between 30-60%, substantial if between 50-90%, and considerable if between 75-100%. Forests plots were produced to present the results of these analyses. Meta-regression analyses and subgroup analyses were used in order to explore sources of heterogeneity.
RESULTS

Ten case series were identified that satisfied the study selection criteria for this systematic review, for a total of 2,947 patients (Figure 4, Table 6). Two of the included studies were performed prospectively, while the remaining eight were performed retrospectively. The majority of patients in the investigated articles were female (60.18%) and had macroadenomas (58.84%). Across all studies, patients’ mean age on the date of the operation was 47.07 years. In five of the ten studies, surgeries were performed solely using the microscope, in three, only the endoscope, and the remaining two, contained a mixture.
**Table 3:** Systematic review of DSH in patients undergoing transsphenoidal resection of pituitary lesions. (Taken and modified from Cote et al 2016).\(^{18}\)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Duration</th>
<th>DSH Events</th>
<th>Sample Size</th>
<th>Age (mean)</th>
<th>Sex (male, no.)</th>
<th>Micro-adenoma (no.)</th>
<th>Macro-adenoma (no.)</th>
<th>DI (no.)</th>
<th>CSF-leak (no.)</th>
<th>Meningitis (no.)</th>
<th>Bleeding (no.)</th>
<th>Single surgeon (y/n)</th>
<th>Single center (y/n)</th>
<th>Event rate of DSH (%)</th>
<th>Country</th>
<th>Study type</th>
<th>Type of TSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas et al. (2014)</td>
<td>N/A</td>
<td>2</td>
<td>50</td>
<td>50</td>
<td>21</td>
<td>9</td>
<td>41</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>4.00</td>
<td>USA</td>
<td>P</td>
<td>eTSS</td>
</tr>
<tr>
<td>Mamelak et al. (2013)</td>
<td>2006-2011</td>
<td>37</td>
<td>300</td>
<td>51.6</td>
<td>130</td>
<td>16</td>
<td>25</td>
<td>36</td>
<td>2</td>
<td>N/A</td>
<td>2</td>
<td>Y</td>
<td>N/A</td>
<td>12.33</td>
<td>USA</td>
<td>R</td>
<td>eTSS</td>
</tr>
<tr>
<td>Zada et al. (2007)</td>
<td>1997-2004</td>
<td>11</td>
<td>241</td>
<td>48</td>
<td>110</td>
<td>183</td>
<td>58</td>
<td>33</td>
<td>5</td>
<td>5</td>
<td>N/A</td>
<td>Y</td>
<td>Y</td>
<td>4.56</td>
<td>USA</td>
<td>R</td>
<td>eTSS</td>
</tr>
<tr>
<td>Kelly et al. (1995)</td>
<td>1990-1992</td>
<td>7</td>
<td>99</td>
<td>45</td>
<td>32</td>
<td>35</td>
<td>64</td>
<td>14</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>N/A</td>
<td>Y</td>
<td>7.07</td>
<td>USA</td>
<td>R</td>
<td>mTSS</td>
</tr>
<tr>
<td>Hensen et al. (1999)</td>
<td>1982-1995</td>
<td>106</td>
<td>1571</td>
<td>44.5</td>
<td>672</td>
<td>454</td>
<td>1078</td>
<td>377</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N</td>
<td>Y</td>
<td>6.70</td>
<td>Germany</td>
<td>R</td>
<td>mTSS</td>
</tr>
<tr>
<td>Sane et al. (1994)</td>
<td>1989-1993</td>
<td>18</td>
<td>91</td>
<td>45</td>
<td>44</td>
<td>30</td>
<td>55</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>1</td>
<td>N/A</td>
<td>Y</td>
<td>19.78</td>
<td>Finland</td>
<td>P</td>
<td>mTSS</td>
</tr>
<tr>
<td>Lee II et al. (2008)</td>
<td>2002-2006</td>
<td>7</td>
<td>94</td>
<td>42.8</td>
<td>51</td>
<td>9</td>
<td>85</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Y</td>
<td>7.40</td>
<td>South Korea</td>
<td>R</td>
<td>mTSS</td>
<td></td>
</tr>
<tr>
<td>Kinoshita et al. (2011)</td>
<td>2006-2008</td>
<td>9</td>
<td>88</td>
<td>47.9</td>
<td>28</td>
<td>N/A</td>
<td>N/A</td>
<td>11</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Y</td>
<td>10.23</td>
<td>Japan</td>
<td>R</td>
<td>mTSS</td>
</tr>
<tr>
<td>Bohl et al. (2015)</td>
<td>2011-2014</td>
<td>15</td>
<td>303</td>
<td>52.9</td>
<td>163</td>
<td>N/A</td>
<td>N/A</td>
<td>4</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N</td>
<td>Y</td>
<td>4.95</td>
<td>USA</td>
<td>R</td>
<td>mTSS/eTSS</td>
</tr>
<tr>
<td>Sata et al. (2006)</td>
<td>2000-2002</td>
<td>4</td>
<td>110</td>
<td>43</td>
<td>39</td>
<td>12</td>
<td>98</td>
<td>3</td>
<td>N/A</td>
<td>2</td>
<td>N/A</td>
<td>N/A</td>
<td>Y</td>
<td>3.64</td>
<td>Japan</td>
<td>R</td>
<td>mTSS/eTSS</td>
</tr>
</tbody>
</table>

Abbreviations: No., Number; Y = Yes; N = No; N/A = Not applicable; P = Prospective; R = Retrospective

* Median was reported.
To assess publication bias for both mTSS and eTSS, the Begg and Mazumdar Rank Correlation Test was used. Neither was found to have any significant publication bias (P=0.500 for both). The level of heterogeneity was considerable and deemed too high for meta-analysis ($I^2=93.28$).

**Rates of DSH**

The event rate of DSH from the ten investigated articles was between 3.6 to 19.8%. Kelly et al reported rates of 7.07%, with serum sodium levels beginning to fall on around post-operative day (POD) 4, and falling to their lowest on the seventh day post-operatively. On average, sodium levels of patients who had symptomatic hyponatremia, fell to 122 mmol/L. A similar rate of DSH was reported by Hensen et al, where the highest incidence occurred on POD7 (n=79). Authors from different study reported slightly higher rates (10.23%), with 92% of all patients experiencing lowest levels of blood sodium on the seventh day post-operatively. Mamelak et al reported a similar event rate for DSH (12.33%). In Bohl et al, the investigators found that DSH developed in 15 out of 303 patients (4.95%), while Lee et al reported DSH occurred in 7 of 94 patients developing DSH. In a study by Thomas et al, the authors found that 4.0% of patients experienced DSH. Two other studies found similar rates of DSH occurrence. Sane et al reported significantly higher incidence of DSH.
Predictors of DSH

In two studies, women were more likely to experience hyponatremia than men were.\textsuperscript{70,86} Although not reaching statistical significance Kelly et. al found that patients who were older, had macroadenomas, and had evidence of pre-operative hypopituitarism were more prone to experience DSH than other patients. In a study by Hensen et. al, the authors reported that patients with Cushing’s Disease were 2.8 times more likely to experience hyponatremia when compared to patients with hormonally inactive tumors. These patients were also at an increased risk for DSH by a factor of 3 in comparison to patients with prolactinoma.\textsuperscript{36} The results from Sane et. al, also seem to suggest a relationship between Cushing’s Disease and DSH incidence for patients. In Kinoshita et. al, the rate of blood sodium level decline was identified as an independent risk factor for DSH, (p=0.006), which also had a tendency to occur in patients over 60 years old (p=0.0346). Patients with a blood sodium decline of 10mEq/L or more between POD 4 and 7 were at an increased risk for symptomatic hyponatremia. Tumor size, tumor type, and gender were not found to be predictors of DSH.\textsuperscript{47} In Lee et. al, the authors found that patients above the age of 50 were at a significantly higher risk in developing DSH than other patients (p<0.05). Bohl et. al were not able to identify any predictors of DSH.
DISCUSSION

Transsphenoidal surgery has undergone significant changes since Schoffler performed the first one in 1909. The use of the microscope and endoscope along with other advancements in transsphenoidal surgery has dramatically impacted the procedure and complications associated with it. While complications following transsphenoidal surgery have been well-documented in the literature, there are some complications such as DSH that are not as well understood. DSH can cause a variety of neurological problems and, if severe enough, even death and so it requires immediate attention. Generally, it has been mostly attributed to SIADH as a result of posterior pituitary damage, causing excess release of ADH. It less frequently reported to be caused by CSWS, where excess sodium is excreted in the urine. A deeper understanding of the predictors for DSH can help physicians identify patients who are at risk. They can then be more active in applying prevention methods/treatments, such as fluid restriction or salt administration, depending on the cause of hyponatremia. Although retrospective case series have investigated DSH, there is still no consensus on predictive risk factors. To our knowledge there is no meta-analysis or systematic review that has compared rates of DSH in patients with pituitary adenomas for mTSS and eTSS nor identified risk factors for DSH.

The goal of the current study was to pool results from the included studies to identify possible predictors of DSH, as well as compare the rates of DSH occurrence for both mTSS and eTSS for patients with pituitary adenomas. Through the systematic
search that was conducted we were able to identify ten articles consisting of risk factors and rates for DSH.

**Preoperative Tumor and Patient Characteristics**

Kinoshita et. al found age (>60) was a predictor of DSH, as did another study for patients who were at least 50 years old. Kelly et. al, found a tendency for older patients to experience DSH, and those with evidence of preoperative hypopituitarism. Age as a predictive risk factor has been reported by other studies as well. In Kelly et. al, patients with macroadenomas were found to be at a statistically higher risk as well, which is supported by recent studies. Kinoshita et. al also found that rate of blood sodium level decline predicted symptoms of hyponatremia. Two of the investigated studies found that women had a greater tendency to experience hyponatremia, a finding that other studies also seem to suggest. In two other included studies, it was found that DSH incidence was significantly greater in patients with Cushing’s Disease in comparison to other patients.

**Endoscopic versus Microscopic Transsphenoidal Surgery**

Event rates for DSH for mTSS and eTSS were found to be between 4 and 12 percent, excluding one study that reported significantly higher rates. However, the authors of the paper with high rates of DSH (19.78%) note that a delayed management of post-operative fluid and electrolytes likely caused the high incidence among these patients. In addition, the reported age range was fairly large (12-76 years), which could have contributed to these high event rates. The majority of the investigated articles
found that blood sodium level reached a nadir around the seventh day post-operatively.\[34\] The onset of symptoms for hyponatremia have been found to typically present between the fourth and seventh day after transsphenoidal surgery.\[34\]

While pooled analysis was not possible, overall, the investigated studies seem to suggest a trend that rates of DSH are decreasing over time. Interestingly, there were no significant differences in event rates for DSH when comparing mTSS and eTSS. Possibly, this trend may be attributed to further developments in both surgical techniques. There has been a great deal of discussion over the advantages and disadvantages of both visualization techniques in this paper. Many surgeons have reported that there is better visualization with the endoscope, however, and it is thought that this can result in reduced damage of sinonasal structures and fewer complications.\[25,28,49\]

**Limitations**

A limitation of the present paper is that the heterogeneity of the included studies was too high for meta-analysis, weakening the conclusions made of the investigated papers as a whole. In addition, it was difficult making meaningful comparisons between mTSS and eTSS for both predictors and rates of DSH due to the lack of studies using only an endoscope. There were two studies that included a mixture of both microscope and endoscope, but failed to differentiate the two for complications. In the study by Kinoshita et. al, the authors reported rates of DSH that were on the higher end of the included studies. However, this may be due to the fact that a significant portion of the patients who were female (68.2%). As previously discussed, women tend to experience
hyponatremia more often than males as reported by two studies, and it is possible that this could have been a contributing factor to the higher reported event rates for DSH. In Hensen et. al, the authors note that the hyponatremia of several patients may have been caused by prolonged treatment with desmopressin, a synthetic ADH analog.

**Future Directions**

One of the difficulties in the selection of studies investigating predictors and rates of DSH is the lack of specification for the type of hyponatremia experienced by patients. Some studies group hyponatremic events by timing, severity, or whether the patient reported symptoms. Future studies might more clearly differentiate between early, delayed, and symptomatic hyponatremia for more accurate identification of high-risk patients. The large range for rates of DSH in the current paper, indicate that further investigation needs to be conducted to pinpoint the reasons for this observation. While it has been noted that there is increased visualization with the endoscope, there is also a steep learning curve that has been reported by many.\(^7,11,43,49\) It is possible that rates of DSH could be affected by this and should be taken into consideration. BMI may also be a variable of interest, as this has been shown to significantly increase the risk of delayed post-operative hyponatremia.\(^56\) Future studies should not only specifically distinguish hyponatremic events, but should also attempt to determine the etiology as this may be a significant and relevant factor in identifying high-risk patients for DSH. A large, prospective study may improve understanding of DSH, its etiology, and its predictors.
Conclusion

To date there has not been a study that has compared rates of DSH between microscopic and endoscopic transsphenoidal surgery. In the current paper, the heterogeneity of the investigated articles was too high to pool the results for reliable meta-analysis, making it difficult to draw accurate conclusions. Rates of DSH in microscopic and endoscopic transsphenoidal surgery were found to occur between 3.6 and 19.8% in patients. In the present paper, age, gender, tumor size, rate of blood sodium level decline, and patients with Cushing’s Disease, were identified as potential risk factors for DSH following transsphenoidal pituitary surgery in patients diagnosed with pituitary adenoma.
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38. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 5:13, 2005


