Original Article

Comparison of outcomes between endoscopic and microscopic transsphenoidal surgery for the treatment of pituitary adenoma: a meta-analysis

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Background: Pituitary tumors are among the most common intracranial tumors. Surgical resection is the most effective treatment for patients with pituitary tumors. Microscopic transsphenoidal surgery has become the first-choice surgical approach to treating this malignancy, although it has certain limitations. Neuroendoscopy has also been widely used for pituitary tumor surgery in recent years. This study aimed to compare the efficacy and safety of these two surgical options for the treatment of pituitary tumors.

Methods: We conducted a literature search of the PubMed, Embase, Cochrane Controlled Center Register of Controlled Trials (CENTRAL), Web of Science database, Google Scholar, and Baidu Scholar. Relevant articles published up to September 25, 2020 were retrieved and then meta-analyzed using RevMan software 5.1.

Results: A total of 29 case-control studies involving 7,774 patients were included in the meta-analysis. There was no significant difference in gross tumor removal (GTR) (RR =1.11, 95% CI: 0.97–1.26, P=0.12) or hormone excess secretion (HES) remission (RR =1.08, 95% CI: 0.97–1.21, P=0.16) between the two groups. Endoscopic transsphenoidal surgery was associated with a lower incidence of diabetes insipidus (DI) than was microscopic transsphenoidal surgery (RR =0.76, 95% CI: 0.60–0.97, P=0.03).

Conclusions: Endoscopic transsphenoidal surgery does not significantly improve GTR or HES remission, but it can reduce the incidence of DI without increasing the rates of other complications.

Keywords: Pituitary tumor, endoscopy, meta-analysis

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Introduction

Pituitary tumors comprise 10% of intracranial tumors, placing them among the most common malignancies of the brain (1). The main clinical manifestations of pituitary tumor are hormone over-secretion and tumor compression. Treatment methods include drug therapy, radiation therapy, and surgery, with surgical resection being the most effective treatment. However, the pituitary tumor is located deep in the pituitary fossa, adjacent to important structures such as the hypothalamus, cavernous sinus, and internal carotid artery, which limits the visual field and makes tumor removal using traditional surgical methods risky. Transsphenoidal resection was first proposed as a treatment for pituitary adenomas by Schloffer in January 1907 (2). Since 1960, transsphenoidal surgery under a microscope has become the first-choice approach for patients who require

intrasellar surgery. The success rate of surgery is high, while the risk and incidence of complications are low. However, surgery still has certain limitations, especially the poor visibility.

With the development of endoscopic technology, surgery has entered a new era. In 1992, Jankowski was the first to apply endoscopy in pituitary tumor surgery (3). The lens angle of the neuroendoscope can be changed to provide a wider operative field of view, facilitating better observation. The anatomic area exposed by the endoscope is anterior to the optic chiasm, lateral to the lateral wall of the cavernous sinus, and posterior to the end of the basilar artery. In 2007, Laufer *et al.* concluded that endoscopic surgery is safe for transsphenoidal enlargement surgery (4).

In recent years, a number of studies have compared the efficacy and safety of the neuroendoscopic and microscopic transsphenoidal approaches in the treatment of pituitary tumor, but the results have been inconsistent. In order to determine the effectiveness of the neuroendoscopic transsphenoidal approach in pituitary tumor treatment, a meta-analysis of all available studies published to date was conducted to comprehensively evaluate the efficacy and safety of neuro-endoscopic transsphenoidal approach in patients with pituitary tumors. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/gs-20-851).

Methods

Literature search

We conducted a literature search of PubMed, Embase, Cochrane Controlled Center Register of Controlled Trials (CENTRAL), Web of Science database, Google Scholar, and Baidu Scholar. The reference lists of retrieved literature were also searched to identify any relevant articles. The databases were searched from inception to August 25, 2020, and there were no language restrictions. The search strategy was formulated with reference to the Cochrane Handbook. English keywords used for searches included "pituitary tumor", "Cushing syndrome", "Cushing disease", "Acromegaly", "pituitary adenomas", "microscopic*", "endoscopic*", "transsphenoidal*".

Inclusion and exclusion criteria

The inclusion criteria were: (I) publicly published case-control studies; (II) study subjects were patients with pituitary tumors aged >18 years; (III) the experimental group was treated with neuro-endoscopic transsphenoidal pituitary tumor resection, and the control group was treated with microscopic transsphenoidal pituitary tumor resection; (IV) the study outcome indicators included: gross tumor removal (GTR); hormone excess secretion (HES) remission; the incidence of adverse reactions, including cerebrospinal fluid (CSF) leakage, diabetes insipidus (DI), epistaxis, hypopituitarism, meningitis, overall complications, visual improvement, and vision loss. Articles that did not meet the inclusion criteria, articles that did not include the main outcome indicators, or without a response from the author, or published repeatedly were excluded.

Information and data extraction

The full texts of the retrieved studies were read to obtain the general study characteristics, as well as the inclusion criteria, basic information of the study subjects, intervention measures, follow-up time, and main results. For data that could not be obtained from the published studies, we contacted the authors via email. The studies were read and the data were extracted by two authors independently. Any inconsistency or disagreement that arose regarding the data was resolved through discussion. If after a discussion, a consensus still had not been reached, a third reviewer was consulted for their opinion.

Literature quality evaluation

Two researchers evaluated the included literature according to the Newcastle-Ottawa Scale (NOS) (5). This quality evaluation standard includes seven items across the following three domains: (I) selection of the study population: whether the case determination was appropriate; representativeness of the cases; selection of the controls, and determination of the controls; (II) comparability between groups: consideration of the comparability of cases and controls in the study design and statistical analysis; and (III) measurement of exposure factors: determination of the exposure factors; whether the same method was used to determine the exposure factors of the cases and controls; and the non-response rate.

Statistical methods

The meta-analysis was performed using RevMan5.1

software (Cochrane Center, London, England), available from Cochrane. Heterogeneity among the studies was analyzed using the χ^2 test and I^2 test. If the homogeneity between studies was good (I^2 <50%, P>0.1), the fixed-effects model was adopted; otherwise, the random-effects model was used. When clinical data could not be meta-analyzed, descriptive analysis was carried out.

Results

Literature search results

The initial search retrieved 577 articles, and after the elimination of duplicates with EndNote software, 443 articles remained. After the titles, abstracts, and full texts of these articles had been read, 29 articles that met the inclusion criteria were finally included in the meta-analysis and are shown in *Table 1*. The literature screening flowchart is displayed in *Figure 1*.

General characteristics of the included articles

A total of 29 studies, involving 4,557 patients, were included in this meta-analysis. All of the studies were designed as case-control studies and were published between 1999 and 2020. Patient populations mainly comprised Europeans, North Americans, and South Americans. Major countries involved in these studies included the United States, the United Kingdom, India, Canada, Italy, Finland, Iran, Norway, Belgium, North Korea, France, and China. The general information of the included articles is shown in *Table 1*.

Quality evaluation

The results of the quality evaluation of the included articles are shown in *Table 2*.

Meta-analysis results

Gross tumor removal

Fourteen studies reported the total tumor resection rates of endoscopic transsphenoidal resection and microscopic transsphenoidal resection in patients with pituitary tumors. The results showed that there was no significant difference in the tumor total resection rate between the endoscopic surgery group and the microscopic surgery group (RR =1.11, 95% CI: 0.97–1.26, P=0.12, *Figure 2*).

Hormone excess secretion remission

Ten studies reported the remission rates of hormone over-secretion in patients with pituitary tumors who underwent endoscopic or microscopic transsphenoidal resection. The results showed that there was no significant difference in the remission rate of hormone over-secretion between the endoscopic surgery group and the microscopic surgery group (RR =1.08, 95% CI: 0.97–1.21, P=0.16, *Figure 3*).

Overall complications

Nine studies reported the total complication rates of endoscopic transsphenoidal resection and microscopic transsphenoidal resection in patients with pituitary tumors. The results revealed no significant difference in the overall complication rate between the endoscopic surgery group and the microscopic surgery group (RR =0.82, 95% CI: 0.54–1.23, P=0.34, *Figure 4*).

Cerebrospinal fluid leakage

Twenty-five studies reported the incidence of postoperative CSF leakage in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. The results showed no significant difference in the incidence of CSF leakage between the endoscopic surgery group and the microscopic surgery group (RR =1.06, 95% CI: 0.88–1.28, P=0.51, *Figure 5*).

Diabetes insipidus

Twenty studies reported the incidence of postoperative DI in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. The results revealed the incidence of DI in the endoscopic surgery group to be significantly lower than that in the microscopic surgery group, and the difference was statistically significant (RR =0.76, 95% CI: 0.60–0.97, P=0.03, *Figure 6*).

Epistaxis

Five studies reported the incidence of postoperative epistaxis in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. The results showed no significant difference in the incidence of epistaxis between the endoscopic surgery

Table 1 Characteristics of the included studies

Study	Study period	Study design	Sample size (end/mic)	Country	Disease	Age		Sex	
						Endoscopic	Microscopic	Endoscopic	Microscopic
Bora SK 2020 (6)	2009.1–2009.6	Retrospective	55/47	India	Cushing disease	28 (9–55)			
Pablo A 2019 (7)	2011.3–2014.12	Retrospective	140/259	Argentina	Pituitary adenomas	48.5 (18–85)	51(17–90)	61/79	109/150
Agam MS 2018 (8)	1992.11–2017.3	Retrospective	170/983	USA	Pituitary adenomas	53.3 (13.6)	49.1 (16.6)		
Akbari H 2018 (9)	2012–2014	Retrospective	16/19	Iran	Pituitary adenomas	39.43±15.2	43.06±11.29	19/16	
Wang AC 2018 (10)	2003.1–2012.8	Retrospective	117/37	USA	Pituitary adenomas	50	52	54/63	10/27
Eseonu CI 2017 (11)	2005.5–2005.8	Retrospective	275/109	USA	Pituitary adenomas	49.0±16.2	48.8±15.8	163/221	
Levi V 2017 (12)	2004–2012	Retrospective	140/81	Italy	Pituitary adenomas	58.5	52	130/91	
Fathalla H 2015 (13)	2000–2013	Retrospective	42/23	Canada	Acromegaly	43.2	42.1	21/21	7/16
Karppinen A 2015 (14)		Retrospective	41/144	Finland	Nonfunctioning pituitary adenomas	58.5±16	58.4±13	118/67	
Lenzi J 2015 (15)	1996–2006	Retrospective	22/15	Italy	Acromegaly				
Dallapiazza R 2014 (16)	2010.6–2013.1	Retrospective	56/43	USA	Nonfunctioning pituitary adenomas	56.2±12.8	56.7±16.9	51/48	
Halvorsen H 2014 (17)	2020.9–2011.2	Retrospective	238/268	Norway	Pituitary adenomas			291/215	
Sarkar S 2014 (18)	2005.1–2013.4	Retrospective	66/47	India	Acromegaly	37.6±10.8	38.7±12.2	30/36	26/21
Alahmadi H 2013 (19)	2000–2010	Retrospective	17/25	Canada	Cushing disease			11/31	
Razak AA 2013 (20)	2008.1	Retrospective	40/40	UK	Pituitary adenomas	47.4	49.3	19/21	22/18
Starke RM 2013 (21)	2004.8–2009.10	Retrospective	72/41	USA	Acromegaly	49.2 (14.9)	47.5 (14.2)	40/32	20/21
Cheng RX 2011 (22)	2003.7–2009.7	Retrospective	68/59	China	Functioning pituitary adenomas	37.2	33.8	51/76	
Massimi L 2011 (23)	2000–2005	Retrospective	17/14	Italy	Pituitary adenomas	10.2	11.4	14/17	
Messerer M 2011 (24)	2006–2009	Retrospective	82/82	France	Nonfunctioning pituitary adenomas	57	56.9	98/66	
D'Haens J 2009 (25)	1995.2–2007.1	Retrospective	60/60	Belgium	Functioning pituitary adenomas				
Choe JH 2008 (26)	1997–2004	Retrospective	12/11	Korea	Functioning pituitary adenomas	47±12	48±10	7/5	9/2
Higgins TS 2008 (27)		Retrospective	19/29	UK	Pituitary adenomas	54.2	52.8	25/23	

Table 1 (*continued*)

Table 1 (*continued*)

Study	Study period	Study design	Sample size (end/mic)	Country	Disease	Age		Sex	
						Endoscopic	Microscopic	Endoscopic	Microscopic
O'Malley BW 2008 (28)	2003.7–2008.5	Retrospective	25/25	USA	Pituitary adenomas	47.9 (18–73)	50.8 (23–78)	15/10	16/9
Neal JG 2007 (29)	1999–2004	Retrospective	21/15	USA	Pituitary adenomas	51	39	9/12	5/10
Cappabianca P 1999 (30)	1997.1–1997.6	Retrospective	10/20	USA	Pituitary adenomas	33–67	20–68	6/4	11/9
Koren I 1999 (31)	1993.1–1997.6	Retrospective	20/20	Israel	Pituitary adenomas				
Sheehan MT 1999 (32)	1995.1–1997.10	Retrospective	26/44	USA	Nonfunctioning pituitary adenomas	59.2 (15.1)	57.8 (14.9)	18/8	31/13
White DR 2004 (33)	1996–2002	Retrospective	50/50	USA	Pituitary adenomas	41.1	43.5	24/26	33/17
Casler JD 2005 (34)	1996.11–2003.7	Retrospective	15/15	USA	Pituitary adenomas	41.6	50.66	6/9	10/5

Figure 1 Flow diagram showing the study selection process.

group and the microscopic surgery group (RR =1.73, 95% CI: 0.80–3.76, P=0.17, *Figure 7*).

Meningitis

Ten studies reported the incidence of postoperative meningitis in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. No significant difference was found in the incidence of meningitis between the endoscopic surgery group and the microscopic surgery group (RR =1.20, 95% CI: 0.68–2.14, P=0.53, *Figure 8*).

Hypothyroidism

Eight studies reported the incidence of postoperative hypopituitarism in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. The results showed no significant difference in the incidence of hypopituitarism between the endoscopic surgery group and the microscopic surgery group (RR =0.80, 95% CI: 0.55–1.18, P=0.26, *Figure 9*).

Visual improvement

Five studies analyzed the visual improvement rate in patients with pituitary tumors who underwent endoscopic transsphenoidal resection and microscopic transsphenoidal

Table 2 Quality assessment of the included studies

Study	Selection				Comparability	Exposure		
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls: most important factor	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate
Bora SK 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pablo A 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Agam MS 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Akbari H 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Wang AC 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Eseonu CI 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Levi V 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fathalla H 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Karppinen A 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lenzi 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dallapiazza R 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Halvorsen H 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sarkar S 2014	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Alahmadi H 2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Razak AA 2013	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Starke RM 2013	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Cheng RX 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Massimi L 2011	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Messerer M 2011	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
D'Haens J 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Choe JH 2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Higgins TS 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
O'Malley BW 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Neal JG 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Casler JD 2005	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
White DR 2004	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Cappabianca P 1999	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Koren I 1999	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Sheehan MT 1999	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

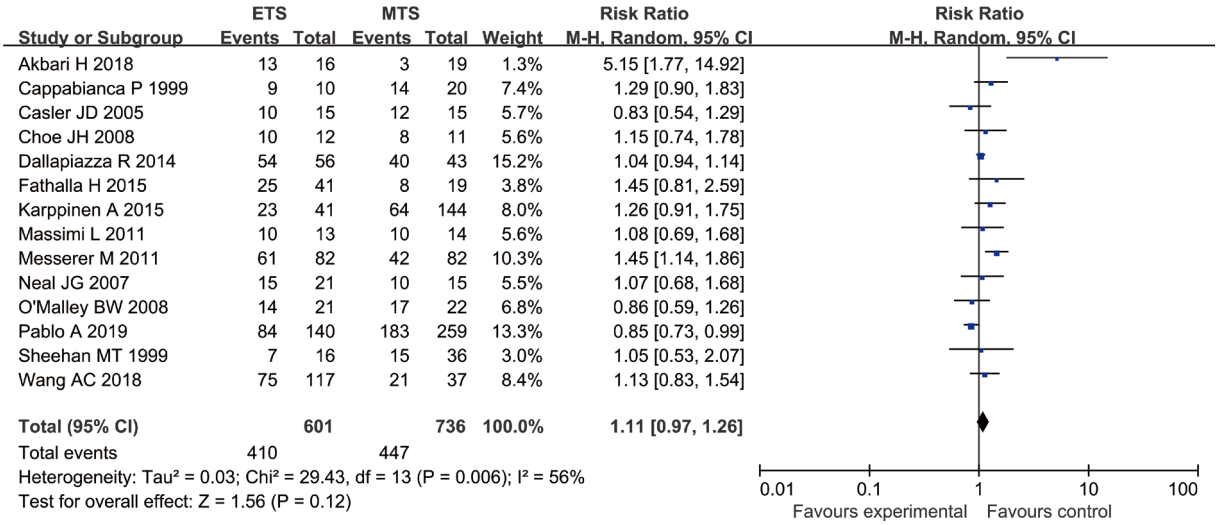

Figure 2 Comparison of gross tumor removal (GTR) between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

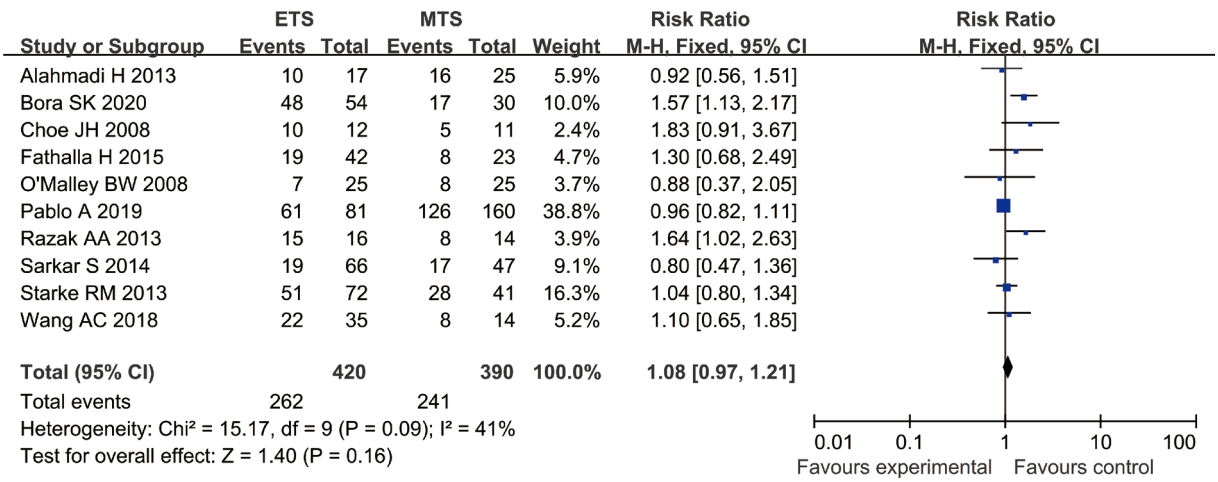

Figure 3 Comparison of the hormone excess secretion (HES) remission rates between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

resection. The results showed that there was no significant difference in the visual improvement rate between the endoscopic surgery group and the microscopic surgery group (RR =1.01, 95% CI: 0.87–1.17, P=0.89, *Figure 10*).

Vision loss

Seven studies reported the incidence of postoperative visual impairment in patients with pituitary tumors who underwent endoscopic transsphenoidal resection or microscopic transsphenoidal resection. The results revealed no significant difference in the incidence of visual impairment between the endoscopic surgery group and the microscopic surgery group (RR =1.05, 95% CI: 0.56–1.96, P=0.89, *Figure 11*).

Publication bias

The funnel chart showed that no publication bias existed (Figures S1-S10).

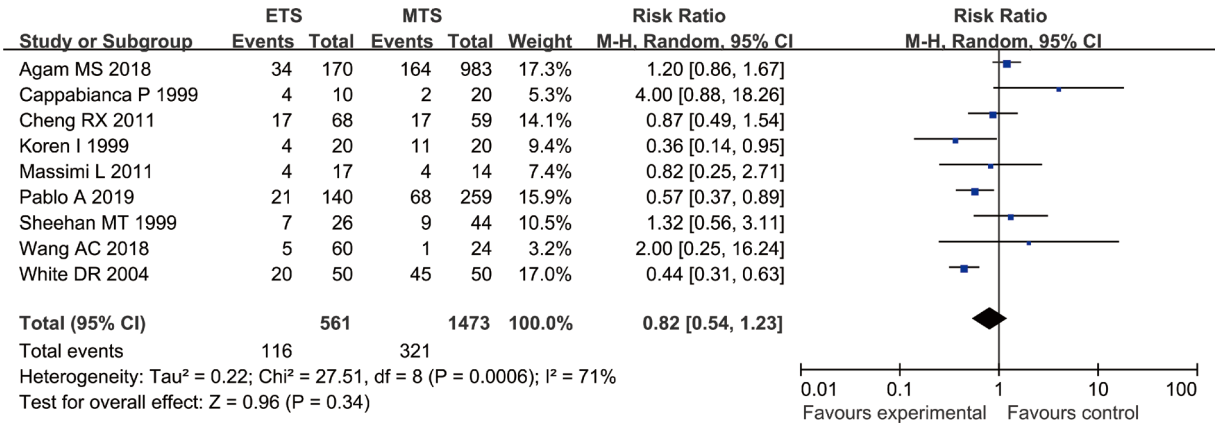

Figure 4 Comparison of the overall complication rates of endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

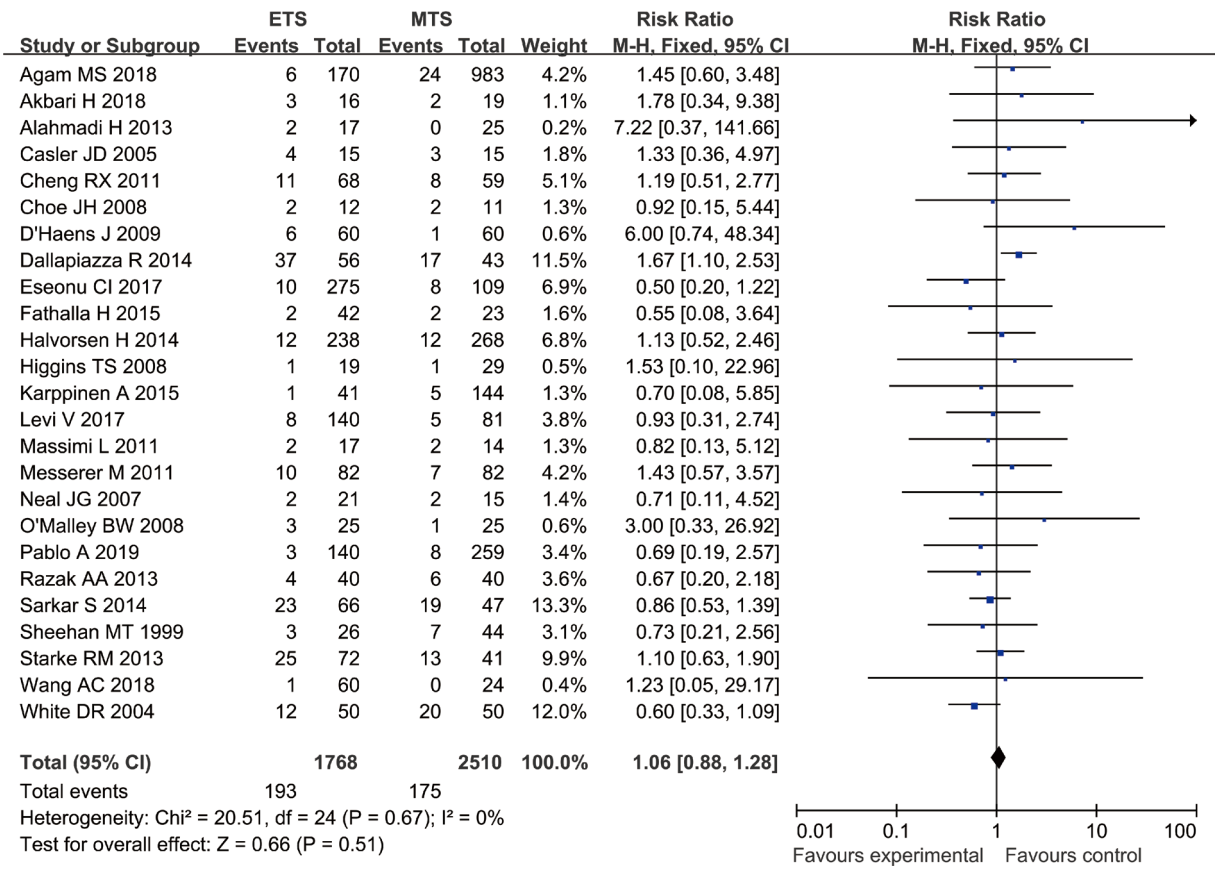

Figure 5 Comparison of the incidence of cerebrospinal fluid (CSF) leakage between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

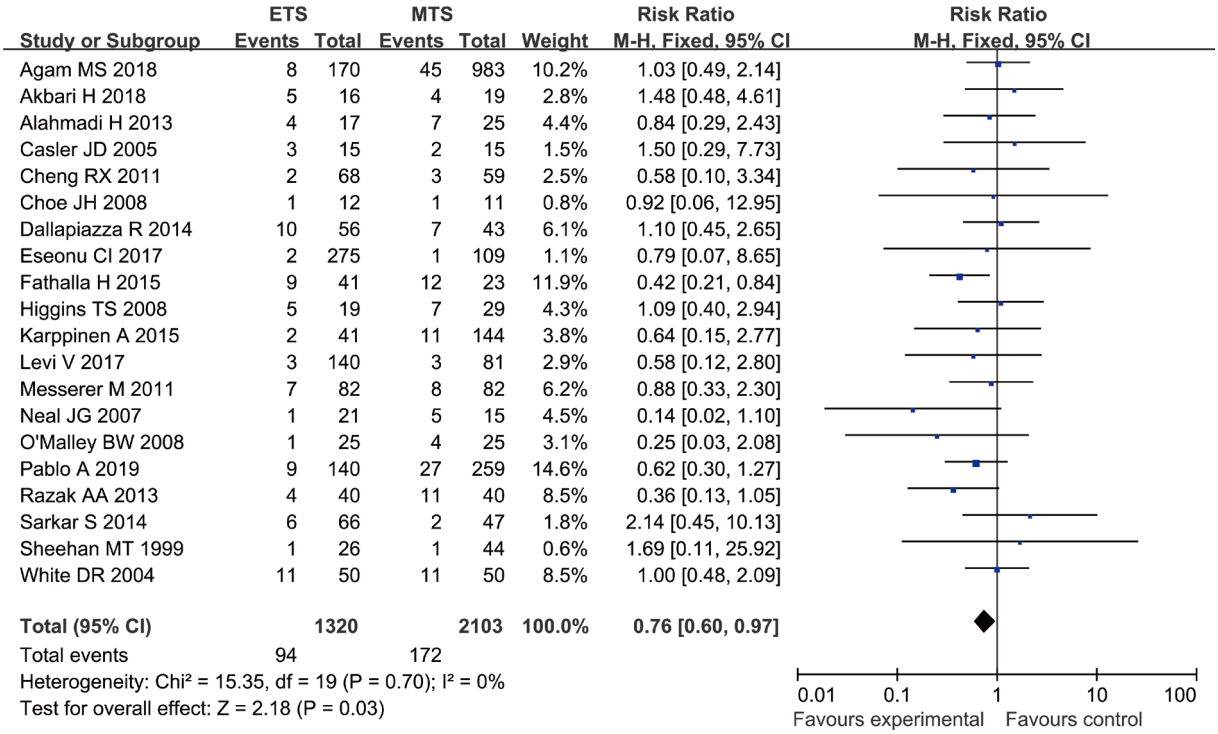

Figure 6 Comparison of the incidence of diabetes insipidus (DI) between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

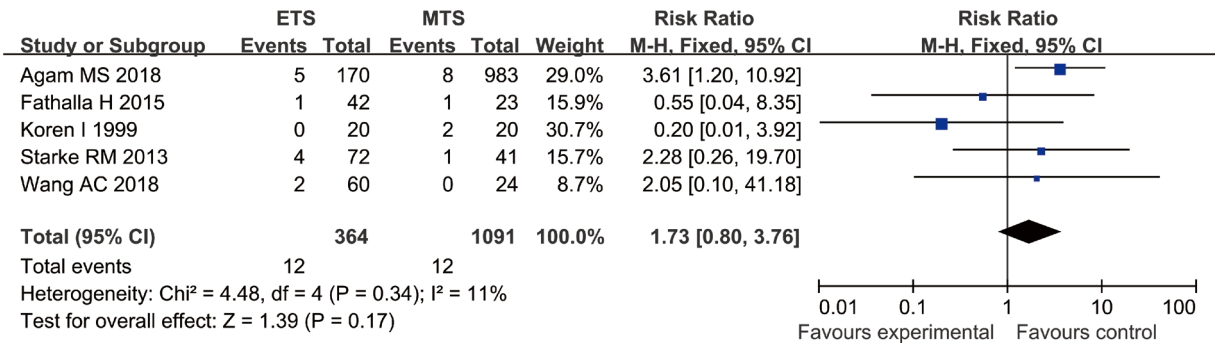

Figure 7 Comparison of the incidence of epistaxis between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

Discussion

At present, transsphenoidal tumor resection employing a neuroendoscopic or microscopic approach is the standard surgical treatment for pituitary tumors. However, the short-term effects of these two surgical methods are still controversial. In recent years, an increasing number of high-quality clinical studies have been conducted on the application of these two surgical methods in the treatment of pituitary tumors. However, the latest result of evidence-based medicine research has not been updated in time.

This meta-analysis of 29 case-control studies compared the efficacy and safety of neuroendoscopic and microscopic transsphenoidal resection for the treatment of pituitary tumors. The results showed that in terms of clinical efficacy,

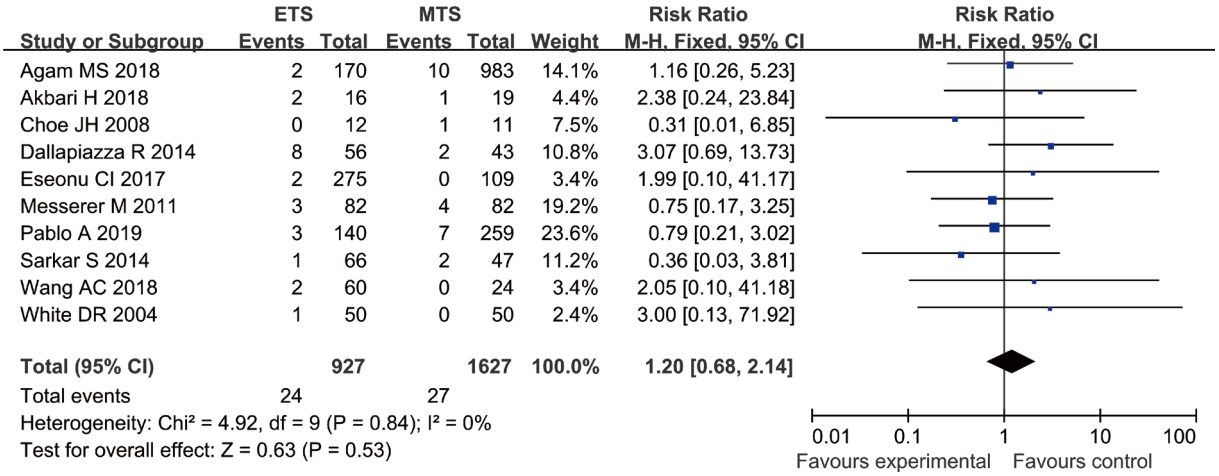

Figure 8 Comparison of the incidence of meningitis between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

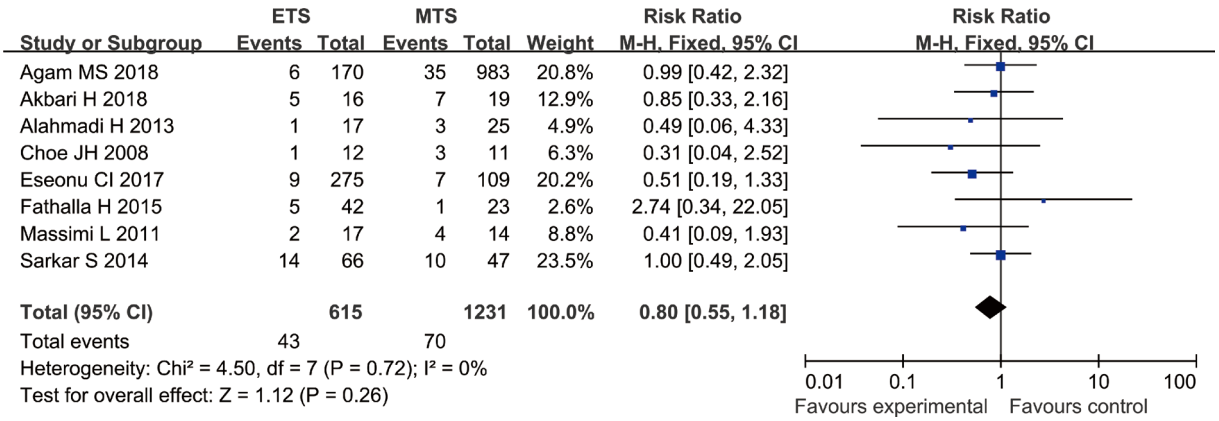

Figure 9 Comparison of the incidence of hypothyroidism between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

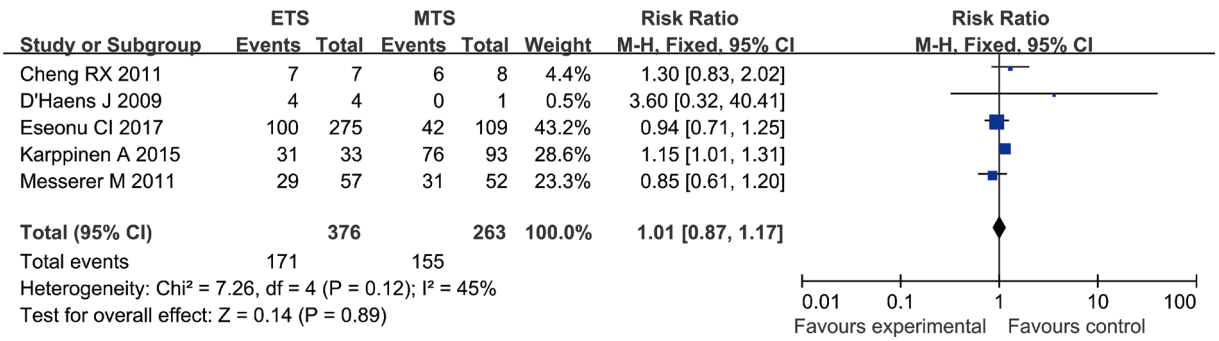

Figure 10 Comparison of the visual improvement rates of endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

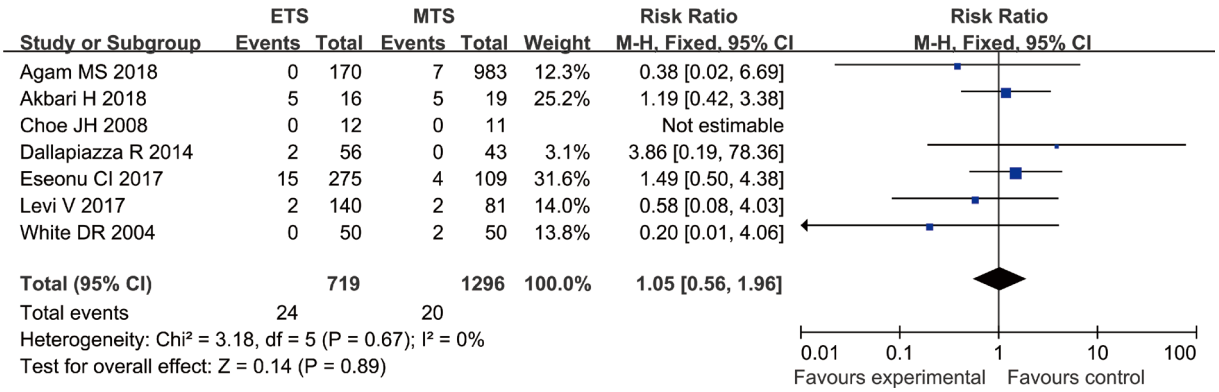

Figure 11 Comparison of the incidence of vision loss between endoscopic transsphenoidal surgery (ETS) and microscopic transsphenoidal surgery (MTS).

there was no statistically significant difference in the rates of tumor total resection, hormone over-secretion, or visual improvement between the two surgical methods. In terms of safety, neuroendoscopic transsphenoidal surgery could significantly reduce the postoperative incidence of DI, although total complications, CSF leakage, epistaxis, meningitis, and other complications did not differ significantly between the two methods.

Although the resection rates of the two techniques did not show a significant difference, the ease of operation of the endoscope is an advantage in more complex operations. The use of an angled endoscope and its large range of movement can facilitate the removal of tumors that cannot be reached using the traditional transsphenoidal approach. Second, due to its flexibility, the endoscope can be inserted into the resected tumor cavity at the end of the operation to look for residual tumor, which makes intraoperative magnetic resonance imaging unnecessary. For large tumors that may be accompanied by CSF leakage, the use of an endoscope offers the advantage of a panoramic field of view.

The postoperative recovery of vision in patients with pituitary tumors is affected by factors including the age of onset, the preoperative degree of visual field defect, tumor size, and other factors. Following surgery, the vision of most patients is improved to varying degrees. However, there is no evidence that the choice of surgical method can affect postoperative recovery of vision, and our results cannot prove this.

Postoperative DI is transient in most cases, and few patients develop permanent DI. The occurrence of DI is affected by the precision of the surgeon. The neuroendoscopic transsphenoidal approach can reduce the incidence of DI, which may be related to the fact that neuroendoscopy can provide a better operative field of view.

CSF leakage is a common postoperative complication. The incidence of CSF leakage for neuroendoscopy and microscopy is 5–7% and 6.34–8%, respectively. Neuroendoscopy allows the diseased tissue and its surrounding structures, as well as the blind corners of the visual field that cannot be seen under a microscope, to be clearly observed. Therefore, the incidence of postoperative CSF leakage with a neuroendoscope is lower than that with a microscope. However, our results showed no significant difference in the incidence of postoperative CSF fistula between the neuroendoscopic and microscopic surgery groups. There may be three reasons for this: First, the studies we included were all case-control studies with a relatively low level of evidence. Secondly, the number of patients was insufficient. Thirdly, the incidence of postoperative CSF leakage was not significantly affected by the surgical method adopted. This result still needs to be verified by more high-quality large-sample randomized controlled studies.

This study has certain limitations. First, only retrospective case-control studies were included, and most of them did not describe the method for evaluating the tumor total resection rate in detail. The studies also included different types of pituitary tumors, and it was impossible to determine whether postoperative results are correlated with the type of pituitary tumor.

Conclusions

The results of this meta-analysis suggest that neuroendoscopic

transsphenoidal surgery does not significantly increase the tumor total resection rate or the remission rate of excessive hormone secretion. However, this surgical method was found to significantly reduce the incidence of postoperative DI without increasing the incidence of other complications.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/gs-20-851

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/gs-20-851). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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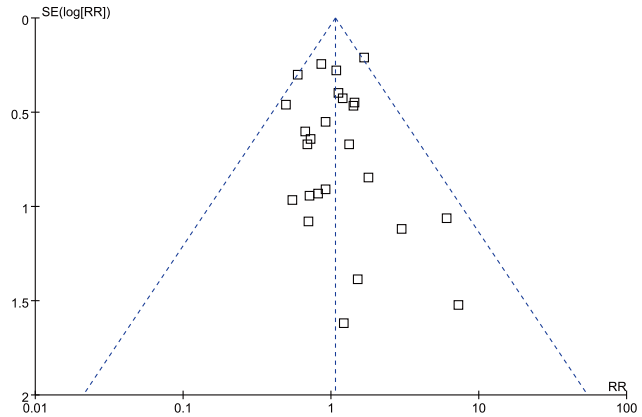

Figure S1 CSF leak Funnel plot.

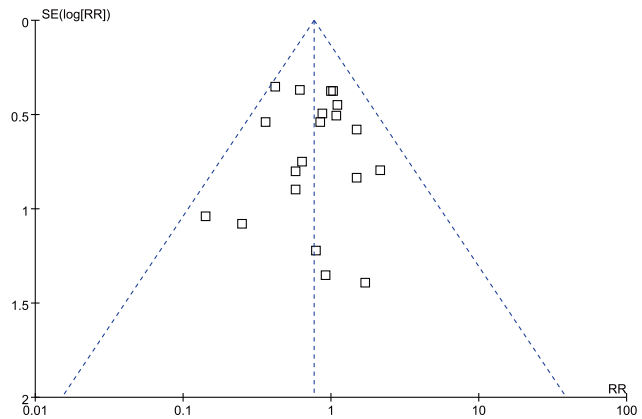

Figure S2 DI Funnel plot.

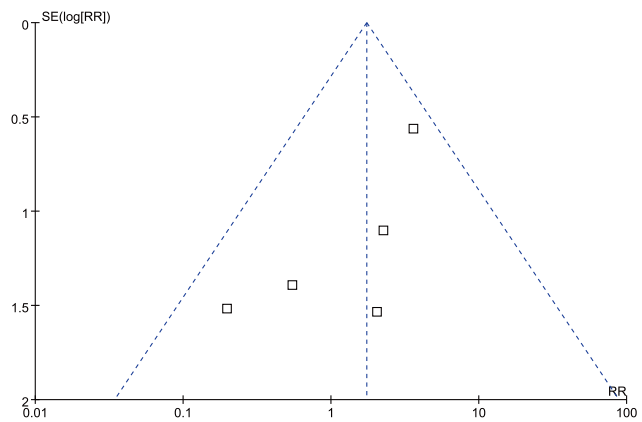

Figure S3 Epistaxis Funnel plot.

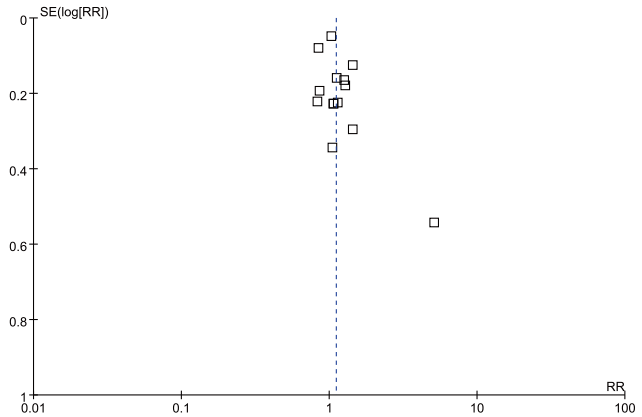

Figure S4 GTR Funnel plot.

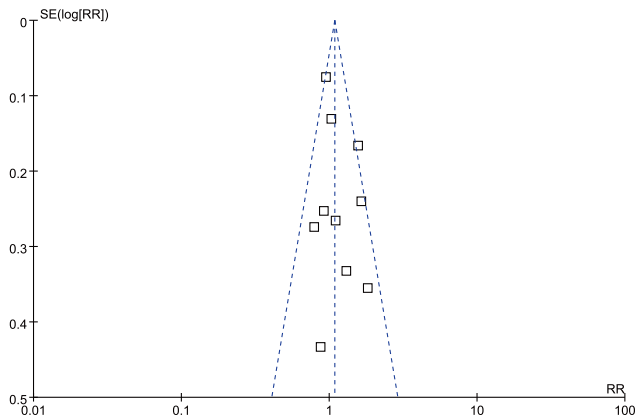

Figure S5 HES remission Funnel plot.

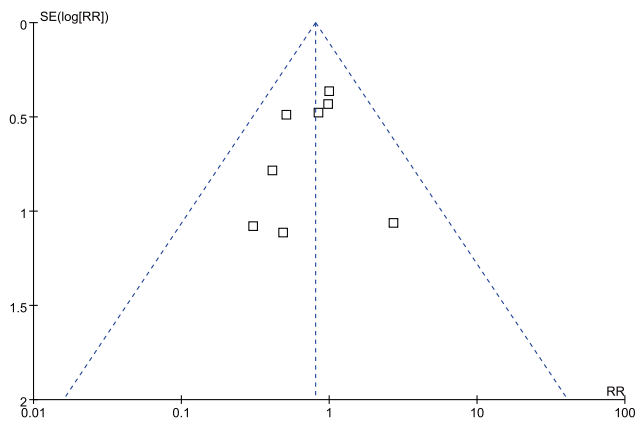

Figure S6 Hypopituitarism Funnel plot.

http://dx.doi.org/10.21037/gs-20-851

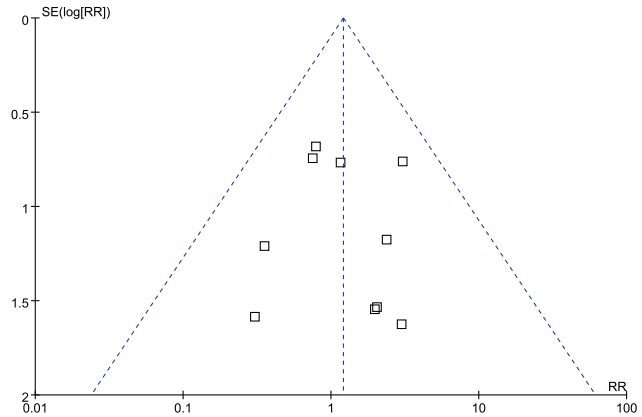

Figure S7 Meningtis Funnel plot.

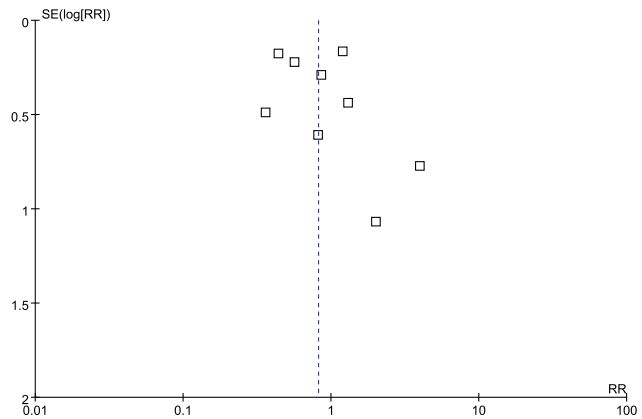

Figure S8 Overall complication Funnel plot.

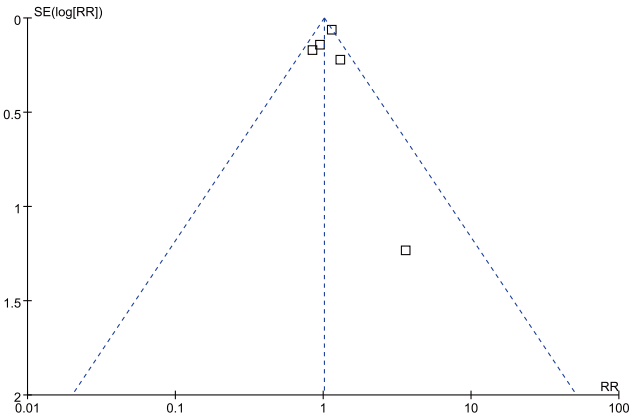

Figure S9 Visual improvement Funnel plot.

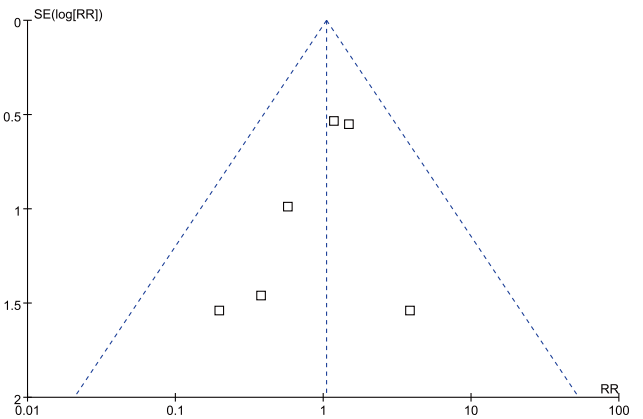

Figure S10 Worsened vision Funnel plot.

http://dx.doi.org/10.21037/gs-20-851