Endoscopic *versus* microscopic trans-sphenoidal pituitary surgery: a systematic review and meta-analysis

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Since Schloffer's first report of trans-sphenoidal approach to sella, in 1907, the field of pituitary surgery has been constantly evolving.[1] The trans-sphenoidal approach was abandoned for the first half of the 20th century, but subsequently evidenced a steady rise in popularity following the introduction of the operative microscope in 1960s and today represents the standard approach to the sellar area.[2,3]

The traditional transseptal/translabial approach is the standard trans-sphenoidal approach, considered as the 'gold standard', associated with minimal morbidity and mortality.[4] In the last 20 years, however, the introduction of the surgical endoscope and the development of specialist instrumentation have redefined pituitary surgery.[5–8] During the past decade, the 'pure' endoscopic endonasal trans-sphenoidal surgery, a minimal invasive approach using the endoscope both for visualisation and resection of tumour, has progressively gained popularity among surgeons, who through the pioneering work of Aldo Stamm, Jho, Cappabianca, Carrau and Anand have redefined the limits of trans-sphenoid approach, using the endoscope to access the whole anterior, middle and posterior skull base.[9–13] A meta-analysis performed by Tabaee in 2009 including studies published up to 2005 and 821 patients showed a 78% pooled gross resection rates and 81–84 pooled rates of hormonal cure.[14]

The aim of the present systematic review and meta-analysis is to analyse and compare the effectiveness of microscopic trans-sphenoidal microscopic approach (sublabial, transseptal) with the pure endoscopic procedure to the pituitary tumours. Additional purpose of our manuscript is to determine the differences in safety and in operative characteristics between microscopic and endoscopic pituitary surgery.

Patients-methods

Search strategy

A computer literature search in MEDLINE, EMBASE, the Cochrane Library and CENTRAL electronic databases was performed by one of the reviewers (J.G) from 10 January 2010 to 10 February 2010 to identify all studies that answered the question of interest. For this purpose, the following free-text terms were used: 'trans-sphenoidal', 'endoscopic/endoscopy', 'microsurgery', 'sublabial', 'transnasal', 'endonasal', 'transseptal' combined with 'pituitary' and 'skull base' and limited to 'human'. Additionally, extensive hand searching of the references of all relevant studies was performed. No time or language limitation was applied.

Selection of studies

All criteria for inclusion/exclusion of studies in the present systematic review were specified prior to the literature search. In order for a study to be eligible, the following criteria should be met: (i) the study should compare cases with pituitary tumours that underwent a microscopic trans-sphenoidal approach (sublabial, transeptal) with those undergoing a pure endoscopic trans-sphenoidal procedure (fully endoscopic approach with endoscopic resection) and (ii) the study should include 20 or more adult patients that had been operated in the same centre.

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Methodological quality

Critical appraisal of the randomised controlled trial was based on the following criteria: (i) detailed allocation sequence, (ii) group size greater than 10 patients, (iii) blinding of outcome assessors, (iv) intention to treat analysis and (v) complete outcome data. Studies graded as follows: 'A' if all the above-mentioned criteria met, 'B' if one or more criteria met and 'C' if none of the criteria fulfilled.

Quality assessment of the retrospective comparative case series was based on Newcastle-Ottawa Scale, a scale that is also recommended by the Cochrane Non-Randomized Studies Methods Working Group.[15] Each study was graded as 'I' if score was ≥6 or 'II' if score was ≤5.

Studies identified

The electronic search resulted in the initial identification of 1095 publications. Subsequently, the titles of these manuscripts were examined to exclude irrelevant studies, resulting in 48 potentially eligible articles. The abstracts of these articles were examined, and 24 manuscripts that could provide data to answer the research question of interest were identified (Figure S1). The full texts of these studies were examined thoroughly, resulting in the exclusion of 13 publications. The main reason of exclusion of each of these studies is presented (Table S1). Eventually, 11 studies, comparing cases with pituitary adenomas that received microscopic approach with those that had endoscopic approach, were identified (Table 1).[16–26]

Eligibility of these studies for the present systematic review was assessed independently by two of the reviewers (J.G. and C.G.). Any disagreement was resolved unanimously by discussion.

Outcomes

The outcome measures chosen for this systematic review and meta-analysis were: (i) the initial post-operative remission rate of hypersecretion for functioning adenomas. The chosen normalisation criteria of hormone secretion were a post-operative basal growth hormone (GH) level below 5 ng/mL and prolactin level below 20 ng/mL for acromegaly and prolactinomas, respectively. In Cushing disease, post-operative normalised serum ACTH and cortisol levels and 24-urinary free cortisol concentrations were set, (ii) the gross complete tumour removal rate. Gross complete tumour removal was considered when surgical observation along with post-operative imaging (magnetic resonance, MRI) confirmed the absence of any visible tumour, (iii) the rate of patients with visual improvement who had pre-operative visual field deficit, (iv) the rate of patients with intraoperative or post-operative cerebrospinal fluid leak (CSF) and diabetes insipidus. Other complications (death, meningitis, loss of visual acuity, lip anaesthesia, anosmia, septal perforation, synechiae etc.) attributable to the surgical approach were also considered and registered and (v) the characteristics (length of hospital stay, blood loss and operative time) of each operation.

Quantitative data synthesis

The REVMAN Software (The Cochrane Collaboration, 2008) was used to combine the results for meta-analysis. Inconsistency of studies (study-to-study variation) was assessed using the x^2-statistic (the hypothesis tested was that the studies are all drawn from the same population, i.e. from a population with the same effect size). A fixed effects model was used, where no heterogeneity was present, whereas a random effects model was applied in the presence of significant heterogeneity.

Results

Characteristics of included studies are summarised in Table 1. The eligible studies were published between 2001 and 2009. Study size ranged from 20 to 176 patients, and a total of 806 patients were reviewed (endoscopic group = 369, microscopic group = 437). The majority of included studies are retrospective case series. Two studies are randomised trials, with one of them using a true randomisation method for allocation of patients to groups and the other a quasi-randomisation method. According to the selected criteria of methodological quality, the certain randomised study is considered of poor quality, grade C. Regarding the retrospective studies, seven studies identified as grade I and two as grade II.

Reviewing the characteristics of the surgical procedures of the included studies, in five studies, pure endoscopic approach was compared with the microscopic transeptal/translabial microscopic approach. In three studies, both pure endoscopic and endoscopy-assisted procedures were performed, while in the remaining three studies, details regarding the performed endoscopic operations were not reported. The follow-up period ranged from 6.8 to 42 months in the endoscopic group and from 4.9 to 61 months in the microscopic group. In the endoscopic group, 51 pituitary tumours were microadenomas and 99 macroadenomas, with 15 of them presenting cavernous invasion. In the microscopic group, 56 patients had from microadenomas and 75 macroadenomas, with 14 of them invading the cavernous sinus. Regarding the hormonal status of the pituitary adenomas, in the endoscopic group, 152 were functioning adenomas and 92 non-

Table 1. General characteristics of the included studies

No.	Study, year, journal	Type of study, grade	Study period		Follow-up (mean, months)		Number of cases		Type of operation	
			Endoscopic	Microscopic	Endoscopic	Microscopic	Endoscopic	Microscopic	Endoscopic	Microscopic
1.	Jain *et al.*, 2007, Br J Neurosurg	Randomized, grade C	Nr		6.95		10	10	Pure	ETA
2.	Cho *et al.*, 2002, Surg Neurol	Quasi-Randomized, grade C	1997–2002		42		22	22	Pure	STTA
3.	D'Haens *et al.*, 2009, Surgical Neurology	Retrospective, grade I	2001–2007	1995–2001	18	61	60	60	Pure	STTA/ETA
4.	Graham *et al.*, 2009, Ann Otol, Rhin & Laryng	Retrospective, grade I	2005–2008	1998–2008	18.8	49.3	58	118	Endoscopic*	Open*
5.	Duz *et al.*, 2008, Acta Neurochir	Retrospective, grade I	1996–2007		28		53	40	Pure, Endoscopy assisted	STTA/ETA
6.	Higgins *et al.*, 2008, Am J Rhinol	Retrospective, grade II	2002–2008		6.8	29.6	19	29	Pure	STTA
7.	O'Malley *et al.*, 2008, Neurosurg Focus	Retrospective, grade I	2003–2008		8.8	4.9	25	25	Pure, Endoscopy assisted	STTA
8.	Neal *et al.*, 2007, Am J Rhinol	Retrospective, grade I	1990–2004		11	50	35	15	Pure, Endoscopy assisted	STT
9.	Casler *et al.*, 2005, Laryngoscope	Retrospective, grade II	1996–2003		Nr		15	15	Endoscopic*	Open*
10.	White *et al.*, 2004, Laryngoscope	Retrospective, grade I	2000–2002	1996–1999	12	54	50	50	Pure	STTA
11.	Shah *et al.*, 2001, Am J Rhin	Retrospective, grade I	1991–2000		12–18		26	55	Endoscopic*	STTA

STTA, sublabial transseptal trans-sphenoidal approach; ETA, endonasal trans-sphenoidal approach; Nr, not reported.
*Details about the performed surgical procedure were not reported.

functioning. In the microscopic group, the distribution according to the type of adenomas was 183 functioning and 144 non-functioning adenomas.

The initial remission rate of hypersecretion of functioning adenomas was not significantly different between the endoscopic and the microscopic group according to the results of three studies [(OR: 1.34(95% CI: 0.73–2.47); $P = 0.35$; 66% remission rate in endoscopic group *versus* 60% in microscopic)] (Figure S2) (Table 2). Subgroup analysis of the remission rate of hypersecretion according to the type of functioning adenomas (acromegaly, prolactinomas and Cushing disease) did not reveal a statistical difference between the endoscopic and microscopic group.

The proportion of patients with gross complete tumour removal was not significantly different between endoscopic and microscopic group in favour of endoscopy, based on the results of seven studies [(OR: 0.83, (95% CI: 0.52–1.33); $P = 0.44$; 71% removal rate in endoscopic group *versus* 69% in microscopic group)] (Fig. 1) (Table 2). Subgroup analysis of the complete tumour removal rate based on the extension of pituitary adenomas was not feasible, because only one study provided the appropriate data.[20]

The occurrence rate of CSF leak attributable to the surgical choice did not differ significantly between endoscopic and microscopic group [(RR: 0.99, (95% CI: 0.92–1.05); $P = 0.69$; 19.5% *versus* 14.4% in endoscopic and microscopic group, respectively] (Figure S3). Regarding the diabetes insipidus in the acute post-operative period, the number of patients with this adverse effect was considerably lower in endoscopic than in microscopic group [(RR: 1.14, (95% CI: 1.04–1.24); $P = 0.003$; 15% *versus*

Table 2. Rates of hypersecretion remission and gross complete tumour removal

No.	Study	Remission of hypersecretion rate No. of cases (%)		Hypersecretion normalisation criteria	Gross complete tumour removal rate No. of cases (%)		Confirmation of gross complete tumour removal
		Endoscopic	Microscopic		Endoscopic	Microscopic	
1.	Jain *et al.*	9 (90)	9 (90)	nr	5 (50)	5 (50)	MRI
2.	Cho *et al.*	14 (64)	16 (73)	PRL: <20 ng.mL	–		–
3.	D'Haens *et al.*	38 (63)	30 (50)	GH: <1 ng/mL ACTH: normal PRL: normal TSH: normal	–	–	
4.	Graham *et al.*	–		–	36 (81)	73 (71)	MRI
5.	Duz *et al.*	–		–	23 (43)	20 (50)	nr
6.	Higgins *et al.*	–		–	17 (89)	24(83)	MRI
7.	O'Malley *et al.*	–		–	14 (67)	17 (77)	MRI
8.	Neal *et al.*	–		–	11 (79)	10 (67)	nr
9.	Casler *et al.*	–		–	10 (67)	12 (80)	nr
10.	White *et al.*	–		–	–		–
11.	Shah *et al.*	–		–	–		–

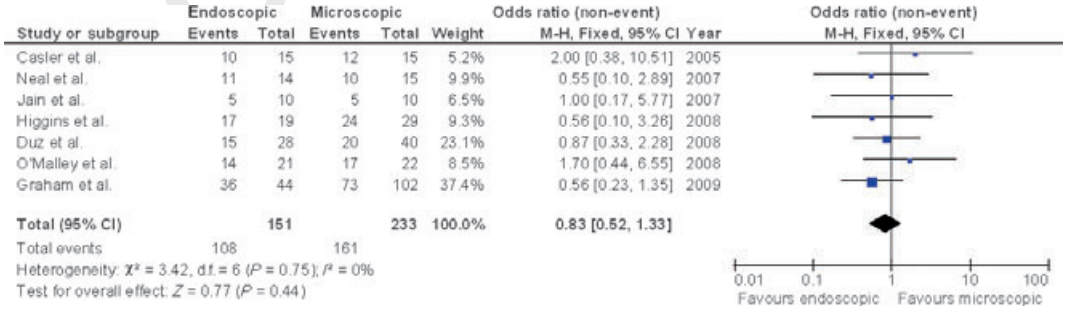

Fig. 1. Odds ratio of gross complete tumour removal rate, evaluating the lack of statistical difference between endoscopic and microscopic group ($P > 0.05$). The measure of effect of each study and of the meta-analysis is represented with a square and a diamond, retrospectively. The vertical line representing no effect is also plotted. CI: confidence interval; M–H: Mantel/Haenszel model.

LOW RESOLUTION FIG

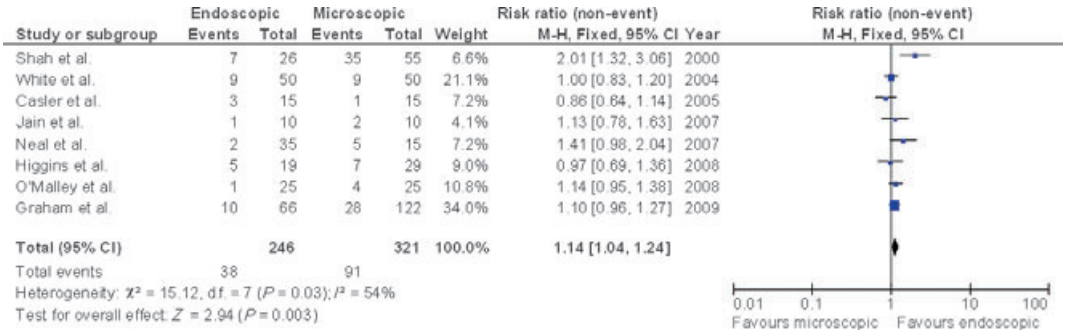

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Fig. 2. Risk ratio of diabetes insipidus occurrence in acute post-operative period, evaluating the statistical difference between endoscopic and microscopic group in favour of endoscopy ($P < 0.05$). The measure of effect of each study and of the meta-analysis is represented with a square and a diamond, retrospectively. The vertical line representing no effect is also plotted. CI: confidence interval; M–H: Mantel/Haenszel model. 14

LOW RESOLUTION FIG

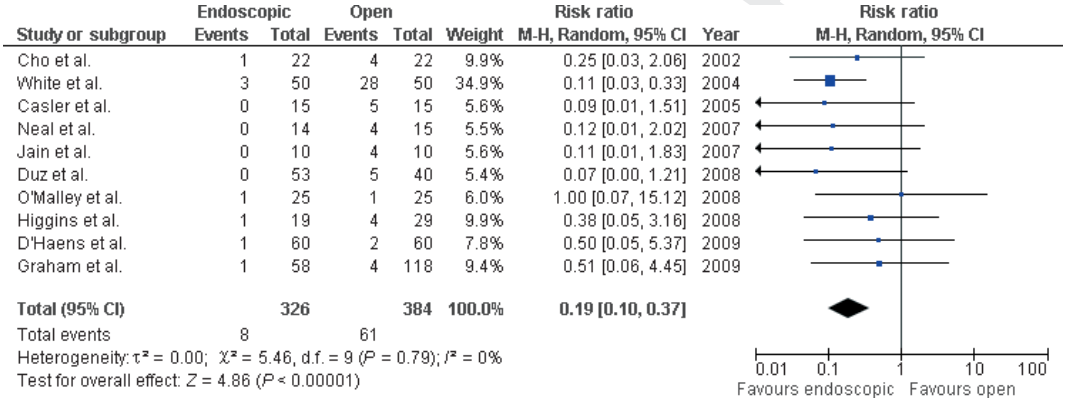

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Fig. 3. Risk ratio of complications occurrence, evaluating the statistical difference between endoscopic and microscopic group in favour of endoscopy ($P < 0.05$). The measure of effect of each study and of the meta-analysis is represented with a square and a diamond, retrospectively. The vertical line representing no effect is also plotted. CI: confidence interval; M–H: Mantel/Haenszel model. 15

28% in endoscopic and microscopic group, respectively)] (Fig. 2). The occurrence rate of permanent diabetes insipidus (duration over 1 month) appeared to be significantly higher in microscopic than in endoscopic group [(RR: 0.30, (95% CI: 0.10–0.86); $P = 0.003$; 2% *versus* 10% in endoscopic and microscopic group, respectively)]. Concerning the other possible complications, related to surgical procedures or associated with poor surgical technique, the overall occurrence rate is higher in the microscopic group [(RR: 0.18, (95% CI: 0.09–0.35); $P < 0.00001$)] (Fig. 3) (Table 3).

A meta-analysis regarding the length of hospital stay revealed that patients of endoscopic group had significant shorter post-operative hospital stay, ranging from 3.7 to 4.4 days, than those of microscopic group, ranging from 5.4 to 5.73 days [(WMD: −1.53, (95% CI: −2.30 to −0.77); $P < 0.00001$)] (Figure S4). Regarding the operative characteristics, the operative time [(WMD: −8.08, (95% CI: −23.36 to −7.21); $P = 0.30$)] and the blood loss were not significantly different between study groups in favour of endoscopy [(WMD: −24.01, (95% CI: −58.64 to −10.22); $P = 0.17$)].

In the analysis of outcomes in which data from retrospective and randomised trials were included, a sensitivity analysis by excluding retrospective studies was performed to check the stability of the results obtained. Performing the sensitivity analysis, the results of the outcomes remained the same. Moreover, sensitivity analysis excluding the poor (grade II)-quality retrospective studies was also performed, but this did not affect the outcomes.

Discussion

Endoscope or microscope?

The main advantage of the endoscope, as opposed to the microscope, is that it gives the surgeon the opportunity to advance his visualising instrument and his light source (his 'eyes') – a few centimetres from his target – and then

Table 3. Other complications

	Endoscopic (n = 326)	Microscopic (n = 384)	P, (CI)
Poor surgical technique			
Loss of visual acuity	1	3	
Meningitis	2	1	
Encephalitis	0	1	
Pneumocephalus	0	2	
Subtotal	3 (0.9%)	7 (1.8%)	>0.05, (−0.029–0.011)
Related to surgery			
Epistaxis	1	11	
Lip anaesthesia	0	9	
Nasal anaesthesia	0	2	
Deviated septum	0	5	
Saddle nose	0	1	
Sinusitis	1	3	
Synechiae	0	4	
Septal perforation	1	14	
Anosmia	1	1	
Subtotal	4 (1.2%)	50 (13%)	<0.05, (−0.156 to −0.082)

CI, confidence intervals.

look around, instead of being limited in a narrow corridor allowed by the light and depth of view of your microscope. What this means for the surgeon is not so much better dissection of the tumour he can see, but being able to visualise tumours he could not see before – and thus, extending his approach to tumours that were previously not accessible – i.e. extending superiorly (suprasellar tumours, up to the 3rd ventricle), inferiorly (down to the lower clivus) and laterally (lateral and beyond the cavernous and carotid). The present systematic review and meta-analysis supports the role of endoscopic trans-sphenoidal approach as a valid alternative to the microscopic technique.

Hormone hypersecretion

The evaluation of the effectiveness and the success of the pituitary surgery are considered in terms of normalisation of hormone hypersecretion and in terms of complete tumour removal. Previous reports support that the success rates of endoscopy were at least comparable with those of the best microsurgical series, being significant superior in certain types of difficulty to reach pituitary tumours (tumours with extrasellar extension).[10,27] In our systematic review and meta-analysis, the endoscopic technique seems to have a trend towards improved initial remission, although the comparison was based in only three studies, precluding any statistical significance and more importantly the criteria of normalisation varied between studies.

Tumour removal

Regarding gross complete tumour removal, the use of pure endoscopic technique seems to provide equivalent success rates compared to microscopic resection. Interestingly, the results from our analysis (71% *versus* 69%) are comparable, albeit lower than of those described in Tabaee's meta-analysis (78%)[14]. Although difficult to explain, one reason could be that as the studies were performed in centres that used both approaches, and as such did not gain great experience in the purely endoscopic technique, or presented their results early in their introduction of the endoscopic approach, where the main approach has still the use of microscope. The main advantage of the endoscope is that surgeons can expand the limits of their trans-sphenoidal surgery, visualising and resecting tumours that they could not assess before. Unfortunately, and although many reports of tumours have been performed endoscopically that could not have been performed before, a subgroup analysis of the gross complete tumour removal rate based on the extension of pituitary adenoma, an important prognostic factor, was not feasible because of lack of available data.[12]

Complications

The avoidance of complications is an essential goal of a successful pituitary procedure. Published studies have indicated endoscopy as a safer procedure than microscopic, reporting a lower complication rate.[12,28–30] The present systematic review and meta-analysis confirmed that endoscopy is safer than microscopic, being associated with fewer complications. The certain notional advantage of endoscopy was certified in our meta-analysis, regarding both for occurrence rate of diabetes insipidus and nasal complications. However, it should be noted that the higher occurrence rates of CSF leaks in endoscopic than in microscopic group can be associated with the efforts of surgeons to extend the limits of their operation, because of improved visualisation and exposure that the endoscopes provide.

Operative characteristics

The fact the endoscopic approach is more direct, obviating the need for a translabial incision, or removing

a significant part of the septum, and, more importantly, the improved visualisation, probably explains shorter operative time needed in endoscopic procedures when compared with the microscopic, as well as the reduced invasiveness, as according to the results of our systematic review and meta-analysis, the endoscopic group had considerable less blood loss than the microscopic group, confirming the above-mentioned advantage of endoscopy. Although the most important outcomes by far are success rates and rates of complications, when all is equal, shorter hospitalisation stays are a definite advantage.

Limitations

The results of the present systematic review and meta-analysis are liable to certain limitations, which are in direct dependence on the inherent characteristics of the included studies. First, the current systematic review and meta-analysis comprises mainly from retrospective studies that because of their small sample size and short follow-up period are underpowered to detect clinically important differences. Moreover, inclusion/exclusion criteria of the studies were often poorly described. It should be noted that in all studies included in the present systematic review and meta-analysis, allocation of patients to each treatment group seems to have been based on subjective criteria and not on a specific protocol. For these reasons, potential selection or performance bias cannot be excluded, and thus, the results of this systematic review should be interpreted with caution.

Keypoints

- Endoscopic trans-sphenoidal surgery has been increasingly replacing microscopic surgery.
- Endoscopic trans-sphenoidal surgery is proposed as a safe, effective, and with low morbidity and mortality approach to sellar pathology.
- Endoscopic approach to pituitary tumours is considered safer procedure than microscopic, being associated with fewer surgical complications (CSF leaks, diabetes insipidus and nasal complications), without compromising the final outcome.
- The present systematic review and meta-analysis supports the role of endoscopic trans-sphenoidal approach as a valid alternative to the microscopic technique.
- Like all new techniques, it needs to be subjected to the test of time, and results after long-term follow-up are vital.

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Conflict of interest

None to declare.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Flow diagram for study selection.

Figure S2. Odds ratio (OR) of hypersecretion remission rate, evaluating the difference between endoscopic and microscopic group in favor of endoscopy, without this difference being statistical significant ($P > 0.05$).

Figure S3. Risk ratio (RR) of post-operative CSF, evaluating the lack of statistical difference between endoscopic and microscopic group ($P > 0.05$).

Figure S4. Weighted Mean Difference (WMD) of rate of length of post-operative hospital stay, revealing the significant difference between the two groups in favor of endoscopic group ($P < 0.05$).

Table S1. Excluded studies.

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