



Headache relief following endoscopic drainage of Rathke's cleft cyst

Anne Jian¹ · Yi Yuen Wang² · Tony Goldschlager³ · Mendel Castle-Kirszbaum³ · Jeremy Kam³ · Yi Chen Zhao⁴ · James King^{1,5}

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Abstract

Purpose Headache is the most common presenting complaint in patients with Rathke's cleft cysts (RCC). The study aimed to assess the headache burden in patients undergoing endoscopic endonasal drainage of RCC.

Methods In this longitudinal cohort study, a prospectively collected database of patients undergoing endoscopic endonasal drainage of RCC between 2017 and 2024 was analysed. The Headache Impact Test (HIT-6) and Anterior Skull Base questionnaire (ABSQ) were collected pre-operatively and at 3 weeks, 6 weeks, 3, 6 and 12 months from July 2020.

Results 64 RCC patients were identified, 24 of whom had HIT-6 scores collected pre-operatively and at least one post-operative time point. 67% had a headache pre-operatively (HIT-6 > 36). Overall, HIT-6 score reduced by 5 points at 6 months (95% CI -0.3, -9.0, $p=0.04$) compared to pre-operatively, adjusted for age. In patients with headache pre-operatively, HIT-6 reduced on average by 7 and 6 points respectively at 6 and 12 months ($p<0.05$). No association was found with sex, pre-operative pituitary dysfunction, cyst location, size, MRI signal, histopathological characteristics or reoperation. Overall QOL decreased within the first 6 weeks postoperatively, but returned to baseline thereafter. A higher HIT-6 score was associated with worse ABSQ at 12 months ($p=0.01$).

Conclusion In the largest prospective study using a validated headache metric, endoscopic endonasal drainage of RCC may improve headache at 6 and 12 months post-operatively, providing long lasting relief. Surgery causes a transient worsening of QOL that resolves after 6 weeks. Headache burden directly correlated with QOL.

Keywords Rathke's cleft cyst · Headache · Endoscopic surgery · Quality of life

Introduction

Rathke's cleft cyst (RCC) is a non-neoplastic cystic remnant from Rathke's cleft arising from the pars intermedia region of the pituitary gland. The majority are small, asymptomatic and detected incidentally, but RCC may grow to exert mass

effect causing visual disturbance or pituitary dysfunction, which are indications for surgery. Headache is an enigmatic symptom of RCC, but is described in up to 60% of patients and can affect their quality of life (QOL) significantly [1, 2]. The role of surgery in headache outcomes is unclear, but is important for patient counselling and surgeons' decision making. Previous studies suggest surgery can lead to headache improvement in up to three-quarters of patients [3], but these are limited by the use of qualitative, self-reported headache outcomes, retrospective reporting of headache burden, short and limited follow up, and small sample size.

In this study, we assess headache burden and QOL longitudinally in patients before and after endoscopic endonasal drainage of RCC using a validated metric, to determine the effect of surgery and pre-operative factors associated with headache outcome, and the effect of headache on QOL.

✉ Anne Jian
anne.jian@mh.org.au

¹ Department of Neurosurgery, Royal Melbourne Hospital, Melbourne, VIC, Australia

² Keyhole Neurosurgery, Melbourne, VIC, Australia

³ Department of Neurosurgery, Monash Medical Centre, Melbourne, VIC, Australia

⁴ Department of Ear, Nose and Throat, Royal Melbourne Hospital, Melbourne, VIC, Australia

⁵ Department of Surgery, University of Melbourne, Melbourne, VIC, Australia

Methods

Study participants

A prospectively collected database of consecutive patients undergoing endoscopic endonasal drainage of Rathke's cleft cyst between January 2017 and May 2024 was analysed. Patients were added from 3 tertiary neurosurgical centres in Victoria, Australia. The Headache Impact Test-6 (HIT-6) survey was introduced to the database from 2020 onwards. Patients were included if they had RCC confirmed on histopathology (or if unavailable or non-diagnostic, had radiological and intra-operative findings consistent with RCC), and had HIT-6 data collected preoperatively and at least one post-operative timepoint. Consent was sought from patients before study enrollment and the study was conducted under institutional board ethics approval (HREC 15386Q).

Data collection

The HIT-6 questionnaire is a six-item survey which measures the severity of headache and its impact on daily activities, work, fatigue and mood [4]. It ranges from 36 to 78 points with a score greater than 36 indicating presence of headache. Previous studies in patients with migraines found that a 6-point decrease represented clinically meaningful response [5]. Overall QoL was assessed using the 35-item Anterior Skull Base Questionnaire (ASBQ) [6], which has been validated in endoscopic pituitary adenoma surgery [7]. It contains items across six domains: performance, physical function, vitality, pain, emotions and specific symptoms rated on a Likert scale from 1 to 5, with higher score indicating better QoL. Participants were asked to complete the surveys preoperatively and at 3 weeks, 6 weeks, 3 months, 6 months and 1 year post-operatively. Non-responsive participants were contacted via email or phone to avoid loss to follow-up. Other data on patient demographics, presenting symptoms, cyst characteristics including MRI features and histopathology, endocrine profile and ophthalmology tests were also recorded.

Statistical analysis

The primary outcome was change in HIT-6 score post-operatively compared to pre-operatively, analysed by random effects model. This was chosen to analyse the changes in the outcome over time to account for clustering given repeated measurements taken from the same individual at multiple timepoints. Secondary outcome was change in ABSQ scores post-operatively. Pre-defined variables, including age, sex, presence of pituitary dysfunction pre-operatively, size of RCC, MRI signal characteristics- T1/T2 signal (hyper/iso/

hypointensity), presence of enhancing cyst wall, reoperation, post-operative CSF leak, new pituitary dysfunction post-op, histopathological features (squamous metaplasia, inflammatory cells) and operation type, which were statistically significant on univariate analysis were input into the model. Association of ABSQ score with HIT-6 score at each time point was analysed by a linear regression model. All tests were performed at a significant level of 0.05, using R [8].

Results

64 patients were identified from the database who underwent endoscopic drainage of RCC. Of these, 24 patients who had HIT-6 data collected pre-operatively and at least one post-operative timepoint were included in analysis. Response rates were: 15 (63%) at 3 weeks, 20 (83%) at 6 weeks, 24 (100%) at 3 months, 19 (79%) at 6 months and 19 (79%) at 1 year. 22 patients completed ABSQ survey, with response rates of 21 (95%) at 3 weeks, 6 weeks and 3 months, 19 (86%) at 6 months and 18 (82%) at 12 months.

Patient demographics

As shown in Table 1, majority (75%) of the cohort were females with a median age of 58. The most common presenting symptoms were headaches and visual disturbance. Pituitary dysfunction and visual deficit on formal ophthalmology testing were present in 42% of patients. Primary indication for surgery was in most cases mass effect on optic apparatus causing visual deficit ($n=9$), as well as growth after previous surgery without symptoms ($n=5$) or with visual disturbance ($n=1$), pituitary dysfunction ($n=4$), growth on surveillance ($n=2$), mass effect on optic apparatus without symptoms ($n=2$) and concurrently with pituitary dysfunction ($n=1$). The majority of RCC were sellar with suprasellar extension with a mean diameter of 17 mm. More than half of the RCCs were T1 hyperintense and T2 hyperintense on MRI, with 52% displaying cyst wall enhancement. On histopathology, intracystic nodule and inflammatory cells were present in 21% of RCCs, with squamous metaplasia seen only in two cases. The most common surgical approach was drainage of RCC with nasoseptal flap closure, however local practice varied between centres based on surgeon practice. There was one case of post-operative CSF leak. Four patients developed post-operative pituitary dysfunction which included AVP-deficiency (diabetes insipidus), hypocortisolism and hypothyroidism. One patient developed the syndrome of inappropriate antidiuresis (SIAD). Six patients were reoperations. There were two recurrences on follow

Table 1 Baseline patient characteristics

	No. of patients (%) of total 24 patients
Age- Median [IQR]	58 [22]
Sex- female	15 (63%)
Presenting complaint	
Headaches	11 (46%)
Visual disturbance	8 (33%)
Endocrinological symptoms	3 (13%)
Incidental	2 (8%)
Reoperation	6 (25%)
Pituitary dysfunction pre-operatively	10 (42%)
Visual deficit	10 (42%)
Rathke Cleft cyst features	
Location	
- sellar with suprasellar extension	22 (92%)
Mean maximal diameter (mm)	17±5
T1 signal [#]	
- hypointense	6(25%)
- hyperintense	14 (58%)
- isointense	3 (13%)
T2 signal [#]	
- hypointense	2 (8%)
- hyperintense	16 (67%)
- isointense	5 (21%)
Cyst wall enhancement [#]	13 (54%)
Intracystic nodule [#]	5 (21%)
Squamous metaplasia [^]	2 (8%)
Presence of inflammatory cells [^]	5 (21%)
Surgical approach	
Drainage with flap [*]	17 (71%)
Drainage without closure	3 (13%)
Drainage and fenestration into subarachnoid space and with flap	3 (13%)
Drainage and resection with flap	1 (4%)
Post-op CSF leak	1 (4%)
Post-op pituitary dysfunction	4 (15%)
Post-op SIADH	1 (4%)
Recurrence	2 (8%)

[#]One patient unable to have MRI due to pacemaker

[^]Three patients did not have histopathology

^{*}Fourteen of the 17 patients had nasoseptal flap, three had sphenoid mucosal flap

CSF, cerebrospinal fluid; SIADH, syndrome of inappropriate diuretic hormone secretion

up imaging which did not require further operation as they were asymptomatic.

Post-operative headache

The mean pre-operative HIT-6 score in the cohort was 46.7 ± 12.6 . There was a non-significant trend for increase in HIT-6 score at 3 weeks post-operatively followed by a

significant reduction at 6 months by an average of 5 points (95% CI -0.3, -9.0, $p=0.04$), adjusted for age (Fig. 1a). An association between increased age and lower HIT-6 severity was observed ($p=0.02$).

Sixteen patients (67%) had headache pre-operatively (HIT-6 score > 36). Of these, three were sudden onset. The mean baseline HIT-6 score in this group was 52.1 ± 12.2 . There was on average a decrease by 7.2 points at 6 months (95%CI -1.5, -11.8 $p=0.02$) and by 6.1 points at 12 months (95%CI -0.4, -11.8, $p=0.04$) which represent clinically meaningful change, adjusted for age (Fig. 1b).

Overall, 67% patients had a HIT-6 score > 36 at 3 weeks, 60% at 6 weeks, 71% at 3 months, 42% at 6 months and 47% at 1 year. Of the sixteen patients with pre-operative headache, 10/16 (63%) patients had improvement in HIT-6 score at their last follow-up within 12 months; 6 of these 10 patients had clinically meaningful improvement with > 6 point decrease. 2/16 (13%) were unchanged and 4/16 (25%) were worse.

There was no association demonstrated between sex ($p=0.1$), cyst size ($p=0.28$), preoperative ($p=0.83$) or postoperative ($p=0.78$) pituitary dysfunction, MRI signal changes- T1 signal ($p=0.76$), T2 signal ($p=0.13$), intracystic nodule ($p=0.89$), cyst wall enhancement ($p=0.77$), reoperation ($p=0.38$), squamous metaplasia ($p=0.22$), inflammatory infiltrate ($p=0.25$) or operative approach ($p=0.67$) with headache outcome post-operatively.

Quality of life

The mean pre-operative ABSQ score in the cohort was 120 ± 22.5 . There was on average a reduction (worsening) by 15 points (95% CI -25.1, -5.5, $p<0.001$) at 3 weeks and 12 points (95% CI -21.5, -2.0, $p=0.02$) at 6 weeks compared to preoperatively, adjusted for sex (Fig. 2a). From 3 months onwards, ABSQ score recovered to baseline level. An association between male sex and improved ABSQ score was observed ($p=0.01$). There was no association with any other patient factors or cyst characteristics.

However, linear regression analysis showed that at higher HIT-6 score was associated with worse ABSQ score at 12 months, with a reduction by 1.3 points in ABSQ score with every point increase in HIT-6 score (95% CI -2.2, -0.3, $p=0.01$). There was no association at the other time points.

Among the patients who had headache pre-operatively (HIT-6 score > 36), the mean preoperative ABSQ score was 115 ± 23.8 . There was a reduction in ABSQ score by 13 points (95% CI -24.5, -1.6, $p=0.03$) at 3 weeks only before recovering to baseline, with a non-significant trend for improvement at 6 months ($p=0.07$) and 12 months ($p=0.11$) (Fig. 2b).

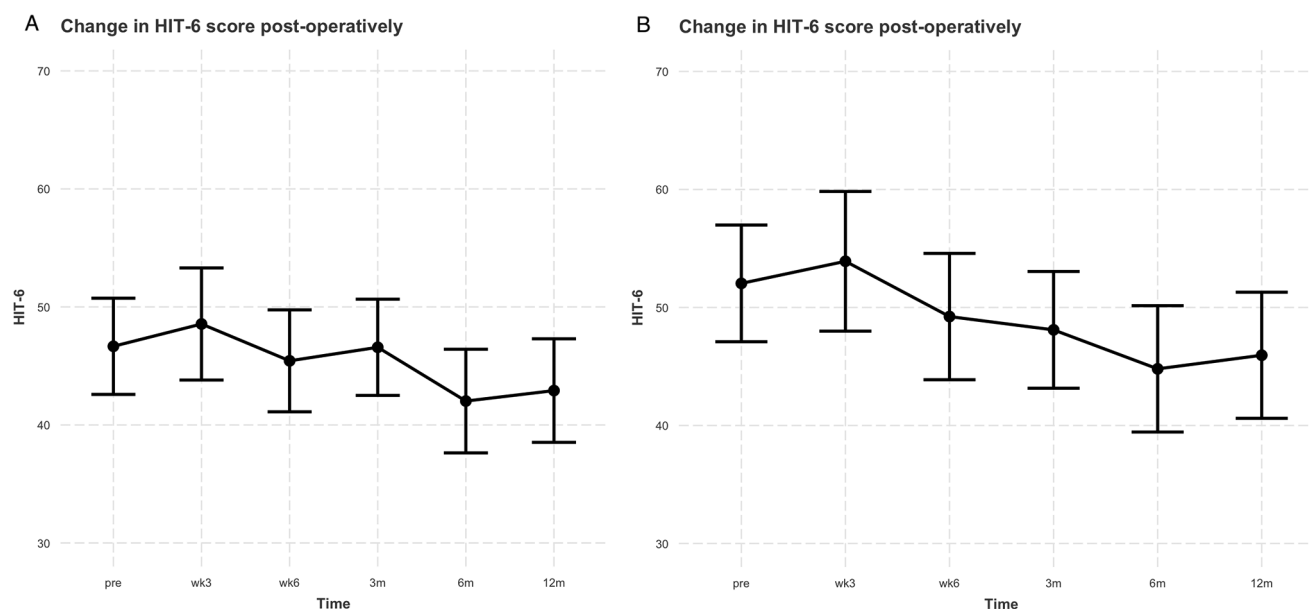


Fig. 1 Change in Headache Impact Test (HIT-6) score post-operatively in (a) the whole cohort and (b) in only patients with pre-operative headache (score greater than 36)

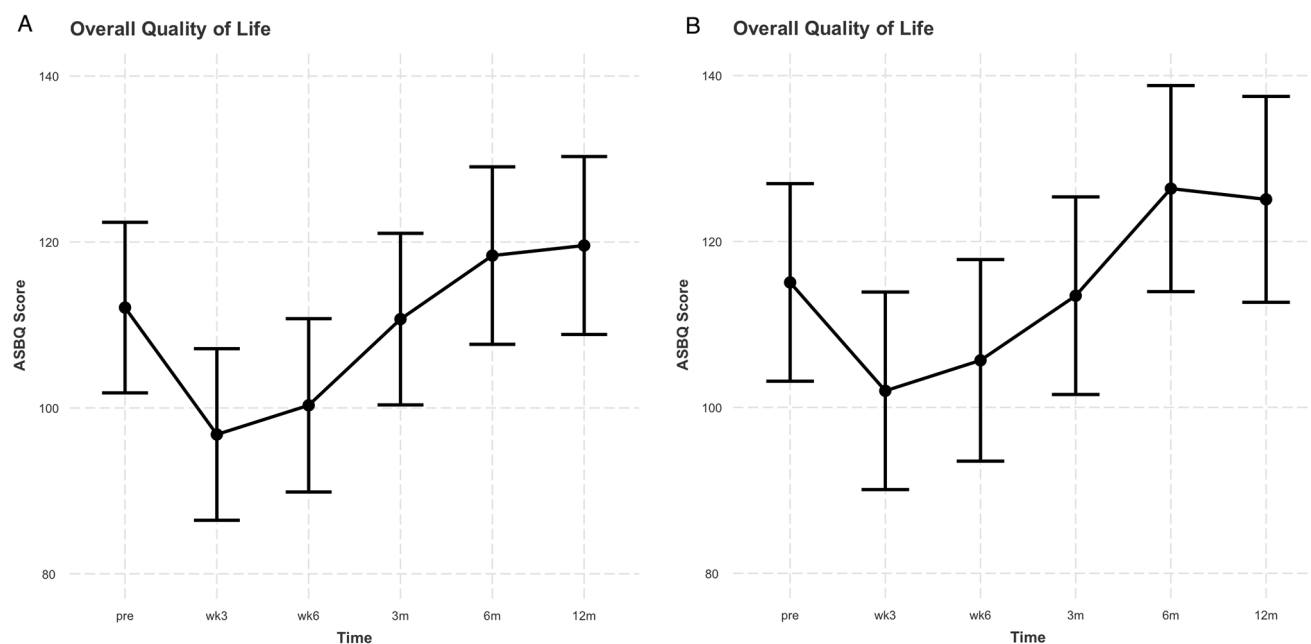


Fig. 2 Change in Anterior Skull Base Questionnaire (ASBQ) score post-operatively in the whole cohort and b) in only patients with pre-operative headache

Discussion

More than two thirds of our cohort with RCC were affected by headaches pre-operatively. Endoscopic drainage of RCC provided headache relief at 6 and 12 months with a mean decrease by 7 and 6 points in HIT-6 score respectively. In total, 63% of patients with pre-operative headache had reduction in HIT-6 score within 12 months. Previous studies were largely retrospective, had poor reporting of time

point and method of assessing headache outcome, or where known, used subjective measure at a single timepoint post-operatively. Our study utilized a prospectively collected database to assess longitudinal change in headache at the individual level over several timepoints post-operatively, and employed a validated, quantifiable assessment tool; it is the largest such study in the literature.

Headache is the most common presenting complaint in RCC patients, found in 58.7% in a retrospective study of

46 patients [1]. Headaches tend to be non-pulsating, usually bilateral and frontal, similar to headaches in patients with pituitary adenoma. In pituitary adenoma, it is thought that stretching of diaphragma sellae and surrounding structures cause headaches [9, 10]. The pathophysiological basis for headaches in RCC is less studied, but may be additionally due to the secretion of cyst contents into the subarachnoid space causing an inflammatory reaction, given the potent stimulating effect of mucous cystic content [1]. In the study by Nishioka and colleagues [1], headaches did not correlate with cyst size (maximum diameter ranged 10–38 mm), but correlated with chronic inflammation in cyst wall on histopathology, and with high- and isointensity on T1 weighted-MRI. The later reflected high protein content compared to RCCs with low T1 intensity which contained CSF-like low viscous fluid. A recent study correlating histopathological characteristics and clinical presentation of RCCs further demonstrated that the prevalence of headache increases with severity of inflammation, and was associated with adjacent adenohypophyseal inflammation [11]. We did not find a significant association between MRI signal or histopathology characteristics with headache relief. In another retrospective study of 62 RCC patients undergoing surgery [12], 71% had headaches on presentation, most of whom had chronic headaches, but 16% developed sudden onset severe headaches possibly due to hemorrhage into cyst contents or secretion of inflammatory cyst contents.

While there is strong evidence for improvement in vision after surgery in up to 83–98% of RCC patients [12–14], and endocrinopathy to a much lesser extent [14, 15], the role of surgery in relieving headache in RCC patients is less well studied. In the absence of symptoms beyond headache, a surveillance approach is traditionally favored. Whether headache alone can be an indication for surgery in RCC requires assessment of its efficacy in providing durable headache relief, balanced against risks of surgery. A previous meta-analysis found a pooled headache resolution prevalence of 71.7% across 10 studies among patients who underwent RCC resection [3]. Interestingly, studies with longer follow-up times showed higher rates of headache reduction, suggesting the effect is durable. However, all except one study used self-reported headache outcomes rather than a validated scale for standardised assessment.

Several comparable studies are summarized in Table 2 [1, 12, 15–20]. Only two studies used a prospectively collected database [15, 18]. Two used validated headache assessment metric with sample size of 10 and 13 [18, 19]. No study collected data at multiple prespecified time-points of follow-up as undertaken in our current study. In the retrospective case series by Nishioka et al. [1], headache improvement was seen in 17 of 21 patients (81%) who underwent transsphenoidal surgery for partial resection

of the cyst wall. However, they did not describe the time point at which headache was assessed, and did not report rates of post-operative complications. Meanwhile, Wait et al. [15] reported resolution of headache in 68% of patients and improvement in 21% of patients who underwent surgery, but the surgical technique was a mixture of sublabial and transnasal approach, with a complete resection of cyst wall undertaken in 18 of 73 patients. In this study, 20% of patients developed new postoperative anterior pituitary deficits, 34% had diabetes insipidus and a high rate of CSF leak was observed (45% intraoperative and 8% persistent). In our study, cysts were commonly drained by puncturing the cyst wall with cyst biopsy. Only one case involved resection of cyst which resulted in post-operative CSF leak and development of diabetes insipidus. Meanwhile, Truong et al. [16] undertook a retrospective observational study comparing 39 RCC patients conservatively managed and 18 surgically treated patients and observed a similar rate of headache resolution in both groups. The interpretation of the results is however limited by significantly larger RCC with more frequent suprasellar extension in the surgical group (70.6% ≥ 10 mm diameter) compared to conservative group (40.5% ≥ 10 mm), and the lack of reporting of time point at which outcomes were assessed.

The efficacy of surgery in providing headache relief is perhaps better examined in two studies of sub-centimeter RCCs where patients were offered surgery solely for intractable headaches, unlike previous studies where patients underwent surgery for varying indications such as visual deficit or mass effect. Fukui and colleagues [19] examined 13 patients with chief complaint of severe headaches with a mean size of cysts 7.0 ± 1.8 mm undergoing endoscopic transsphenoidal drainage. All patients had relief within 1 week of surgery, with significantly lower mean HIT-6 score of 37.2 at 3 months post-operatively. In this cohort, most of cyst contents were T1 hyperintense with pathologic inflammation observed at cyst wall. Similarly, in a retrospective study by Mathios et al. [18], 10 patients with $\text{RCC} \leq 1$ cm who had seen a specialist for their headache and had at least 3 months of medical treatment for it underwent RCC fenestration. They found that the average intensity of headache reduced from 8.7 to 2.9 at 1 month and 0.9 at 1 year in 8 patients with available data. However, the study was limited by significant recall bias with response received at average of 38.8 months after surgery and lack of formal statistical analysis. It is unclear at present whether the efficacy of surgery for headache relief differs for small and large RCCs. These preliminary studies suggest that RCCs can cause headaches even if volume is small, possibly through release of inflammatory cystic contents. In fact, Hayes et al. [11] demonstrated a correlation between inflammatory infiltrate and prevalence of headache, but not for pituitary

Table 2 Summary of recent studies on headache outcomes in patients with Rathke's cleft cyst post-operatively

Study	Study design	No. of patients	No. of patients with headaches pre-operatively	Mean cyst size	Surgical technique	Headache assessment	Timepoint of headache assessment/ mean follow-up (range)	Headache resolved/ improved	Limitations
Current study	Prospectively maintained database	24	16	17 mm	Endoscopic endonasal drainage in all cases except 1 case of cyst resection	HIT-6 score	3 weeks, 6 weeks, 3 months, 6 months, 1 year	63% Mean reduction of HIT-6 score by 7 points at 6 months and 6 points at 12 months	Loss to follow-up
Nishioka et al. 2006 [1]	Retrospective	46 (13 conservative, 33 surgical)	21	17.9 mm (10–38)	32 transsphenoidal 1 transcranial	Common Terminology Criteria for Adverse Events	Unclear 42 months (6–112 months)	81%	Non-standardised assessment of headache, complications and specific surgical technique not reported
Wait et al., 2010 [15]	Prospectively maintained database	73	55	2.1 ml (0.2–32.3 mL)	24 sublabial 49 transnasal First 18 had attempt at complete resection, subsequently biopsy only if cyst wall could not be removed safely	Patient reported resolved, improved, unchanged or worsened	At last follow-up with mean 27 months (0–129 months)	89%	Data collected over period of 15 years where changes in practice e.g. surgical technique may influence outcomes, high rates of postoperative CSF leak and diabetes insipidus with complete resection observed

Table 2 (continued)

Study	Study design	No. of patients	No. of patients with headaches pre-operatively	Mean cyst size	Surgical technique	Headache assessment	Timepoint of headache assessment/ mean follow-up (range)	Headache resolved/ improved	Limitations
Truong et al. 2021 [16]	Retrospective	57 (39 conservative, 18 surgical)	15	3.5–20 mm	17 transphenoidal 1 subfrontal 3 microscopic and 15 endoscopic All underwent total/ near total resection	Patient reported resolved/improved/stable	Unclear 71.8 months	60%	Greater number of large RCC ≥ 10 mm in surgical than conservative group may affect interpretation, comparative statistics not undertaken
Algattas et al. 2024 [17]	Retrospective	148	116	13.7 mm (6–37.9)	All endoscopic 26 fenestration 62 marsupialization 60 fenestration with at least partial resection	Patient reported complete/ partial resolution/ no improvement	Unclear 37 months (1–192 months)	75%	Non-standardised assessment of headache outcome
Lin et al. 2019 [20]	Retrospective	109	66	14.7 mm	44 microscopic sublabial 42 microscopic endonasal 14 endoscopic endonasal 1 endoscopic extended 11 capsular wall resection 92 fenestration and biopsy	Patient reported improvement, stabilisation or worsening	Unclear 67 months (3–220 months)	44%	Non-standardised assessment of headache outcome

Table 2 (continued)

Study	Study design	No. of patients	No. of patients with headaches pre-operatively	Mean cyst size	Surgical technique	Headache assessment	Timepoint of headache assessment/ mean follow-up (range)	Headache resolved/ improved	Limitations
Benveniste et al. 2004 [12]	Retrospective	61	44	1.63 ml (0.06–5.51 ml)	23 endonasal 37 sublabial 1 endonasal endoscopic Cyst decompression and biopsy in 56 patients, complete resection of cyst wall in 6 patients	Patient reported resolution, improvement or unchanged	Unclear 22.8 (1–166 months)	91%	Non-standardised assessment of headache outcome
Mathios et al. 2023 [18]	Prospective database	10	10	6 mm (3–9 mm)	Endoscopic endonasal fenestration	Modified AAN-AHS Follow-up Headache Questionnaire Adult or Pediatric	Response received on average 38.8 months (1–98.5 months) about headache at 1 month, 3 months and 1 year	Average intensity reduced from 8.7 pre-operatively to 2.9 at 1 month, 1.6 at 3 months and 0.9 at 1 year	Small sample size, included only sub-centimeter RCCs, lack of statistical analysis, likely recall bias as response received significantly later then when outcomes were assessed for
Fukui et al. 2017 [19]	Retrospective	13	13	7 mm (4.3–9.9 mm)	Endoscopic endonasal drainage and partial resection	HIT-6	3 months	All had relief within 1 week Average HIT-6 score 64 pre-operatively and 37 post-operatively	Small sample size, focused on sub-centimeter RCCs
AAN-AHS American Academy of Neurology and American Headache Society, HIT-6 Headache Impact Test-6.									

dysfunction or visual impairment. The site of inflammation and concentration of inflammatory cells influenced the prevalence of headache, but cyst volume was not different in patients with and without headache, nor associated with presence of inflammation. This provides further evidence for the potential mechanism by which subcentimeter RCCs can also cause intractable headaches.

Our group previously showed that RCC patients had transiently worsened overall QoL which normalized by 6 weeks in addition to worsening of sinonasal QoL which resolved within 3 weeks post-operatively [13]. Here, in the group of RCC patients affected by headache, overall quality of life returned to baseline at 6 weeks with a trend for improvement at 6- and 12- months, although this was not statistically significant. Greater headache severity at 12 months however was associated with reduced overall QoL.

In this study, we showed that durable and clinically meaningful headache improvement can be achieved safely from endoscopic endonasal drainage of RCCs. While ongoing prospective data for patients with RCCs with mass effect is being collected, our findings lend support to considering surgery in patients with intractable headaches as primary indication. The two aforementioned studies showed dramatic improvement in headache after drainage of subcentimeter RCCs, albeit with study limitations. This is worthy of further investigation in a clinical trial, ensuring patients have other potential causes of headache excluded following specialist consultation, and medical management trialed. In this setting, there would also be greater equipoise for including a control group of subcentimeter RCCs managed conservatively. Alternate means to address potential mechanism of inflammatory infiltrate, such as steroids could also be considered [11, 21].

Limitations

This study aimed to assess the change in headache outcome after endoscopic endonasal drainage of Rathke's cleft cyst using the validated HIT-6 questionnaire assessed longitudinally during the first postoperative year. Limitations include small sample size and surgeon selection bias for large RCCs that caused visual deficits, pituitary dysfunction or demonstrated concerning radiological features. Self-selection bias is possible, where loss to follow-up may have been due to those experiencing worse headache outcome, thereby leading to an overestimation in headache relief post-operatively. Equally, the study may attract follow-up from those who experience ongoing symptoms, with those experiencing relief not completing surveys. The subtle distinction between headache as the initial presenting complaint and headache at time of presentation was not captured in our data, nor in previous studies. Potential confounding factors

such as other headache syndrome not related to RCC or concurrent illness that affected their headache could be present. Specific features and duration of headache pre-operatively were not available to allow further characterization. Future studies should incorporate larger sample size and consider inclusion of a comparison group of patients conservatively managed. Longer follow-up period is required to assess potential improvement in overall QoL not detected in this study.

Conclusion

Headache is the most common presenting symptom in patients with RCCs and can significantly affect patients' daily activities. In the largest prospective study using a validated metric, endoscopic endonasal drainage of RCC improved headache at 6 and 12 months post-operatively. Worse headache severity was associated with reduced overall QoL at 12 months. Endoscopic endonasal drainage of RCCs may provide durable and clinically meaningful improvement in headache, with a low risk of complications.

Author contributions All authors contributed to the study conception and design. AJ (data analysis, manuscript preparation and revision), YYW (data collection, data revision), TG (data collection, revision), MCK (manuscript revision), JKa (data collection, revision), YCZ (data collection), JKl (data collection, revision, study supervision). All authors read and approved the final manuscript.

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Code availability. N/A.

Declarations

Ethical approval HREC 15386Q (Institutional Approval).

Informed consent Informed consent was obtained from all individual participants included in the study.

Competing interests The authors declare no competing interests.

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