Intraoperative Monitoring of Visual Evoked Potentials in Patients Undergoing Transsphenoidal Surgery for Pituitary Adenoma: A Systematic Review

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Abstract

Background

Transsphenoidal surgery is the gold standard for pituitary adenoma resection. Although rare, a serious complication of surgery is worsened vision post-operatively.

Objective

To determine whether, in patients undergoing transsphenoidal surgery for pituitary adenoma, intraoperative monitoring of visual evoked potentials (VEP) is a safe, reproducible and effective technological adjunct in predicting postoperative visual function.

Methods

The MEDLINE database was searched between January 1993 and June 2019 to identify publications that (1) featured patients undergoing transsphenoidal surgery for pituitary adenoma, (2) used intraoperative optic nerve monitoring with VEP and (3) reported on safety or effectiveness. Reference lists were cross-checked and expert opinion sought to identify further publications.

Results

Ten studies were included comprising nine case series and one cohort study. All employed techniques to improve reliability. No safety issues were reported. The only comparative study included described a statistically significant improvement in post-operative visual field testing when VEP monitoring was used. The remaining case-series varied in conclusion. In nine studies, surgical manipulation was halted in the event of a VEP amplitude decrease suggesting a widespread consensus that this is a warning sign of injury to the anterior optic apparatus.

Conclusions

Despite limited and low-quality published evidence regarding intra-operative VEP monitoring, our review suggests that it is a safe, reproducible and increasingly effective technique of predicting postoperative visual deficits. Further studies specific to transsphenoidal surgery are required to determine its utility in protecting visual function in the resection of complex pituitary tumours, and of other tumours in the anterior skull base.

Introduction

Transsphenoidal surgery is the gold standard for pituitary adenoma resection, yet in one third of patients it is incomplete. [1] Advances in endoscopic surgery have opened possibilities for more complete tumour resections. However, the close relationship between the pituitary and the optic pathway implies that the benefits of complete resection must be balanced against the risk of post-operative visual dysfunction.

Visual-evoked potentials (VEP), as a means of intraoperative monitoring of visual function were first used during intra-orbital surgery in 1973[2] and in our institution since 1985[3] but have been criticised for being both unreliable and poorly reproducible and therefore not standardly adopted into common practice.

In recent years, the use of total intravenous anaesthesia (TIVA)[4, 5], the incorporation into the hardware of light-emitting diode (LED) technology [6-8] and adjuncts such as electroretinography (ERG)[6-8] and electroencephalography (EEG)[9] have attempted to overcome technical setbacks previously encountered in VEP neuromonitoring.

This being said, there are comparatively few reports of intraoperative VEP monitoring during transsphenoidal pituitary surgery despite the close relationship that this surgical approach maintains with the optic apparatus. Accordingly, conclusions on the current clinical usefulness of VEPs have yet to be drawn.

The aim of the present systematic review was to determine whether, in patients undergoing transsphenoidal surgery for pituitary adenoma, intraoperative visual evoked potential monitoring is a safe, reliable and effective technological adjunct in intra-operatively alerting the surgeon of compromise to the anterior visual pathway, and in predicting post-operative visual outcome.

Materials And Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used in the preparation of this manuscript. [10]

Search Methods

The MEDLINE database was searched over a 26-year period between January 1993 and June 2019. The Boolean search term (pituitary OR hypophysectomy OR transsphenoidal OR endonasal) AND ("visual evoked potential" OR VEP OR monitoring) AND (intraoperative) was used. Reference lists of included articles were also reviewed, and expert opinion sought, to identify further eligible publications. Two authors (FA and JB) independently identified articles using the above search criteria. Expert opinion (IC) was sought to find additional papers.

Inclusion and exclusion criteria

Titles and abstracts were screened to identify publications that (1) featured patients undergoing transsphenoidal surgery for pituitary adenoma, (2) used intraoperative VEP monitoring and (3) reported on safety or effectiveness. Full articles were obtained and further assessed for eligibility. Discrepancies were resolved by discussion with the senior author (HJM).

Data extraction

The following data was extracted from eligible full articles: (1) study design, (2) study group characteristics including the number of patients and pathology, (3) VEP monitoring equipment details including mode of anaesthesia, (4) safety, (5) stability and reproducibility, and (6) effectiveness. With respect to the effectiveness of VEP, we considered the extent to which intra-operative VEP allowed for prediction in post-operative visual waveform and visual function outcomes.

Appraisal of evidence

The Methodological Index for Non-Randomised Studies (MINORS) scoring systems were used to guide evaluation of the quality of studies [11]. Studies of greater quality were given greater weighting in the qualitative analysis.

Results

A total of 201 articles were pooled from the electronic database (Figure 1). Of these, one was a duplicate. Three further articles were identified via expert opinion. 181 articles were excluded on the basis of their title and abstract as they did not feature patients undergoing specifically transsphenoidal surgery for pituitary adenoma, did not include VEP monitoring or did not report on safety or effectiveness.

Full text screening was conducted on the remaining 22 articles. This led to the exclusion of a further 12 articles. It was not possible to obtain the full text of two articles. One of these was an article from 1993[12] and the other, a case report on craniopharyngioma was written in Japanese and not available in English.[13] Two articles did not present any original data; one was looking at cerebral aneurysms; two studies did not mention use of the transsphenoidal approach, five studies did not use visual evoked potentials and one was looking at the abducens nerve.

STUDY DESIGN AND STUDY GROUP CHARACTERISTICS

In all, 10 studies were identified that satisfied the inclusion criteria comprising one cohort study and nine case series (Table 1)[6, 7, 9, 14-20]. No randomised studies were found. It is important to note that only the cohort study by *Chacko et al* looked exclusively at patients with pituitary adenoma. The remaining nine studies identified from the electronic database looked at patients undergoing all endoscopic surgery for sellar or parasellar tumours; whilst the bulk of this was pituitary adenoma, other pathology included meningioma, Rathke's cleft cyst, arachnoid cyst and craniopharyngioma amongst others. The papers identified by expert opinion, *Luo et al*, *Houlden et al* and *Sasaki et* al, describe a broader use of VEPs in neurosurgery and therefore also include patients undergoing craniotomy; where possible, information specifically related to patients undergoing transshpenoidal surgery for pituitary adenoma has been extracted from these.

The quality of the included studies was variable (Table 2). The only comparative study reviewed was also the oldest. Performed by *Chacko et al* in 2009 it is of fair quality (MINORS 16/24). Limitations are a lack of mention of consecutive patients, blinding, prospective calculation of study size, and length of follow up. The remaining studies were case series of similar quality (MINORS SCORE ranging 9/16 to 13/16.) None of these studies documented a prospective calculation of study size. There was variability in the inclusion of consecutive patients, unbiased assessment of the study end-point and adequate follow-up period.

VEP MONITORING EQUIPMENT

The manufacturer and monitoring device used to analyse VEP waveform was mentioned in all studies except by *Feng et al.* The remaining nine studies used a combination of eight different signal processors (Table 3).

Mode of Anaesthesia

Kurozumi et al did not comment on anaesthetic regimen used. The majority of the remaining studies reported the use of total intra-venous anaesthesia (TIVA) (Table 4). 3 studies utilised Bispectral Index (BIS) monitoring to maintain the depth of anaesthesia between BIS-values of 40-60.[7, 15, 18]. These values represent the recommendation given by the National Institute for Health and Care Excellence (NICE).[21] *Feng et al* describe one exclusion for an unreliable VEP secondary to anaesthetic regimen. *Houlden et al* commented on the use of simultaneous EEG.

Chacko et al, was the only study to use solely gas anaesthesia; a combination of 60% nitrous oxide and 0.5% halothane with muscle relaxants and morphine. As gas anaesthesia is thought to cause VEP instability, they attempted to reduce this by taking baseline recordings more than 30 minutes after the induction of anaesthesia. *Houlden et al* also used inhalation agents for two of their patients and whilst they found they could initially maintain a stable VEP, the reproducibility was subsequently impaired by bolus injections of propofol and a high MAC of desflurane.

Light Stimulus Delivery Device

Four of the studies [9, 14, 18, 19] report the use of LED goggles for stimulus delivery. The study by *Chung et al* names the manufacturer as XLTEK (Ontario, Canada.) *Feng et al* report two exclusions due to technical malfunctions of the optic goggles.

Luo et al describe the placement of a light stimulating device between two transparent eye patches on top of the eye.

In their study, *Sasaki et al* introduced a 2cm round silicone disk embedded with 16 red high luminosity (100mCd) LEDs to reduce light axis deviation from frontal scalp-flap reflection. The remaining four studies all describe the use of this method. [7, 15-17] *Toyama et al* also used a black light shield patch on the device to avoid interference between light stimulations. No other study commented on this.

ERG Monitoring

ERG confirms the arrival of adequate light stimulation at the retina. The use of simultaneous ERG monitoring was reported by five of the studies.[6, 7, 15-17] Toyama et al report one case of intra-operative wire breakage leading to loss of ERG signal.

SAFETY

There were no cases of operative mortality reported in the any of the studies or any operative complications directly related to intra-operative VEP monitoring. *Kamio et al* reported three cases of detachment of the VEP recording electrode from its occipital position but this did not result in any adverse effects. The device introduced by Sasaki, and utilised by several others, *"incorporates a safety system that shuts it down if continuous illumination by the LEDs exceeds [four]seconds."[6]*

There was no report of any pressure-related eye problems from the goggles or silicone disk in any study.

STABILITY AND REPRODUCIBILITY

All of the studies commented on stability of VEP waveforms. This ranged from 67% in the study by *Chung et al* to 100% in the study by *Kurozumi et al.* The study by *Houlden et al* suggested that "low amplitude EEG" plays an important role in maintaining VEP stability but did not disclose the number of stable VEP waveforms from their study. The cohort study by *Chacko et al* also did not provide the number of stable waveforms but did assess stability by performing serial VEP recordings at baseline, 30 minutes after induction of anaesthesia and then continuously until dural opening.

Many of the studies required at least two consecutive VEP recordings or recording sessions of light stimulation prior to surgical manipulation to confirm reproducibility of the waveforms [6, 7, 9, 16-18, 20].

Other techniques used to increase stability and reproducibility included the use of total intra-venous anaesthetic (TIVA), the use of LED goggles or silicone discs for light stimulus delivery, a black shield patch placed over the eyes and braided electrode cables, [15] and the use of simultaneous electroretinography (ERG) monitoring. One or more of these techniques were employed in all studies (Table 4).

VEP Amplitudes

VEP amplitudes were monitored throughout the operation in all studies. The changes observed in baseline VEP amplitude were described in all of the case series except *Houlden et al* (Table 5). Except for the study by Chacko et al, all studies reported common criteria to measure changes in VEP amplitude: For improvement, a greater than 50% increase in baseline VEP amplitude; and for deterioration, a greater than 50% decrease in baseline VEP amplitude [14-18].

Aside from *Chung et al,* the remaining case series commented on whether the baseline VEP amplitude remained unchanged or whether it showed an improvement, temporary deterioration or permanent deterioration. Chung et al did not comment on whether VEP amplitude deterioration was temporary or permanent. All studies reported that in the event of a VEP amplitude deterioration, the surgeon was alerted and surgical manipulations were stopped temporarily.

The VEP waveforms remained unchanged in the majority of operations across all the studies (54-90%). VEP deterioration was more often reported to be temporary than permanent. Permanent VEP deterioration ranged from 0 – 15%. Four studies showed an improvement in VEP waveform [14, 15, 18]. In the cohort study by *Chacko et al,* all eyes in the testing group (with VEP monitoring) exhibited a transient decrease in VEP amplitude. This was also noted in the study by *Houlden et al* in relation to amplifier blocking caused by electrocautery.

EFFECTIVENESS

Here we define effectiveness as the capacity of intra-operative VEPs to predict visual function outcomes. All of the studies except *Houlden et al* commented on this.

The majority of the studies looked at the visual outcomes pre- and post-operatively by looking at both visual acuity and visual fields. *Nishimura et al, Luo et al,* and *Sasaki et al* did not report on these separately but commented on outcomes of post-operative visual function which took both of these into consideration. *Table 6* provides an overview of associations observed between changes in VEP and patient visual outcomes.

The studies by *Feng et al*, *Kodama et al, Sasaki et al, Kamio et al* and *Luo et al* suggested that there was a correlation between intra-operative VEP changes and post-operative visual outcomes. The study by *Feng et al* describes this association with visual fields whereas *Kodama et al* suggest that VEP monitoring is more useful for visual acuity. *Luo et al* and *Sasaki et al* describe an association with visual function as a whole and do not distinguish between visual fields and acuity. *Toyama et al*, *Chung et al* and Chacko et al found no association. *Nishimura et al* speculate in favour of a correlation between the two.

Table 7 calculates the sensitivity, specificity, positive predictive value and negative predictive value of each these studies from the data provided. Where visual field and visual acuity data was reported separately [7, 14, 15, 18, 19, 22], the visual field outcomes only were used to calculate new post-operative visual deficit as visual fields have been found to be the more consistent measure of post-operative visual function for VEP monitoring in the literature. In the studies by Nishimura et al, Luo et al, Sasaki et al and Kurozumi et al, whilst post-operative visual outcome data was reported, this was not split into visual field and visual acuity therefore the figures provided have been used.

Feng et al found a direct correlation between intra-operative VEP changes – specifically amplitude – and post-operative changes in visual fields, with an odds ratio of 3.15 (95% CI 1.15-8.59). They calculated the sensitivity and specificity of VEP amplitude in detecting changes in visual field outcome as 75% and 79%

respectively.

Luo et al calculated the association between intra-operative VEP and post-operative visual function to have a specificity of 96% [88–100%] and a negative predictive value (NPV) of 90% [79–96%] but reported ' the positive predictive value (PPV) could not be calculated because there was no true positive (TP) loss of VEP in [their] series. These statistics were influenced by the three patients who developed homonymous hemianopia post-operatively without any change in intra-operative VEP. It must be noted that these three patients did not have pituitary tumours and these changes reflect a failure to detect changes in the posterior visual pathway. They did comment that intraoperative VEPs were sensitive enough to detect mechanical manipulation of the anterior visual pathway in an early reversible stage.

Toyama et al studied 39 eyes of which none experienced a worsening in visual acuity or visual fields post-operatively. We calculated a specificity of 85% and a negative predictive value of 100% however the authors comment that they did not observe any significant relationship between intra-operative VEP changes and post-operative improvement in visual field defect.

Kamio et al described one case where VEP amplitude decreased. This correlated directly with resecting a piece of tumour adherent to the optic chiasm. Despite halting surgical manipulation and administering methylprednisolone, the VEP waveforms did not improve; the patient experienced complete bi-temporal hemianopsia post-operatively and the resection was sub-total. As this was the only case of VEP amplitude deterioration in the study, both sensitivity and PPV were 100%. For patients who experienced a transient decrease in VEP waveforms, there were no post-operative visual deteriorations; 50% had improved visual outcome and 50% were unchanged. No statistical analysis was performed by the authors.

The study by *Chung et al* found no association between intra-operative VEP waveforms and post-operative visual acuity or visual fields. Spearmanns correlation analysis was used (P >0.05). From 95 eyes with reproducible VEP waveforms, 14% demonstrated worsened visual acuity and 14% demonstrated worsened visual fields post-operatively. Whilst this was higher in the group with decreased VEP amplitude (17% of eyes in this group had worsened post-operative visual acuity and 25% demonstrated deterioration in visual fields) it was also noted in the group with improved VEP amplitude (11% in both domains).

Kodama et al reported 100% post-operative visual impairment in patients who demonstrated a permanent decrease in VEP intra-operatively therefore concluding that a “permanent VEP loss means post-operative severe visual dysfunction”. They also commented that transient VEP decreases do not indicate post-operative visual disturbance and that visual field defects alone, particularly minor visual field defects, (without decrease in visual acuity) cannot be predicted by VEP monitoring. Looking at the effect of VEP monitoring on visual fields alone, we reach a sensitivity and specificity of 80% and 97% respectively.

The cohort study by *Chacko et al* reported no cases of worsened post-operative visual outcome in either group (with or without VEP monitoring.) They did however report a superior improvement in post-operative visual fields of the test group (with monitoring) compared to the control group with mean percentage improvement of 12.4% (two sample t-test significant, t = 2.98, p = 0.003). No statistical difference in the improvement of visual acuity between the test group and the control group was found.

Nishimura et al also reported zero incidences of worsened visual outcome. Of the 158 eyes tested, 5% experienced a decrease in VEP amplitude; visual function was reported to be unchanged in all of these (false positives). In the unchanged VEP group, 50% of eyes had improved visual outcome post-operatively; this was 31% in the transient decrease VEP group. Of those with unchanged VEP amplitudes there were no post-operative visual deteriorations (100% negative predictive value.)

Sasaki et al reported that 100% of eyes demonstrating a permanent deterioration in VEP amplitude also showed deterioration in post-operative visual outcome whilst 89% of those with stable VEP amplitudes had unchanged visual outcomes. They therefore concluded that the two were well correlated and that in some patients this could avoid or minimize post-operative visual deterioration. Of note, only 1 of the 14 eyes demonstrating a permanent deterioration in VEP was secondary to pituitary adenoma. The only eye which showed an improvement in VEP amplitude and subsequent post-operative improvement in visual function also belonged to a patient with pituitary adenoma and of three eyes with temporary VEP amplitude deteriorations one patient had a pituitary adenoma. For this patient, after decompression of the tumour the VEP recovered and the visual function improved.

Discussion

The first descriptions of VEP recordings date back to 1934. [23] By the 1960s VEPs were being utilised as a diagnostic aide in many conditions affecting the optic pathway including multiple sclerosis, compressive tumours, optic atrophy, amblyopia and stroke. [24] Utilisation for intra-orbital surgery was first described in 1973 [2] and although a series of subsequent case-reports and two larger series appeared favourable these were later largely disregarded as anecdotal. *Cedzich et al* concluded in 1987 that VEP was “too susceptible to non-specific influences” to be a reliable indicator for intraoperative visual change. [25] Interest in the technique rekindled with the observation of improved reliability of VEP recordings under total intravenous anaesthesia (TIVA) as compared to with inhalational anaesthesia [4, 26]. However, its enhanced recordability did not make intraoperative VEP monitoring clinically meaningful as yet. Indeed, Chung et al. report no association between the intraoperative fluctuation of VEPs and patients’ postoperative visual outcomes [18]. Diverging reports on the usefulness of VEPs have therefore led more recent research to focus on identifying further means of improving their reliability and interpretability: Instead of goggles as a photo-stimulation device, *Sasaki et al.* use soft silicone discs that increase the device’s surface application to patients’ eyelids, along with electroretinography (ERG) to ensure that the light stimulus indeed reaches the retina [6]. *Houlden et al.* propose dual intraoperative monitoring of electroencephalography (EEG) and VEPs, based on their observation of improved VEP reproducibility in the presence of low – rather than high – amplitude EEG [9]. *Sato* investigated the impact on VEPs of photo-stimulation parameters – namely the light emission time and amount of light delivered per stimulus – and observed that the cortical wave responses measured following cessation of light stimulation represent a more reliable means of VEP monitoring than the waves measured during photo-stimulation proper [27]. And *Gutzwiller at al.* venture that the use of white light flashes, instead of the previously standardly

used red light stimuli, may provide better visual field monitoring, as white light not only stimulates cones within the macula, but also the rod-rich regions outside the macula [8]

These advances testify to a renewed, albeit cautious interest in the use of intra-operative VEP monitoring in neurosurgery. Also of note, the literature has not made a distinction so far in the technical considerations of VEP monitoring for posterior versus anterior visual pathways. Accordingly, our review aimed to determine whether, in patients undergoing transsphenoidal surgery for pituitary adenoma, intraoperative monitoring of visual evoked potentials is a safe, reliable and effective technological adjunct in predicting postoperative visual function.

Summary of evidence

At present, there is limited and low-quality evidence on the safety, reliability and effectiveness of intraoperative visual evoked potential monitoring in patients undergoing transsphenoidal surgery for pituitary adenoma.

Safety

There were no cases of operative complications directly related to intra-operative VEP monitoring reported in any of the 10 studies included, therefore suggestive that VEP monitoring is safe in transsphenoidal surgery.

Reproducibility

All studies used methods such as LED goggles, silicone discs, simultaneous ERG monitoring or TIVA to try and optimise stability and reproducibility and the VEP waveform stability ranged from 67%-100%.

Intra-operative EEG has been shown to “greatly contribute” to intra-operative VEP reproducibility[9] but was only used in one of the studies. Its usage can complement depth of anaesthesia monitoring and facilitate a steady state anaesthesia.

Practical considerations to increase reproducibility not mentioned in the studies include the physical application of the electrodes (which should be placed according to *the ten twenty electrode system of the International Federation* for scalp electrode placement [28]); protection of the visual stimulation to the visual pathways from interference from intraoperative lights (using foil or a black light shield patch) and ensuring a secure fixation of the light stimulating device.

Effectiveness

The analysis of the technique’s effectiveness is limited by the number of studies available. Furthermore, whilst they all looked at visual outcome pre- and post-operatively there was variation in the methodology and the outcomes reported. The only comparative study that we found did not look at the association between VEP amplitude and visual outcome but did describe a statistically significant improvement in post-operative visual field testing when VEP monitoring was used. The remainder of the studies – all case series – varied in their conclusions on the relationship between intra-operative VEP and post-operative visual outcome. Whilst *Kodama et al* suggested that permanent VEP loss means post-operative severe visual dysfunction, they felt that visual field defects alone could not be predicted. Conversely, *Feng et al* described a direct correlation between intra-operative VEP changes and visual fields whereas *Toyama et al and Chung et al* found no significant correlation between VEP waveforms and post-operative visual outcome. However, as all studies involved the surgeon temporarily halting surgical manipulation at the point of a VEP amplitude decrease there is an underlying assumption that all teams believed that this may indeed be a contemporaneous warning sign of optic injury.

There was gross heterogeneity in the statistical analysis performed in each of the studies. Due to the small number of true positives across all studies, the sensitivities calculated must be interpreted with caution. Conversely however, the high specificity (85-100%) and negative predictive value (90-100%) found in these studies should be recognised.

As the technique reaches a greater level of refinement in the future, it is imaginable that it may allow to reliably predict increasingly discrete visual deficits that can be taken into account intraoperatively - in real-time - in confirming or altering surgical strategy.

Limitations

Our review had a number of limitations. Firstly, study size; with only ten studies ultimately included, our review is likely underpowered to observe small effect sizes. Secondly, study design; as nine out of the ten studies included were retrospective case series with variation in patient selection, methodology and outcomes measurement, a meta-analysis was not performed as it would be unlikely to glean any firm conclusions from such heterogeneous sources. Thirdly, the technical specifications of the monitoring equipment used in the studies varied greatly making generalisations difficult. Finally, as demonstrated in table 1 despite the inclusion criteria there are very few studies which examine VEP monitoring in patients undergoing transshpenoidal surgery for pituitary adenoma alone; *Chacko et al* was the only one identified (Table 1). The remainder of the studies also included some patients with other pathology not limited to: craniopharyngioma, meningioma, Rathke’s cleft cyst and metastatic disease. Where possible, we have attempted to highlight the information specific to pituitary adenoma alone.

Conclusions

Whilst there is limited and low-quality evidence surrounding the use of intra-operative VEP monitoring during transsphenoidal resection of pituitary adenoma, our review nonetheless suggests that it is a safe and reproducible technique of seemingly increasing reliability in predicting post-operative visual deficits.

As is the case for other neuromonitoring techniques, its intraoperative interpretation still requires it to be confronted with findings from the surgical field. Whether VEP neuromonitoring helps to achieve more aggressive resections without compromising visual outcome in cases of more expansive tumours has yet to be determined through prospective and comparative case studies.

Also to be determined in the future is whether specific adaptations are required to the VEP technique to optimize its reproducibility during transsphenoidal surgery in particular, and whether specific alarm thresholds may be better suited for transsphenoidal procedures in predicting post-operative visual outcome.

Declarations

Ethical Approval: not applicable

Informed consent: not applicable

Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

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Authors contributions: All authors contributed to study conception and design. The literature search and data analysis were performed by Farizeh Ahmed, Ivan Cabrilo, Jarnail Bal and Hani J Marcus. The first draft of the manuscript was written by Farizeh Ahmed and critically appraised by Ivan Cabrilo, Brett Sanders and Hani J Marcus. All authors read and approved the final manuscript.

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Tables

Table 1. Summary of included studies. pts = patients; TSS = Transsphenoidal surgery

Study	Study design	Patients	Patients with Pituitary Adenoma
Feng et al (2019)*	Case series	42 pts with primary sellar neoplasms undergoing endoscopic TSS	40
Toyama et al (2018)	Case series	20 pts undergoing endoscopic TSS (39 eyes tested)	13
Nishimura et al (2018)	Case series	82 pts undergoing endoscopic TSS (164 eyes tested)	Not reported
Kurozumi et al* (2017)	Case series	19 pts with sellar/parasellar tumours undergoing endoscopic TSS	17
Luo et al (2015)	Case series	46 pts undergoing cranial surgery or TSS (85 eyes tested)	12
Kamio et al* (2014)	Case series	33 pts with sellar or parasellar tumours undergoing TSS	25
Houlden et al* (2013)	Case series	10 pts undergoing TSS for tumours near optic nerve or chiasm 2 pts undergoing craniotomy for an occipital lobe tumour and glial based tumour	Not reported
Chung et al (2012)	Case Series	53 pts with sellar or parasellar lesions undergoing endoscopic TSS (106 eyes tested)	37
Sasaki et al (2010)	Case Series	100 pts at intraoperative risk of visual impairment including 28 pts with parasellar lesions (200 eyes tested)	Not reported
Chacko et al (1996)	Cohort	36 pts undergoing TSS for pituitary adenomas; 22 with VEP monitoring, 14 without (72 eyes tested; 44 with VEP monitoring, 28 without)	36

* These studies did not comment on individual eyes tested.

Table 2. Quality of studies using MINORS criteria

Study (year)	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	B e o
Feng et al (2019)	2	2	2	2	1	1	2	0	n/a	n/a	n,
Toyama et al (2018)	2	2	2	1	2	1	2	0	n/a	n/a	n,
Nishimura et al (2018)	2	1	2	1	1	1	2	0	n/a	n/a	n,
Kurozumi et al (2018)	1	2	1	2	1	1	2	0	n/a	n/a	n,
Luo et al (2015)	2	2	1	1	1	2	1	0	n/a	n/a	n,
Kamio et al (2014)	2	2	2	1	0	2	2	0	n/a	n/a	n,
Holden et al (2013)	1	0	2	1	2	1	2	0	n/a	n/a	n,
Chung et al (2012)	2	2	2	2	2	2	1	0	n/a	n/a	n,
Sasaki et al (2010)	2	0	2	1	0	2	2	0	n/a	n/a	n,
Chacko et al (1996)	2	0	2	2	0	0	2	0	2	2	2

Table 3. Visual evoked potential signal processing devices used in each study

Study (Year)	VEP SIGNAL PROCESSING DEVICE	
Feng et al (2019)	Not reported	
Toyama et al (2018)	Neuropack X1 MEB 2312	(NIHON KOHDEN, Japan)
	MEE 1232,	(NIHON KOHDEN, Japan)
Nishimura et al (2018)	MEE 1232,	(NIHON KOHDEN, Japan)
Kurozumi et al (2017)	NIM-ECLIPSE E4	(MEDTRONIC)
Luo et al (2015)	ISIS System	(INOMED, Germany)
Kamio et al (2014)	Neuropack X1 MEB-2312, (	(NIHON KOHDEN, Japan)
Houlden et al (2013)	Cadwell Elite intraoperative monitoring machine	(CADWELL INSTRUMENTS, USA).
Chung et al (2012)	PROTEKOR TM 10M	(XLTEK, Canada)
Sasaki et al (2010)	Synax 1100	(NEC MEDICAL SYSTEMS, USA)
	Neuropack	(NIHON KOHDEN, Japan)
Chacko et al (1997)	Brain Atlas III system	(BIOLOGIC SYSTEMS, USA)

Table 4. Methods used to promote stability of visual evoked potential waveform

Study (Year)	VEP Waveform Stability	Mode of Anaesthesia	Stimulus delivery device	Simultaneous ERG Monitoring
Feng et al (2019)	74%	TIVA	Flexible silicone patch LED goggles	No
Toyama et al (2018)	97%	TIVA	Round silicone disc embedded with 16 red high luminosity flashing (100mCd) LEDs	Yes
Nishimura et al (2018)	98%	TIVA	Silicon discs with 16 red LEDs (100mCd)	Yes
Kurozumi et al (2017)	100%	Not mentioned	2cm round silicone disc embedded with 16 red high luminosity flashing (100mCd) LEDs	Yes
Luo et al (2015)	81%	TIVA	Transparent eye patches placed on the closed eyes. Then the light-stimulating device was placed on the eyelids and covered with another transparent eye patch.	No
Kamio et al (2014)	82%	TIVA	2cm soft silicone disc embedded with 16 red high luminosity flashing (100mCd) LEDs	Yes
Houlden et al (2013)	Not mentioned	TIVA/ Gas inhalation	Goggle 3000mCd LED stimulators (3 LEDs on each side)	No
Chung et al (2012)	90%	TIVA	Bright LED goggles (XLTEK, Ontario, Canada)	No
Sasaki et al (2010)	94%	TIVA	2cm silicone disc embedded with 16 red high-luminosity (100mCd) LEDs	Yes
Chacko et al (1996)	97%	Gas inhalation	Red LEDs fitted on goggles	No

Table 5. Intra-operative changes in Visual-Evoked Potential Waveforms Visual-Evoked Potential = VEP

Title	Unchanged	VEP Improvement	Temporary VEP deterioration	Permanent VEP deterioration
Feng et al (2019)	73.8%	2.4%	14.3%	9.5%
Toyama et al (2018)	53.8%	7.6%	23.1%	15.4%
Nishimura et al (2018)	77.5%	n/a	16.3%	5.0%
Kurozumi et al (2017)	89.5%	5.9%	5.9%	0%
Luo et al (2015)	72%	16%	20%	12%
Kamio et al (2014)	82.1%	0%	14.3%	3.6%
Houlden et al(2013)	n/a	n/a	n/a	n/a
Chung et al (2012)	67.4%	20.0%		12.6%*
Kodama et al(2010)	90.0%	0.0%	2.9%	6.8%
Sasaki et al (2010)	90.3%	0.5%	1.6%	7.5%
Chacko et al (1996)	-	-	100%	-

**Did not report whether this deterioration was temporary or permanent.*

Table 6. Relationship between intra-operative visual-evoked potential (VEP) and post-operative visual function

Study (Year)	Intra-operative VEP	Post-operative Visual Acuity n (%)			Post-operative Visual Fields n (%)			Notes
		Improved	Stable	Worsened	Improved	Stable	Worsened	
Feng et al (2018)	Improved	0 (0)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	Sensitivity and specificity of VEP amplitude in detecting changes in visual field outcomes are 75% and 79%, respectively.
	Stable	27 (87)		4 (13)	30 (97)		1(3)	
	Worsened (transient)	1 (17)	2 (33)	3(50)	2 (33)	3 (50)	1 (17)	
	Worsened (permanent)	2 (50)	1 (25)	1(25)	1 (25)	1 (25)	2 (50)	
Toyama et al (2018)	Improved	3 (100)	0 (0)	0 (0)	1 (33)	2 (66)	0 (0)	No significant relationship observed between VEP and visual field outcome.
	Stable	11 (53)	10 (48)	0(0)	9 (43)	12 (57)	0(0)	
	Worsened (transient)	6 (66)	3 (33)	0 (0)	5 (56)	4 (44)	0 (0)	
	Worsened (permanent)	3 (50)	3 (50)	0 (0)	1 (17)	5 (83)	0 (0)	
Kamio et al (2014)	Improved	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	No statistical analysis performed.
	Stable	11 (48)	12 (52)	0 (0)	5 (22)	18 (78)	0 (0)	
	Worsened (transient)	2 (50)	2 (50)	0 (0)	2 (50)	2 (50)	0 (0)	
	Worsened (permanent)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	
Chung et al (2012)	Improved	4 (22)	13 (68)	2 (11)	13 (68)	4 (22)	2 (11)	No association found between intraoperative VEP waveforms and post-operative visual acuity or visual fields.
	Stable	13 (20)	42 (66)	9 (14)	39 (64)	17 (26)	8 (13)	
	Worsened (transient / permanent)	5 (42)	5 (42)	2 (17)	6 (50)	3 (25)	3 (25)	
Kodama et al (2010)	Improved	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	"Permanent VEP loss means postoperative severe visual dysfunction. Transient VEP changes do not indicate postoperative visual disturbance. Visual field defects without decreases in the visual acuity may not be predicted by VEP monitoring"(1)
	Stable	0 (0)	93 (100)	0 (0)	0 (0)	92 (99)	1 (1)	
	Worsened (transient)	0 (0)	3 (100)	0 (0)	0 (0)	3 (100)	0 (0)	
	Worsened (permanent)	0 (0)	4 (57)	3 (43)	0 (0)	3 (43)	4 (57)	
Chacko et al (1996) Group A	Improved	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	There was statistically significant improvement in post-operative visual field testing between the test group A (with VEP monitoring) and the control group B (without VEP monitoring) There was no statistical difference in visual acuity between the two groups.
	Stable	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
	Worsened (transient)	n/a	n/a	n/a	34 (77)	10 (23)	0 (0)	
	Worsened (permanent)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Nishimura		Post-operative Visual Function*						"Intraoperative monitoring of VEP predicts

et al (2018)		Improved n (%)	Stable n (%)	Worsened n (%)	postoperative visual function, and a reversible change in VEP indicates that visual function will be preserved"(2)
	Improved	0 (0)	0 (0)	0 (0)	
	Stable	62 (50)	62 (50)	0 (0)	
	Worsened (transient)	8 (31)	18 (69)	0 (0)	
	Worsened (permanent)	0 (0)	8 (100)	0 (0)	
Luo et al** (2015)	Improved	0 (0)	0 (0)	0 (0)	Intra-operative VEP has a specificity of 96% and a negative predictive value of 90% in detecting post-operative visual function. Preservation of VEPs predicted preserved visual function
	Stable	8 (16)	36 (72)	6 (12)	
	Worsened (transient)	0 (0)	10 (100)	0 (0)	
	Worsened (permanent)	0 (0)	2 (2)	0 (0)	
Sasaki et al** (2010)	Improved	1 (100)	0	0(0)	"Changes in intraoperative VEP findings, especially in the VEP amplitude, were well correlated with postoperative visual function"(3)
	Stable	17 (10)	150 (89)	2 (1)	
	Worsened (transient)	1 (33)	2 (67)	0	
	Worsened (permanent)	0	0	14 (100)	
Kurozumi et al (2017)					80% of patients with pre-operative visual disturbances had an improved visual acuity immediately after surgery 80% of patients had improved visual fields immediately after surgery.

*Looked at visual function (if either or both of visual acuity/visual fields were improved, unchanged or worse then the outcome was considered improved, unchanged or worse)

***It was not possible to separate the data of the patients undergoing transsphenoidal surgery from other approaches in these studies.*

Table 7. Sensitivity, specificity, positive predictive value and negative predictive value of VEP amplitude in predicting visual function outcomes[1].

Study	True Positive[2] (TP)	False Positive[3] (FP)	True Negative[3] (TN)	False Negative[5] (FN)	Sensitivity[6] (Sn)	Specificity[7] (Sp)	Positive Predictive Value[8] (PPV)	Negative Predictive Value[9] (NPV)
Feng et al (2019)	1	1	37	3	25%	97%	50%	93%
Toyama et al (2018)	0	6	33	0	n/a	85%	n/a	100%
Nishimura et al (2018)	0	8	150	0	n/a	95%	n/a	100%
Luo et al** (2015)	0	2	54	6	n/a	96%	n/a	90%
Chacko et al (1996)	0	0	44	0	n/a	100%	n/a	100%
Kamio et al (2014)	1	0	27	0	100%	100%	100%	100%
Chung et al* (2012)	-	-	-	-	-	-	-	-
Kodama et al (2010)	4	3	95	1	80%	97%	57%	99%
Sasaki et al** (2010)	14	8	171	2	88%	96%	64%	99%

*[1] Where possible (7, 12, 13, 16, 17, 20), visual field outcomes only were used to predict visual function outcomes. In the studies by Nishimura et al, Luo et al, Sasaki et al and Kurozumi et al this was not possible therefore combined visual acuity/field data has been used. [2]TP= a permanent decrease in VEP amplitude and new post-operative visual deficit. [3]FP = a permanent decrease in VEP amplitude but no new post-operative visual deficit. [4]TN = no permanent decrease in VEP amplitude and no new post-operative visual deficit. [5]FN= no permanent decrease in VEP amplitude but new post-operative visual deficit. [6] Sn = TP/ (TP+FN) [7] Sp = TN (TN + FP) [8] PPV = TP / (TP + FP) [9] NPV = TN/ (TN + FN) *Unable to derive figures for Chacko et al as they combined transient and permanent VEP amplitude loss in their results. **It was not possible to separate the data of the patients undergoing transsphenoidal surgery from other approaches in these studies; figures demonstrated are for all approaches.*

Figures

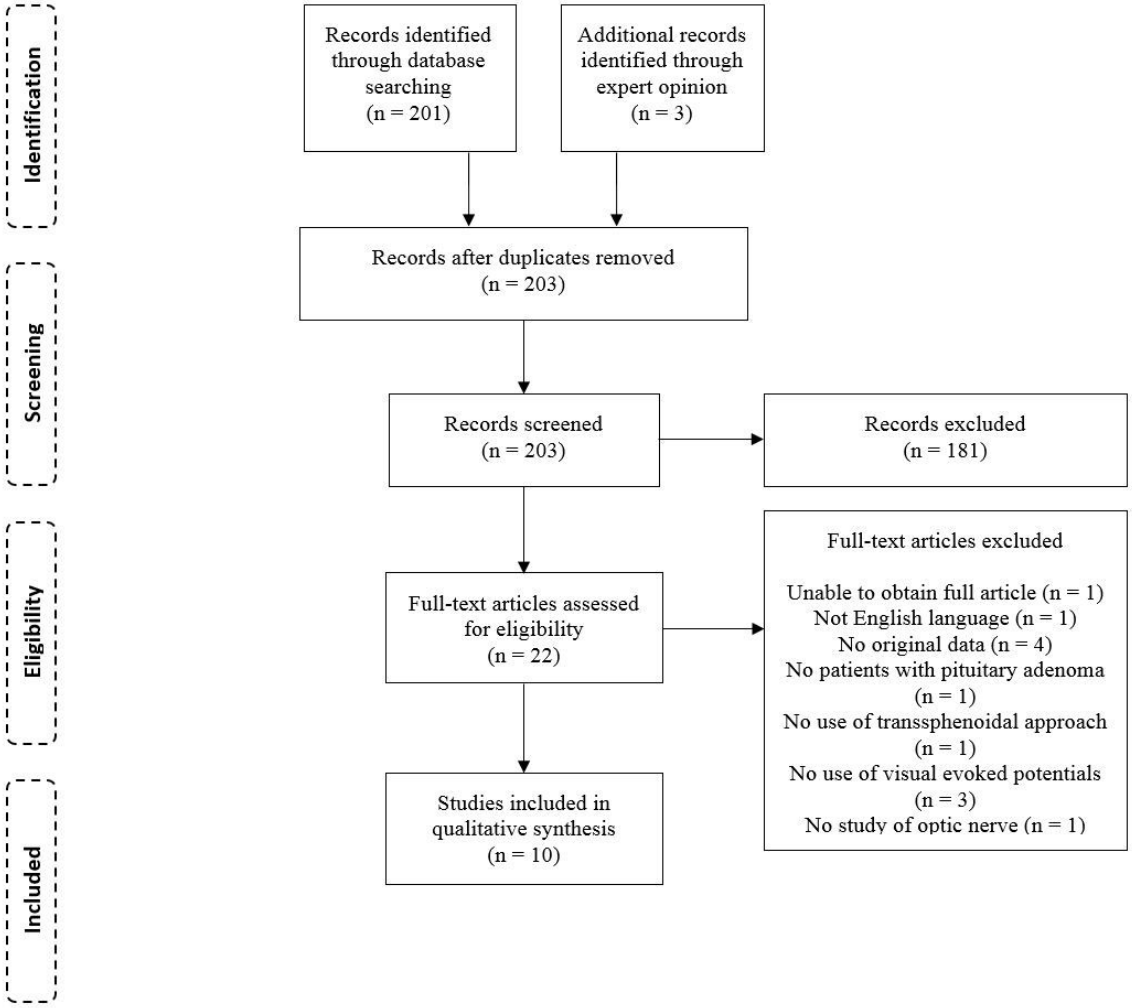

Figure 1

PRISMA flow chart of included studies