Quantitative evaluation of headache severity before and after endoscopic transsphenoidal surgery for pituitary adenoma

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OBJECTIVE The relationship between headaches, pituitary adenomas, and surgical treatment of pituitary adenomas remains unclear. The authors assessed the severity and predictors of self-reported headaches in patients referred for surgery of pituitary adenomas and evaluated the impact of endoscopic transsphenoidal surgery on headache severity and quality of life (QOL).

METHODS In this prospective study, 79 patients with pituitary adenomas underwent endoscopic transsphenoidal resection and completed the Headache Impact Test (HIT-6) and the 36-Item Short Form Health Survey (SF-36) QOL questionnaire preoperatively and at 6 weeks and 6 months postoperatively.

RESULTS Preoperatively, 49.4% of patients had mild headache severity, 13.9% had moderate severity, 13.9% had substantial severity, and 22.8% had intense severity. Younger age and hormone-producing tumors predisposed greater headache severity, while tumor volume, suprasellar extension, chiasmal compression, and cavernous sinus invasion of the pituitary tumors did not. Preoperative headache severity was found to be significantly associated with reduced scores across all SF-36 QOL dimensions and most significantly associated with mental health. By 6 months postoperatively, headache severity was reduced in a significant proportion of patients. Of the 40 patients with headaches causing an impact on daily living (moderate, substantial, or intense headache), 70% had improvement of at least 1 category on HIT-6 by 6 months postoperatively, while headache worsened in 7.6% of patients. The best predictors of headache response to surgery included younger age, poor preoperative SF-36 mental health score, and hormone-producing microadenoma.

CONCLUSIONS The results of this study confirm that surgery can significantly improve headaches in patients with pituitary adenomas by 6 months postoperatively, particularly in younger patients whose preoperative QOL is impacted. A larger multicenter study is underway to evaluate the long-term effect of surgery on headaches in this patient group.

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KEY WORDS pituitary adenoma; headache; endoscopic transsphenoidal surgery; quality of life; pituitary surgery

PITUITARY tumors are relatively common, with reported prevalence rates ranging from 10% to 22% and accounting for 10% to 15% of all intracranial tumors.^{3,5,22} With the advent of neuroimaging, the incidental finding of pituitary adenoma has become much more frequent. Chronic headache is a common reason for undergoing neuroimaging. The incidence of headache in patients with pituitary adenomas has been reported to range between 33% and 72%.^{1,6,23} The existence of any clear re-

lationship between headaches, pituitary tumors, and surgical treatment of pituitary tumors remains to be elucidated.

Chronic headache in patients with pituitary tumors may arise from several putative mechanisms, including tumor volume and its relationship with the sellar structures, functional disturbance within the hypothalamopituitary axis, patient predisposition, and family history.^{8,9} Invasion of the cavernous sinus is a proposed etiology of headache given that the sinus contains the ophthalmic branch of

ABBREVIATIONS BP = bodily pain; GH = general health perceptions; HIT-6 = Headache Impact Test; MH = mental health; PF = physical function; QOL = quality of life; SF-36 = 36-Item Short Form Health Survey; RE = role-emotional; RP = role-physical; SF = social functioning; VT = vitality.

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the trigeminal nerve and the internal carotid artery, the compression of which has the potential to generate pain.⁴ Gondim et al. found a direct association between the presence of headache and tumor size, optic chiasm compression, sellar destruction, and cavernous sinus invasion.⁹ Headaches can also occur in patients with hormone-producing adenomas, particularly growth hormone-secreting tumors and prolactinomas, and demonstrate improvement with medical endocrinological treatments.¹⁹ Few studies have investigated the impact of surgery on headaches in patients with pituitary adenomas.^{7,15}

The purpose of the present study was to determine the severity of self-reported headaches in patients with pituitary masses before surgery and to prospectively evaluate the impact of purely endoscopic transsphenoidal surgery on headaches and QOL at 6 weeks and at 6 months postoperatively. The relationship between headache severity and factors, including hormone production, tumor volume, sellar extension, and cavernous sinus involvement, was examined along with potential predictors of headache response to surgery.

Methods

Study Participants

Our study prospectively collected data on 79 patients who underwent endoscopic transsphenoidal resection of pituitary adenomas between July 2009 and February 2014. This study was reviewed and approved by the Research Ethics Committee at London Health Sciences Centre. All patients gave written informed consent prior to inclusion in the study. At our institution, patients were managed by a multidisciplinary pituitary team consisting of a neurosurgeon, neurologist, otolaryngologist, neuroradiologist, neuroophthalmologist, and endocrinologist. All patients underwent endoscopic transsphenoidal surgery either for visual deterioration and/or endocrinological reasons. No patient underwent surgery for the treatment of headaches as the sole indication.

All patients underwent preoperative contrast-enhanced MRI of the head as well as postoperative MRI at 6 months to assess the extent of resection. Chiasm compression, cavernous sinus invasion, and suprasellar extension were determined on the basis of the radiological appearance and considered present or absent. Tumor volume was determined by the maximal diameters in 3 dimensions using the following formula: volume = anteroposterior × cranio-caudal × transverse/2. In addition, patients underwent a complete ophthalmological assessment and visual field analysis using the Humphrey Field Analyzer (Zeiss) before and after resection. Prior to surgery, all patients were followed up closely by the endocrinology and neurology teams and underwent routine testing of their pituitary hormones and target hormones.

Resection was performed jointly by an otolaryngologist and neurosurgeon. Generally, posterior nasal septectomy was performed to allow binasal access, and the face of the sphenoid and intersphenoidal septations were drilled away. The dura was incised, and the tumor was resected using standard endoscopic instruments. Any complex intraoperative CSF leak was repaired in a layered fashion, which consisted of a combination of Gelfoam; fat, muscle,

and fascia grafting; dura matrix overlay; and a vascularized nasoseptal flap, followed by the placement of a lumbar drain postoperatively.

Outcome Assessments

The study participants were requested to complete the Headache Impact Test (HIT-6) and 36-Item Short Form Health Survey (SF-36) QOL questionnaires at 3 different time points: preoperatively and 6 weeks and 6 months postoperatively.

HIT-6

HIT-6 is a validated tool used to measure the impact that headaches have on daily functioning.^{10,17} The final HIT-6 score is obtained from the simple summation of 6 items and ranges between 36 and 78 points, with larger scores reflecting a greater impact. The 4 headache impact severity categories are: little or no impact (≤ 49), moderate impact (50–55), substantial impact (56–59), and intense impact (60–78).

SF-36

SF-36 assesses the general well-being of patients. This taxonomy has 3 levels: 1) items; 2) 8 scales that aggregate 2–10 items each; and 3) 2 summary measures that aggregate the scales. The 8 components are as follows: physical function (PF), role-physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The PF scale has been shown to be the best all-around measure of physical health, while the MH scale is the most valid measure of mental health in studies to date.^{16,24}

Statistical Analyses

SPSS 20.0 (IBM Corp.) was used for all data analyses. The HIT-6 and SF-36 scores were expressed as the mean $\pm$ SD. The student paired t-test or ANOVA was used to compare mean HIT-6 and SF-36 preoperatively and 6 weeks and 6 months postoperatively. Pearson's correlation was used to assess the correlations between continuous variables. The chi-square test was used to compare categorical variables. The Wilcoxon sign-rank test was used to compare ordinal data across time points. Predictors of headache response to surgery were determined using logistic regression analysis. The α level was set to 5%. All tests were 2-tailed analyses.

Results

Study Patient Characteristics

The baseline clinical characteristics of the 79 patients with pituitary adenomas are listed in Table 1. The mean age $\pm$ SD was 55.9 ± 14.3 years, and 36 patients were female. The mean tumor volume was 6.3 ± 6.7 cm³. Seventy patients (88.6%) had a sellar lesion with a maximum diameter greater than 10 mm, and 9 patients (11.4%) had microadenomas. Nineteen patients (24%) had clinically relevant hormone-producing tumors, including tumors that resulted in acromegaly (growth hormone producing; $n = 10$), produced thyroid-stimulating hormone ($n = 1$), resulted in Cushing's disease (adrenocorticotrophic hormone

TABLE 1. Baseline characteristics of the study patients who underwent endoscopic transsphenoidal resection of pituitary adenomas

Characteristic	Value*
Mean age, yrs	55.9 ± 14.3
Sex	
Female	36 (45.6)
Male	43 (54.4)
Mean tumor size, cm ³	6.3 ± 6.7
Tumor characteristic	
Microadenoma	9 (11.4)
Macroadenoma	70 (88.6)
Suprasellar extension	66 (83.5)
Chiasm compression	54 (68.4)
Cavernous sinus invasion	35 (44.3)
Tumor histology	
Null cell	60 (75.9)
Somatotroph	10 (12.7)
Corticotroph	5 (6.3)
Prolactinoma	3 (3.8)
Thyrotroph	1 (1.3)

* Values are presented as the number of patients (%) unless indicated otherwise. Mean values are presented as the mean ± SD.

producing; n = 5), or resulted in prolactinoma (prolactin producing; n = 3). Of the hormone-producing tumors, all but 2 patients with acromegaly achieved a biochemical cure postoperatively. Twenty-nine patients (36.7%) had preoperative partial or complete anterior hypopituitarism. Based on the MRIs acquired preoperatively, 83.5% of patients had a tumor extending into the suprasellar space. Chiasmal compression was present in 68.4% of patients, and cavernous sinus invasion was reported in 44.3% of patients. Only 1 patient had a clinical history of pituitary apoplexy. Two patients had blood products reported on MRI.

Fifty-two percent of patients were not taking any regular analgesic medications. Forty percent of patients were reportedly taking ibuprofen or acetaminophen more than 3 days per week. Approximately 8% of patients were taking daily morphine or hydromorphone.

Does Hormone Production Impact Headache Severity?

The self-reported headache severity in the preoperative period, as categorized according to impact severity and measured by the HIT-6 questionnaire, was as follows: mild in 39 (49.4%) patients, moderate in 11 (13.9%) patients, substantial in 11 (13.9%) patients, and intense in 18 (22.8%) patients (Fig. 1, “preoperative”). Younger age was correlated with increased preoperative headache severity (Pearson correlation: $r = -0.54$, $p < 0.001$). Headache severity did not significantly differ between male and female patients. Hormone-producing tumors were significantly associated with increased severity of headaches compared with nonsecreting tumor ($\chi^2 = 11.6$, $p = 0.009$). Of the patients with hormone-producing tumors, 14 of 19 (73.6%) patients had moderate, substantial, or intense headache se-

verity compared with 26 of 60 (43.3%) patients with non-secreting adenomas. Hormone-producing tumors associated with increased severity of headache included 7 of 10 somatotrophs, 3 of 5 corticotrophs, 3 of 3 prolactinomas, and 1 of 1 thyrotroph.

Does Tumor Volume, Suprasellar Extension, or Cavernous Sinus Invasion Impact Headache Severity?

No statistically significant correlation was found between preoperative tumor volume and headache severity (Pearson correlation; $r = -0.105$; $p = 0.419$). Furthermore, suprasellar extension, chiasmal compression, and cavernous sinus invasion of a pituitary tumor did not significantly predispose the patient to greater severity of headache ($\chi^2 = 4.5$, $p = 0.21$; $\chi^2 = 2.8$, $p = 0.41$; $\chi^2 = 3.6$, $p = 0.31$, respectively). In fact, patients with microadenomas (< 10 mm) were more likely to have greater headache severity (moderate, substantial, or intense) that impacted their daily life ($\chi^2 = 5.9$, $p = 0.029$). The 2 patients with blood products on MRI reported moderate headaches preoperatively.

What Is the Association Between Preoperative QOL and Headache Severity?

Preoperative headache severity was found to be significantly associated with reduced scores across all SF-36 QOL dimensions, including MH (Pearson correlation, $r = -0.60$; $p < 0.001$), BP ($r = -0.58$, $p < 0.001$), PF ($r = -0.26$; $p = 0.02$), RE ($r = -0.52$, $p < 0.001$), RP ($r = -0.39$, $p < 0.001$), SF ($r = -0.56$, $p < 0.001$), VT ($r = -0.31$, $p = 0.006$), and GH ($r = -0.50$, $p < 0.001$). Figure 2 depicts the scatterplot of the preoperative HIT-6 scores and the 2 strongest inversely correlated factors: preoperative MH and BP.

What Is the Impact of Surgery on Headache Severity?

A significant proportion of patients had decreased headache severity by 6 months postoperatively (Wilcoxon sign-rank test, $p < 0.001$) (Fig. 1). The percentage of patients with intense headache decreased from 22.8% in the preoperative period to 19.0% at 6 weeks and 7.6% at 6 months. The percentages of patients with substantial headaches decreased from 13.9% preoperatively to 10.1% and 5.1%, respectively. Of the 40 patients with headaches causing impact on daily living (moderate, substantial, or intense headache), 70% patients had improvement in at least 1 category on HIT-6 by 6 months postoperatively. Six patients (7.6%) showed worsening of headache at 6 months by 1 grade (from Grade 1 to 2; or mild to moderate on the HIT-6 scale), and no patients had worsening by 2 grades.

Repeated measures ANOVA, which was used to compare the mean HIT-6 scores preoperatively and 6 weeks and 6 months postoperatively, shows a significant difference in the mean values across the 3 time points ($F = 3.2$, $p = 0.042$). The post hoc Tukey's test showed a significant difference between the preoperative HIT-6 (mean = 48.9 ± 11.8) and 6-month postoperative HIT-6 scores (mean = 44.9 ± 8.5) ($p = 0.03$), but not between preoperation and 6 weeks postoperation.

Similarly, when looking exclusively at the 60 patients with non-hormone-producing pituitary adenomas, there was a significant proportion of patients with decreased

FIG. 1. Bar graph depicting the percentages of patients with mild, moderate, substantial, or intense headaches, as measured by the HIT-6 questionnaire, in the preoperative period and at 6 weeks and 6 months postoperatively.

headache severity by 6 months postoperatively (Wilcoxon sign-rank test, $p = 0.001$). As well, the mean HIT-6 scores were significantly reduced at 6 months postoperatively (paired t -test, $p = 0.009$).

Significant CSF leaks occurred in 12.7% of patients, which required the insertion of a lumbar drain. This patient population was more likely to have persistent headache at 6 months following surgery ($\chi^2 = 8.7$, $p = 0.03$).

What Is the Impact of Surgery on QOL?

A significant improvement in the mean SF-36 MH score was present when comparing the preoperative and 6-week (paired t -test, $p = 0.012$) and 6-month postoperative scores ($p = 0.023$) (Table 2). In addition, a significant improvement in the mean general health score was seen between the preoperative and 6-week ($p < 0.001$) and 6-month postoperative scores ($p = 0.012$). The BP, SF, and RP scores showed significant improvement in comparison with the preoperative and 6-month postoperative scores ($p = 0.038$, $p = 0.008$, $p = 0.02$ respectively). No significant change was seen in the other SF-36 dimensions, including PF, RE, and VT. For patients with nonfunctioning macroadenomas, improvement in the MH scores was present at 6 weeks ($p = 0.037$) and 6 months ($p = 0.050$), as well in GH at 6 weeks ($p = 0.002$).

What Are the Predictors of Headache Response to Surgery?

Age, functional microadenoma, preoperative pituitary insufficiency, and the SF-36 preoperative MH score were all associated with improvements in headache in response to surgery ($\chi^2 = 11.9$, $p = 0.001$; $\chi^2 = 4.1$, $p = 0.04$; $\chi^2 = 3.8$, $p = 0.05$; $\chi^2 = 13.5$, $p < 0.001$, respectively), but not sex,

suprasellar extension, chiasmal compression, or cavernous sinus invasion of pituitary tumors. Multiple logistic regression analyses were performed to determine the best predictors of response to surgery in all patients with pituitary adenomas using the factors that were significant on the univariate analysis. The logistic regression model was statistically significant ($\chi^2 = 17.9$, $p < 0.022$). The model explained 36.2% (Nagelkerke R^2) of the variance in response to surgery and correctly classified 68.0% of cases. The 2 best predictors are younger age and poor preoperative SF-36 MH score (Table 3).

Discussion

In this novel prospective study, we found that endoscopic pituitary surgery significantly improved headaches and QOL in patients with pituitary adenomas by 6 months postoperatively in comparison with preoperative baseline. Factors associated with increased headache severity preoperatively include hormone overproduction and younger age. Sex, tumor volume, suprasellar extension, chiasmal compression, and cavernous sinus invasion of pituitary tumors did not predispose patients to headaches. Younger patients with functional microadenomas and a significantly impacted MH QOL were more likely to improve with surgery.

The wide range in the reported incidences (33%–72%) and severity of headaches in patients with pituitary adenomas may be related to differences in pituitary tumor histology, size, and functional status. Factors previously reported to be associated with headache in patients with pituitary masses may be divided into either mechanical and/or biochemical causes.^{1,9,13,15} Our results are concordant with some previous reports showing that tumor vol-

FIG. 2. Scatterplots showing a significant inverse correlation between preoperative HIT-6 scores and the SF-36 MH score (**upper**) (Pearson correlation: $r = -0.60$, $p < 0.001$) and the SF-36 BP score (**lower**) ($r = -0.58$, $p < 0.001$).

ume and cavernous sinus invasion are not prerequisites for headache.^{1,13,15} It is unclear why disagreement exists in the literature regarding the impact of dural stretch and cavernous sinus invasion on the presence of headache. One possible explanation is that the phenotypic characteristics of pituitary tumor-related headaches and their outcome assessments differ across studies. This study focused on quantifying the severity of headaches that resulted in an impact in daily function.

Hormonal hypersecretion may be the underlying mechanism for some aspects of pituitary disease-related headaches. Growth hormone-secreting tumors and prolactinomas may be particularly nociceptive tumors and can potentially demonstrate improvement with endocrinological treatments.^{14,15,19} In our study, increased headache severity occurred in functioning tumors. Almost 74% of

TABLE 2. Summary of SF-36 scores for the study patients preoperatively and 6 weeks and 6 months postoperatively*

SF-36 Domain	Preop	6 Wks Postop	6 Mos Postop
MH	0.71 ± 0.21	0.78 ± 0.16†	0.77 ± 0.18†
PF	0.70 ± 0.28	0.67 ± 0.26	0.73 ± 0.28
BP	0.64 ± 0.29	0.68 ± 0.28	0.71 ± 0.26†
RP	0.58 ± 0.44	0.37 ± 0.42	0.71 ± 0.39†
RE	0.71 ± 0.40	0.72 ± 0.39	0.79 ± 0.34
SF	0.73 ± 0.26	0.72 ± 0.26	0.81 ± 0.23†
GH	0.62 ± 0.22	0.70 ± 0.20†	0.68 ± 0.22†
VT	0.50 ± 0.34	0.49 ± 0.22	0.54 ± 0.25

* The results are presented as the mean ± SD, with 0 representing a very low QOL for that item and 1 representing a very positive response. Changes over time were analyzed using the paired t-test.

† $p < 0.05$ vs the preoperative score.

patients with hormone-producing tumors in our study had headaches that impacted daily living (moderate, substantial, or intense) compared with 43% of patients with non-secreting tumors. There were too few patients with each subtype of hormone-producing tumors to determine if a specific hormone was more prone to causing headaches, although all 3 patients with prolactinomas reported moderate headaches. In female patients with prolactinomas, there may be a higher frequency of headaches that were exacerbated by menstrual disturbances and related to prolactin hypersecretion.¹ Inflammatory processes within the pituitary region, which result in enlargement of the pituitary due to edema and lymphocytic infiltration, is another putative mechanism of pituitary tumor-related headaches. To date, no specific biochemical factor has been directly associated with headache, including neuropeptide Y, calcitonin gene-related peptide, substance P, or vasoactive intestinal polypeptide.^{11,12,18}

Headache and hormonal disturbances can significantly worsen QOL in patients with pituitary adenomas.² Pereira-Neto et al. demonstrated that both the mental and physical dimensions of QOL, as measured by the RAND SF-36 measurement, were inversely correlated with headache intensities on the HIT-6 scale.²⁰ Similarly, this study has found that preoperative headache severity is significantly associated with reduced scores across all SF-36 QOL dimensions, including mental health and general health. These results are intuitive in that patients with the greatest headache severity would suffer the greatest impact of the pain on their daily life and limitations in their individual capabilities.

Few studies have examined the impact of surgery on headaches and QOL in pituitary patients. Prior work by our group has shown that patient pain and discomfort are both decreased when undergoing endoscopic transsphenoidal resection in comparison with open microscopic surgery.²¹ For headaches, specifically, a single retrospective study with 41 patients found a significant improvement or resolution of headaches after endoscopic transsphenoidal resection in 90% of patients with nonfunctioning microadenomas and small Rathke cleft cysts.⁷ Another study

TABLE 3. Multiple logistic regression analysis used to determine which factors predict the response of headache to endoscopic transsphenoidal resection in patients with pituitary masses

Predictor	B Value	p Value	95% CI
Age	0.952	0.026 *	0.912–0.994
Functional microadenoma	3.01	0.205	0.547–16.5
SF-36 MH (preop)	0.02	0.005 *	0.001–0.313
Preop pituitary insufficiency	0.561	0.137	0.171–1.833

* p < 0.05.

reported that 49% (27 of 54) of patients who underwent either transsphenoidal or transcranial resection of pituitary tumors demonstrated an improvement in headache following surgery, 36% experienced no change in symptoms, and 15% reported worsening of headache.¹⁵ Our study is unique in that it prospectively evaluated the impact of purely endoscopic transsphenoidal surgery on headache severity at 6 weeks and 6 months postoperatively, without a confounding transcranial arm. By 6 months, 70% of patients who had been experiencing moderate, substantial, or severe headaches preoperatively reported reduced headache severity in at least 1 category on HIT-6. Improvement in headaches was seen at 6 weeks, but was statistically significant only at 6 months. Patients who had a significant postoperative CSF leak were less likely to show improvement of headache at 6 months. Surgery was also associated with significant improvement in several QOL dimensions, including MH and GH. When analyzed independently, both nonfunctioning adenomas and hormone-producing adenomas benefited from surgery at 6 months. This suggests that there may be different underlying mechanisms at play that result in the improvement of headache severity after surgery.

The surgical indications in our study were 1) visual compromise secondary to chiasmal compression and/or 2) endocrinological abnormalities that were uncorrectable by medical therapy. Our results demonstrated that a patient's headaches significantly improve after endoscopic transsphenoidal surgery. However, the factors that determine who will benefit from intervention are unclear. Factors including tumor volume, suprasellar extension, and chiasmal compression did not correlate with headache severity or predict response to surgery. Predictors of headache response to surgery by at least 1 class on the HIT-6 scale included patients with functional microadenomas and younger patients. Furthermore, patients with lower scores on SF-36's preoperative MH dimension were more likely to benefit from surgery.

There are several limitations to this study. A range of headache phenotypes can be found in patients with sellar masses, with migraine being the most frequent type.¹⁵ The headache characteristics and temporal profiles were not directly studied, but rather the impact of headaches on daily function. We did not have an adequate sample size of functional adenomas to comment on the impact of the subtype of hormone overproduction on headache severity. Follow-up times consisted of 6 weeks and 6 months and, as such, the long-term impact of surgery on headache remains unknown.

Conclusions

Headache is commonly associated with pituitary adenomas and may be an incapacitating symptom by impacting QOL and daily living. The goal of this study was not to determine whether headache alone should be considered an indication for surgical treatment of pituitary adenomas, but rather to describe the impact of surgery on the symptoms of headache and daily function in patients with pituitary tumors and visual dysfunction or endocrine abnormalities. We found that surgery can significantly improve headaches and QOL in patients with pituitary adenomas by 6 months. A larger prospective study is necessary to evaluate the long-term effects of surgery on headaches in patients with pituitary tumors and further develop the issue of headache as being a stand-alone indication for pituitary adenoma surgery.

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Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Duggal, Cooper, Van Uum, Lee, Rotenberg. Acquisition of data: Duggal, Goncalves, Salehi, Bird, Cooper, Van Uum, Lee, Rotenberg. Analysis and interpretation of data: Duggal, Wolf, Goncalves, Salehi, Bird, Van Uum, Lee, Rotenberg. Drafting the article: Duggal, Wolf, Van Uum, Rotenberg. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Duggal. Statistical analysis: Wolf, Goncalves. Administrative/technical/material support: Cooper. Study supervision: Duggal, Cooper, Rotenberg.

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