Transient Exacerbation of Nasal Symptoms following Endoscopic Transsphenoidal Surgery for Pituitary Tumors: A Prospective Study

Benjamin M. Davies[1] Erica Tirr[1] Yi Yuen Wang[1,2] Kanna K. Gnanalingham[1,3]

[1] Department of Neurosurgery, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Manchester, United Kingdom
[2] Department of Neurosurgery, Department of Surgery, The University of Melbourne, St Vincent's Hospital, Fitzroy, Victoria, Australia
[3] Manchester Academic Health Sciences Centre, University of Manchester, Manchester, United Kingdom

Address for correspondence Kanna K. Gnanalingham, FRCS(SN), PhD, Department of Neurosurgery, Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Stott Lane, Salford, M6 8HD, Manchester, United Kingdom (e-mail: kanna.gnanalingham@srft.nhs.uk).

J Neurol Surg B 2017;78:266–272.

Abstract

Object Endoscopic transsphenoidal surgery is the commonest approach to pituitary tumors. One disadvantage of this approach is the development of early postoperative nasal symptoms. Our aim was to clarify the peak onset of these symptoms and their temporal evolution.

Methods The General Nasal Patient Inventory (GNPI) was administered to 56 patients undergoing endoscopic transsphenoidal surgery for pituitary tumors preoperatively and at 1 day, 3 days, 2 weeks, 3 months, and 6 to 12 months postoperatively. Most patients underwent surgery for pituitary adenomas ($N = 49$; 88%) and through a uninostril approach ($N = 55$; 98%). Total GNPI (0–135) and scores for the 45 individual components were compared.

Results GNPI scores peaked at 1 to 3 days postoperatively, with rapid reduction to baseline by 2 weeks and below baseline by 6 to 12 months postsurgery ($p < 0.01$). Of the 45 individual symptoms on the GNPI scale, 19 (42%) worsened transiently after surgery ($p < 0.05$). Functioning tumors had a higher GNPI scores at postoperative day 1 and 3 than nonfunctioning tumors, although their temporal evolution was the same ($p < 0.05$).

Conclusions Nasal morbidity following endoscopic transsphenoidal pituitary surgery is common, but transient, more so in the functioning subgroup. Nasal symptoms improve below baseline by 6 to 12 months, without the need for specific long-term postoperative interventions in the vast majority of patients.

Keywords
- endoscopic
- transsphenoidal
- pituitary tumor
- adenoma
- nasal symptoms
- GNPI

Introduction

The endoscopic transsphenoidal approach for pituitary surgery is now the favored approach to the pituitary fossa, having progressively replaced the microscopic approach in most centers over the last 10 to 15 years.[1–7] The cranial approaches are mostly reserved for residual pituitary tumors that are deemed too difficult to resect through the transsphenoidal route. The popularity of the endoscopic approach is in part due to the improved surgical access, visibility, the potential for greater tumor resection, reduced nasal trauma, and thus shorter hospital stay and greater patient satisfaction.[4–11]

received
May 25, 2016
accepted after revision
November 20, 2016
published online
January 23, 2017

DOI https://doi.org/10.1055/s-0036-1597814.
ISSN 2193-6331.

With the transsphenoidal approach, patients frequently report nasal symptoms such as nasal discharge, congestion, bleeding, crusting, pain, and loss of smell shortly after surgery. Strategies to combat and/or prevent these symptoms vary widely and include the use of postoperative nasal decongestants, saline irrigation, and endoscopic debridement in the outpatient setting.[1,2,4,12,13]

We and others have previously reported on the prevalence of postoperative patient-perceived rhinological symptoms following endoscopic transsphenoidal surgery[4,6,8,14–16] Using the validated General Nasal Patient Inventory (GNPI) questionnaire, we identified that by 3 to 6 months postoperatively, the majority of patient undergoing endoscopic surgery for pituitary tumors were largely asymptomatic from a nasal point of view.[4] However, the temporal evolution of these symptoms in the early postoperative period remains less clear. This remains of interest when considering the treatment length of preventative therapies.

In this study, we more closely evaluated the onset and early progression of patient-perceived nasal symptoms following endoscopic transsphenoidal surgery for pituitary tumors by administering the GNPI preoperatively and at 1 day, 3 days, 2 weeks, 3 and 6 to 12 months postoperatively.

Method

Patients undergoing transsphenoidal pituitary surgery for pituitary tumors by a single surgeon over an 18-month period (2007–2009) were approached to complete an audit questionnaire prospectively. Of the 58 patients, 56 provided complete follow-up data and were included for analysis. Patient demographics, tumor type, operative details (including cerebrospinal fluid [CSF] leak and method of repair), and complications (including hemorrhage and intervention for ongoing nasal symptoms) were recorded.

Operative Technique

All patients underwent endoscopic transsphenoidal surgery as described previously.[1,4] Cophenylcaine (Aurum Pharmaceuticals Ltd, Romford, United Kingdom) was applied to both nostrils as preoperative nasal preparation. Perioperatively, all patients received a single dose of antibiotics (intravenous cefuroxime and metronidazole). No antiseptic nasal wash or other vasoconstrictors were routinely used during surgery. Typically, surgical approach was through a single nostril, the side chosen taking into account the laterality of the tumor and any anomaly in nasal anatomy. On occasion, surgery required the use of both nostrils, with a small posterior septostomy. The middle turbinate was gently lateralized and turbinectomy (partial or complete) was not performed. The posterior nasal septal mucosa overlying the anterior sphenoid wall, on the side of the approach, was cauterized before opening the sphenoid sinus. The sphenoid sinus mucosa was reflected laterally using cotton patties. In the event of CSF leakage, a graded operative repair was undertaken using combinations of hemostatic gelatin sponge (Spongostan, Ethicon, Edinburgh, United Kingdom), dural substitute (Durafoam, Codman, United Kingdom), and dural sealant (Duraseal, Confluent Surgical, Waltham, Massachusetts) for grade 1 leaks (minor leak with no obvious arachnoid defect).[1] In the event of a grade 2 (i.e., moderate CSF leak with visible arachnoid defect) or grade 3 CSF leak (i.e., large CSF leak with large dural defect), in addition to the aforementioned combinations, a fat graft and/or vascularized nasoseptal flap was used on a selective basis.[1]

At the end of tumor removal, nasal cavities in both nostrils were inspected and any significant mucosal bleeding points were controlled with diathermy. The deflected middle turbinate and nasal septum were medialized and nasal packing was not routinely employed.

Postoperative Course

A topical nasal decongestant (Xylometazoline 0.1% spray, Novartis, Surrey, United Kingdom) was prescribed for 7 days postoperatively. Additional therapies, such as saline irrigation, nasal debridement, and review by an otolaryngologist, were not routinely undertaken and only considered for those patients with persistent nasal symptoms, in conjunction with otolaryngologist referral.

Nasal Symptoms

The GNPI is a patient reported outcome tool developed to cover all rhinological conditions.[14] The GNPI questionnaire considers 45 different nasal symptoms and patients choose one of 4 numerical answers for each: 0 (not present), 1 (mild), 2 (moderate), or 3 (severe). Therefore, the higher the score, the greater the symptom burden; the score ranges between 0 and 135.

In this study, patients completed the GNPI questionnaire preoperatively and at 1 day, 3 days, 2 weeks, 3 months, and 6 to 12 months postoperatively. The 45 individual nasal symptoms and the total GNPI score (range: 0–135) at each time points were analyzed.

Statistical Analysis

Analysis was performed using SPSS (version 20, Chicago, Illinois, United States). Comparison between time points was assessed using repeated measures analysis of variance (ANOVA), with posthoc Bonferroni tests for parametric data and the chi-square tests for nonparametric data.

Results

Population Characteristics

Mean patient age (± SD) was 58 ± 16 years (range: 23–87) and both sexes were equally represented (M:F 27:29). The majority of patients ($N = 33$; 60%) had nonfunctioning pituitary adenomas. The functioning tumors included acromegaly ($N = 6$; 11%), Cushing syndrome ($N = 6$; 11%), and prolactinomas ($N = 3$; 5%). The remainder included Rathke's cysts ($N = 4$; 7%), one each of a craniopharyngioma, squamoid cyst, pituitary apoplexy, and a mucocoele. GNPI scores did not differ between adenomas and the small number of nonadenomas ($N = 8$) and were analyzed together ($p = 0.8$; ANOVA). The majority of lesions were macroadenomas ($N = 40$; 83%). Baseline demographics are summarized in ►**Table 1**.

Table 1 Baseline patient demographics

Covariate	*N* (%)
Male	27 (48)
Functional	15 (27)
Macro Micro Nonadenoma	40 (71) 8 (14) 8 (14)
Uninostril approach	55 (98)
CSF leak	20 (36)
Age (mean ± SD)	58 ± 16

Abbreviation: CSF, cerebrospinal fluid; SD, standard deviation.
Note: Percentages are expressed as a proportion of patients with complete follow-up data ($N = 56$).

Procedural Variation and Complications

The majority ($N = 55$; 98%) of procedures were undertaken through a single nostril, and none of the patients required postoperative nasal packing. In this series, no patients underwent extended endoscopic transsphenoidal surgery for other skull base pathology. Intraoperative CSF leaks complicated 20 (36%) procedures. These were grade 1 ($N = 19$) and grade 2 ($N = 1$) CSF leaks. Repairs were made with a combination gelatin sponge (Spongostan), dural substitute (Durafoam), and dural sealant (Duraseal) as described previously.[1] No fat grafts were used, and the repair was effective in all but two patients (i.e., one patient with Cushing disease and another with a Rathke's cyst), who represented with recurrent CSF leaks that were successfully treated with lumbar drains ($N = 2$) and further transsphenoidal repair ($N = 1$).

On discharge, three patients suffered early postoperative nose bleeds, requiring readmission and management with nasal packing, oral antibiotics ($N = 3$), and transfusion/cautery ($N = 1$). One patient was reviewed at 3 months in an ear, nose, and throat clinic with symptoms of persistent nasal crusting and headaches that responded to a course of steroid nasal spray and saline irrigation.

General Nasal Patient Inventory Scores

Out of a maximum score of 135, the mean postoperative GNPI scores peaked at day 1 (19 ± 14), before gradually returning to baseline at 2 weeks ($p < 0.01$, repeated measures ANOVA and posthoc Bonferroni test; ►**Fig. 1**). The mean GNPI score at 6 to 12 months follow-up (6.7 ± 7) was significantly lower than the preoperative baseline ($p = 0.03$, repeated measures ANOVA and posthoc Bonferroni test; ►**Fig. 1**).

Functioning tumors had a higher GNPI score than the corresponding score for the nonfunctioning tumor types, at day 1 and day 3 ($p = 0.02$, repeated measures ANOVA and posthoc Bonferroni test; ►**Fig. 2**). Age ($p = 0.1$) and patient sex ($p = 0.6$) were not associated with the mean GNPI scores (repeated measures ANOVA). The postoperative trends in GNPI scores did not significantly interact for patients suffering a CSF leak ($p = 0.4$, repeated measures ANOVA).

Of the 45 individual symptoms considered by the GNPI, 19 (42%) showed significant variation across different time points during follow-up ($p < 0.05$, chi-square test; ►**Table 2**). All of these symptoms improved to or beyond baseline at 6 to 12 months postoperatively (►**Table 2**). The majority of these symptoms (18/19; 95%) peaked between 1 to 3 days following the operation (►**Fig. 3**). Only the GNPI symptom, "my work is affected" peaked at 2 weeks postoperatively (►**Fig. 3**).

Discussion

The main findings of this study were that the majority of patients reported some nasal morbidity following transsphenoidal endoscopic pituitary surgery, more so among patients

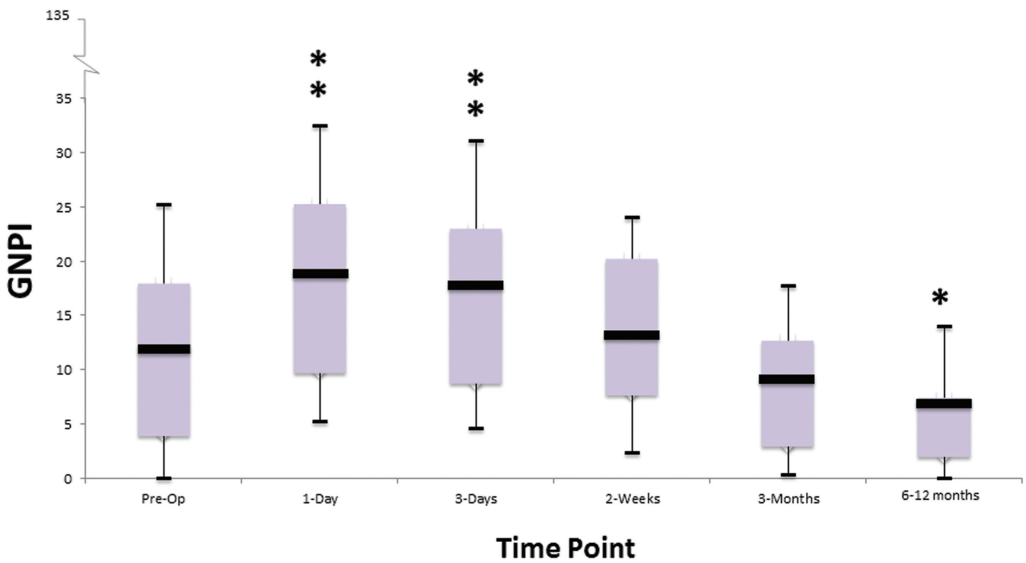

Fig. 1 Changes in total General Nasal Patient Inventory scores over time. Box plots depict the mean (horizontal black line), interquartile range (box), and the standard deviation values (tails). $^{*}p < 0.05$; $^{**}p < 0.01$ versus preoperative value; repeated measures analysis of variance and posthoc Bonferroni test.

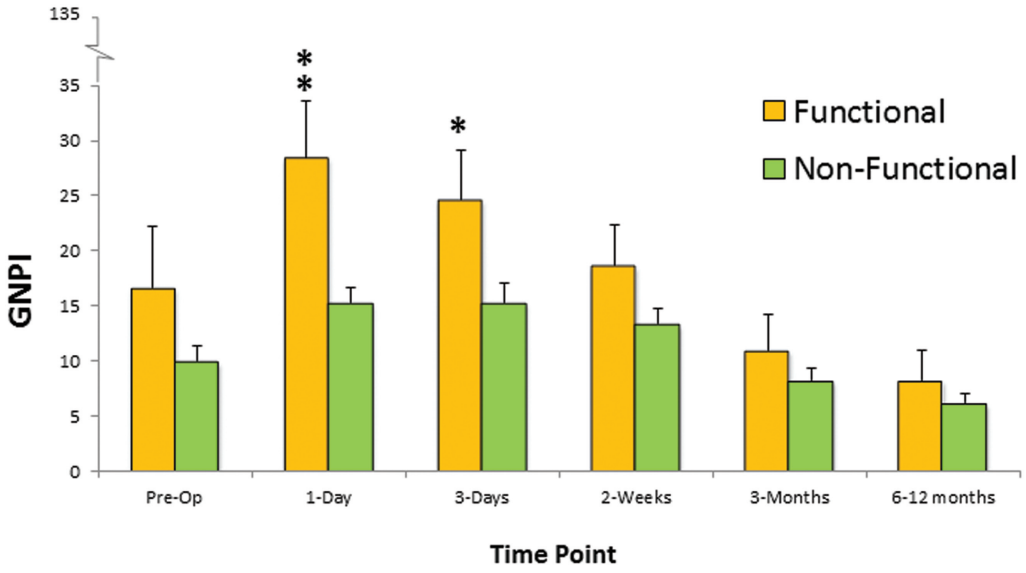

Fig. 2 Comparison of the total General Nasal Patient Inventory scores (mean ± standard error) over time for functioning compared with nonfunctioning pituitary tumors. $^{*}p < 0.05$; $^{**}p < 0.01$ versus corresponding score for the other group at same time point; repeated measures analysis of variance and posthoc Bonferroni test.

with functional adenomas. Regardless, the nasal symptoms were relatively mild and recovered quickly and with minimal input postoperatively. Our findings indicate that the majority of symptoms peak at 1 to 3 days and show rapid improvement by 2 weeks thereafter. This and the discrepancies between functioning and nonfunctioning adenomas, alongside the very early recovery without significant intervention, represent new findings in transsphenoidal endoscopic surgery.

A variety of scoring systems have been developed to evaluate patient experience of nasal symptoms following pituitary surgery.[3,4,7,8,16] Most of these scales have been validated in patients with rhinological conditions, and only a few, such as the anterior skull base nasal inventory (ASK Nasal-12), have been validated in the pituitary surgery patient group.[8] In this study, the GNPI was used primarily to allow comparison with the results of our previous study.[4] The GNPI inventory provides a comprehensive list of possible nasal symptoms and includes the more refined symptom list of the anterior skull base nasal inventory.

A significant difference in postoperative patient reported nasal morbidity between functioning and nonfunctioning tumors was observed 1 to 3 days after surgery. This has not been previously described in other studies. This may in part be due to previous studies considering later postoperative time points, when as mirrored in our study there is no difference.[2–4] The higher GNPI scores in the functioning group of tumor patients may reflect the influence of excess hormone production. Thus, for example, the growth hormone excess in acromegaly is associated with hypertrophy of nasal passages and pharyngeal tissues, leading to increased nasal symptoms and sleep apnea preoperatively.[1,17,18] Likewise, excess cortisol production in Cushing disease is likely to delay early postoperative healing in the nasal passages.[1,19] Reassuringly, the increase in GNPI scores in the functioning group is short lived and beyond 2 weeks, and there is little difference when compared with nonfunctioning tumor patients. The improvement in symptoms in the functioning group is likely related to reduction in excess hormone production in functioning tumors postoperatively. Consistent with our observations, Actor et al demonstrated a more pronounced improvement in olfaction and nasal patency among patients with acromegaly compared with others, a change likely due to the reduction in nasal hypertrophy postoperatively and related to reduction in growth hormone levels postoperatively.[1,17]

The overall mean GNPI score at 6 to 12 months follow-up was lower than the preoperative baseline. This was also apparent in the progressive improvements in several individual symptoms considered by the GNPI such as "I get headaches," "My nose is blocked," "My voice changes," and "I get toothache." The progressive improvement in the overall GNPI score may reflect the reduction in mass effect and improved quality of life secondary to pituitary tumor surgery and the normalization of hormonal excesses in functioning adenomas.

Given the prevalence of early postoperative nasal symptoms following transsphenoidal surgery for pituitary tumors, most patients require ongoing postoperative nasal care on discharge.[2,14,20] However, the exact practice differs widely across centers in part due to the relative lack of evidence basis to guide postoperative therapies following endoscopic pituitary surgery.[1,2,20] In our unit, where endoscopic surgery for most pituitary tumors is typically undertaken through a uninostril approach, the use of a topical nasal decongestant for a short period (i.e., 1 week) postoperatively is preferred. Others recommend a more interventional approach including outpatient endoscopic debridement and/or a longer course of topical nasal agents such as saline irrigation.[2,15] We reserve these measures mostly for the extended transsphenoidal cases, typically requiring a binostril approach, with a partial

Table 2 The GNPI and the evolution of symptoms over time

Symptom		Preoperative (%)	Postoperative (%)					Chi-square *p*-value
			1 d	3 d	2 wk	3 mo	6–12 mo	
1	I have sores inside my nose	89	70	68	79	86	98	<0.0001
2	I get headaches	59	46	39	45	54	63	0.07
3	I take too many painkillers	82	73	82	86	82	84	0.79
4	There is an unpleasant smell in my nose	93	98	91	84	88	91	0.4
5	My nose bleeds	91	32	73	82	95	95	<0.0001
6	My sinuses are painful	89	84	75	71	89	95	0.07
7	My nose is blocked	77	34	29	52	80	88	<0.0001
8	I feel dripping at the back of my nose	89	63	71	75	88	91	0.001
9	I have an unpleasant taste in my mouth	82	80	71	68	77	89	0.24
10	I have feelings of nausea	84	77	77	88	93	96	0.04
11	My mouth is dry	68	38	32	48	64	75	<0.0001
12	My nose feels uncomfortable	89	55	45	61	88	91	<0.0001
13	My taste is affected	84	70	57	61	75	79	0.03
14	My work is affected	82	73	68	63	79	84	0.04
15	My voice changes	79	68	71	82	93	95	0.01
16	My jaws are sore	89	86	91	89	96	98	0.35
17	I feel tired	45	25	18	18	36	39	0.02
18	I have sore ears	89	89	96	95	96	96	0.67
19	My nose makes unusual noises	91	82	80	80	89	93	0.4
20	My sleep is disturbed	59	39	43	52	63	68	0.23
21	My nose is painful to touch	100	73	75	89	93	95	<0.0001
22	My sense of smell is affected	73	48	52	54	73	75	0.01
23	I have a choking feeling	96	95	93	93	96	96	0.73
24	My nose looks out of shape	89	88	89	93	98	98	0.49
25	I have sneezing attacks	80	88	88	82	84	88	0.4
26	I have pains in my face	89	88	80	88	95	96	0.48
27	I have to breathe through my mouth	89	48	45	57	84	95	<0.0001
28	I suffer from hayfever	89	93	93	93	93	93	0.88
29	I have difficulty breathing	96	80	82	91	91	96	0.09
30	I have difficulty talking or eating	93	89	89	89	96	96	0.71
31	I have sore watering eyes	71	75	79	73	84	86	0.5
32	I feel moody, depressed, or irritable	71	88	73	66	71	79	0.59
33	My nose feels itchy	89	88	82	80	84	95	0.71
34	I am constantly sniffing	91	64	61	68	93	100	<0.0001
35	My hearing is affected	86	89	95	91	95	95	0.82
36	I speak through my nose	88	64	64	75	86	91	<0.0001
37	I have a sore throat	88	73	84	96	96	100	<0.0001
38	My gums bleed	86	96	98	98	100	100	0.001
39	I feel dizzy	79	71	75	73	86	89	0.61
40	I suffer from a cough	84	71	79	88	91	93	0.52
41	People ask me if I have a cold	77	75	68	77	93	96	0.001
42	My nose runs	79	43	43	73	93	96	<0.0001

Table 2 (*Continued*)

Symptom		Preoperative (%)	Postoperative (%)					Chi-square *p*-value
			1 d	3 d	2 wk	3 mo	6–12 mo	
43	I snore	43	46	48	48	46	48	0.97
44	I have bad breath	77	77	84	84	86	89	0.95
45	I get toothache	82	88	93	91	91	100	0.16

Abbreviation: GNPI, General Nasal Patient Inventory.
Note: Percentage of asymptomatic patients at each time point ($N = 56$). The *p*-value indicates whether there was significant change in a symptom over time (chi-square test).

or complete middle turbinectomy and/or a nasoseptal flap, resulting in greater nasal morbidity. Likewise the use of perioperative broad spectrum antibiotics is common practice in endoscopic pituitary surgery. However, routine provision of postoperative antibiotics is not common, and we prefer to reserve this for extended transnasal procedures, particularly where a temporary nasal packing is used to support the repair.

Despite the different approaches, and accepting the caveats of interstudy comparison, the results from several recent studies including the present confirm that the proportion of patients with persistent nasal symptoms after endoscopic pituitary surgery is relatively small.[4,6,8,15,21] These observations together with findings of recent meta-analysis reaffirm the efficacy and safety of the endoscopic approach in relationship to the more established microscopic approach.[5,6]

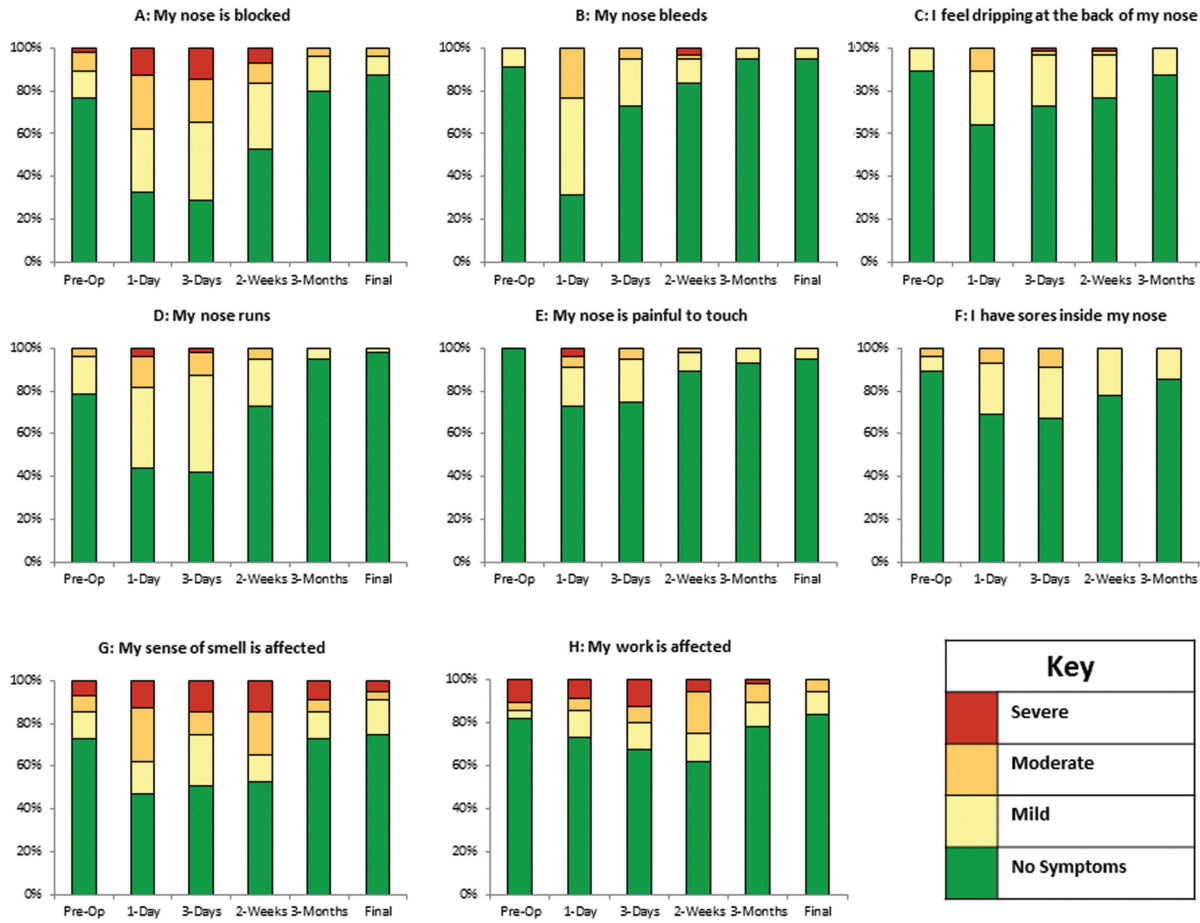

Fig. 3 Temporal evolution of selected nasal symptoms. **(A)** My nose is blocked. **(B)** My nose bleeds. **(C)** I feel dripping at the back of my nose. **(D)** My nose runs. **(E)** My nose is painful to touch. **(F)** I have sores inside my nose. **(G)** My sense of smell is affected. **(H)** My work is affected. All symptoms peaked at 1 to 3 days postoperatively with the exception of "My work is affected" **(H)**.

Disclosure

The results of this study have been presented at the International Society of Pituitary Surgeons, Liverpool, United Kingdom, November 2015.

References

1 Zador Z, Gnanalingham K. Endoscopic transnasal approach to the pituitary–operative technique and nuances. Br J Neurosurg 2013; 27(6):718–726

2 Little AS, Kelly D, Milligan J, et al. Predictors of sinonasal quality of life and nasal morbidity after fully endoscopic transsphenoidal surgery. J Neurosurg 2015;122(6):1458–1465

3 McCoul ED, Anand VK, Schwartz TH. Improvements in site-specific quality of life 6 months after endoscopic anterior skull base surgery: a prospective study. J Neurosurg 2012;117(3):498–506

4 Wang YY, Srirathan V, Tirr E, Kearney T, Gnanalingham KK. Nasal symptoms following endoscopic transsphenoidal pituitary surgery: assessment using the General Nasal Patient Inventory. Neurosurg Focus 2011;30(4):E12

5 Gao Y, Zhong C, Wang Y, et al. Endoscopic versus microscopic transsphenoidal pituitary adenoma surgery: a meta-analysis. World J Surg Oncol 2014;12:94

6 Little AS, Kelly DF, Milligan J, et al. Comparison of sinonasal quality of life and health status in patients undergoing microscopic and endoscopic transsphenoidal surgery for pituitary lesions: a prospective cohort study. J Neurosurg 2015;123(3):799–807

7 Kirkman MA, Borg A, Al-Mousa A, Haliasos N, Choi D. Quality-of-life after anterior skull base surgery: a systematic review. J Neurol Surg B Skull Base 2014;75(2):73–89

8 Little AS, Kelly D, Milligan J, et al. Prospective validation of a patient-reported nasal quality-of-life tool for endonasal skull base surgery: The Anterior Skull Base Nasal Inventory-12. J Neurosurg 2013;119(4):1068–1074

9 Fathalla H, Cusimano MD, Alsharif OM, Jing R. Endoscopic transphenoidal surgery for acromegaly improves quality of life. Can J Neurol Sci 2014;41(6):735–741

10 Gaillard S. The transition from microscopic to endoscopic transsphenoidal surgery in high-caseload neurosurgical centers: the experience of Foch Hospital. World Neurosurg 2014;82(6, Suppl): S116–S120

11 Jane JA Jr, Han J, Prevedello DM, Jagannathan J, Dumont AS, Laws ER Jr. Perspectives on endoscopic transsphenoidal surgery. Neurosurg Focus 2005;19(6):E2

12 Humphreys H. Preventing surgical site infection. Where now? J Hosp Infect 2009;73(4):316–322

13 Little AS, Chapple K, Jahnke H, White WL. Comparative inpatient resource utilization for patients undergoing endoscopic or microscopic transsphenoidal surgery for pituitary lesions. J Neurosurg 2014;121(1):84–90

14 Douglas SA, Marshall AH, Walshaw D, Robson AK, Wilson JA. The development of a General Nasal Patient Inventory. Clin Otolaryngol Allied Sci 2001;26(5):425–429

15 Balaker AE, Bergsneider M, Martin NA, Wang MB. Evolution of sinonasal symptoms following endoscopic anterior skull base surgery. Skull Base 2010;20(4):245–251

16 Dusick JR, Esposito F, Mattozo CA, Chaloner C, McArthur DL, Kelly DF. Endonasal transsphenoidal surgery: the patient's perspective-survey results from 259 patients. Surg Neurol 2006;65(4): 332–341, discussion 341–342

17 Actor B, Sarnthein J, Prömmel P, Holzmann D, Bernays RL. Olfactory improvement in acromegaly after transnasal transsphenoidal surgery. Neurosurg Focus 2010;29(4):E10

18 Leach P, Abou-Zeid AH, Kearney T, Davis J, Trainer PJ, Gnanalingham KK. Endoscopic transsphenoidal pituitary surgery: evidence of an operative learning curve. Neurosurgery 2010;67(5): 1205–1212

19 Wicke C, Halliday B, Allen D, et al. Effects of steroids and retinoids on wound healing. Arch Surg 2000;135(11):1265–1270

20 Rudmik L, Soler ZM, Orlandi RR, et al. Early postoperative care following endoscopic sinus surgery: an evidence-based review with recommendations. Int Forum Allergy Rhinol 2011;1(6): 417–430

21 de Almeida JR, Snyderman CH, Gardner PA, Carrau RL, Vescan AD. Nasal morbidity following endoscopic skull base surgery: a prospective cohort study. Head Neck 2010;33(4):547–551