Paradoxical Hyperalgesia of Supra-orbital and Infra-orbital Nerve Blocks when Anesthetizing the Trigeminal Nerves in Trans-Sphenoidal Endonasal Pituitary Surgery: A Prospective, Randomized, Double-blinded Clinical Trial

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Abstract

Background: Pituitary neurosurgery executed via the transsphenoidal endonasal approach is commonly performed for pituitary adenomas. Reasons for prolonged hospital stay include postoperative migraine headache pain and protracted nausea with or without vomiting. Bilateral superficial trigeminal nerve blocks of the supra-orbital V1 and infra-orbital V2 (SION) nerves performed intra-operatively as a regional anesthetic adjunct to general anesthesia were hypothesized to reduce pain exposure and thus 6 hours post-operative morphine PCA (patient-controlled analgesia) use by patients.

Methods: 49 patients, following induction of general anesthesia for their transsphenoidal surgery, were prospectively randomized in a double-blinded fashion to receive additional regional anesthesia as either a block (0.5% ropivacaine with epi 1:200,000) or placebo/sham (0.9% normal saline). The primary endpoint was the pain exposure and resulting systemic morphine PCA opioid consumption by the two groups in the first 6-hours post-operatively. The secondary endpoints included (1) incidence of post-operative nausea and vomiting and (2) time to eligibility for PACU discharge.

Results: Of the 49 patients that were enrolled, 3 patients were excluded due to protocol violations. Ultimately, there was no statistically significant difference between morphine PCA use in the 6-hours post-operatively between the block and placebo/sham groups. There was, however, a slight visual tendency of the block group for higher pain scores, morphine use p=0.046, and delayed PACU discharge. False discovery rate corrected comparisons at each time point then revealed no statistically significant difference between the two groups. There were no differences between the two groups for secondary endpoints.

Conclusion: 6-hour post-operative migraine headache pain after endoscopic trans-sphenoidal pituitary surgery likely has a more complicated mechanism involving more than the superficial trigemino-vascular system and perhaps is neuro-modulated by other brain nuclei.

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Introduction

Regional anesthesia combined with general anesthesia for minimally invasive procedures has become a common anesthetic technique. The goal of this approach is to reduce pain and promote a rapid recovery. [1]

If regional anesthesia facilitates the administration of less systemic pain medications, patients could benefit in several ways: (1) reduced postoperative discomfort and opioid use, (2) decreased post-operative nausea and vomiting, (3) shortened PACU (post anesthesia care unit) stay time and (4) shortened time to discharge from hospital. A more streamlined, shorter and more pleasant hospital course for the patient could lead to increased patient satisfaction and potential economic gains to the hospital.

Pituitary tumor surgery is primarily executed through a minimally invasive approach through the nose and sinuses as an endoscopic procedure called the: “Trans-Sphenoidal Hypophysectomy”. More recently, it is performed entirely endoscopically through the nose as the earlier modification, the “Caldwell Luc” approach, involved opening a bony window through a sub-labial oral (at the upper gum line under the top lip) approach leading to the maxillary sinus and then ultimately to the sellar cavity housing the pituitary tumor. Patients who have this endonasal endoscopic trans-sphenoidal pituitary surgery are usually same day admission patients who, following their operation, stay in hospital up to 24 hours post-operatively. Prolonged post-op admissions are often caused by persistent headaches or nausea with or without vomiting.[2,3,4,5]

By administering regional anesthesia to the patient intra-operatively after induction of anesthesia, pain scores may be reduced [6], PONV decreased, and PACU stay shortened. Bilateral infra-orbital nerve blocks (V2 maxillary) have been shown to provide adequate pain control following trans-sphenoidal pituitary surgery such that systemic opioid use can be reduced or eliminated, and the patient discharged earlier or same day of surgery. [7] The aim of our study was to investigate the effect of infra-orbital V2 and supra-orbital V1 nerve blocks to reduce pain scores and thus morphine opioid use in the first 6 h post procedure. Secondary end points of the study were: (1) presence of PONV, (2) time to eligibility for PACU discharge, and (3) duration of hospital stay until discharge.

Methods

This is a prospective, randomized, double-blinded sham controlled (preservative free normal saline) regional anesthetic (supra-orbital and infra-orbital nerve (SION)) study to compare the systemic post-operative pain medication requirements in patients having trans-sphenoidal endoscopic, endo-nasal pituitary surgery under general anesthesia. The study protocol is performed in accordance with the relevant guidelines and is included in detail below. The primary endpoint was the systemic morphine sulfate PCA (patient-controlled analgesia) opioid consumption by the 2 groups during the first 6 hours post-operatively (regional + general anesthesia vs. general anesthesia alone). The secondary endpoints included: (1) incidence of PONV, (2) time to eligibility for PACU discharge, and (3) length of hospital stay/discharge. To our knowledge, this is the first published clinical trial examining the use of SION block to control postoperative pain after endonasal pituitary surgery. The results from the two groups were compared using unpaired student t-test. $P< 0.05$ was considered to indicate a statistically significant difference.

Following Institutional Review Board approval at the University of California, San Francisco, USA (UCSF) study enrollment was offered to adult patients (male and female) (aged 18-65), having an ASA (American Society of Anesthesiologists) physical status I or II scheduled for same day admit endo-scopic endo-nasal trans-sphenoidal hypophysectomy to be performed by a single surgeon (SK). Additional inclusion criteria were: (1) elective pituitary surgery for tumors less than or equal to 2 cm diameter within the sella turcica and without cavernous sinus invasion, (2) both male or female patients, (3) English speaking patients providing informed consent, (4) not on chronic pre-op pain medications (non-narcotics) in the last week prior to surgery per patient report, (5) no opioid pain medications pre-op in the last month before surgery per patient report, (6) no abuse of recreational drugs (cocaine, methamphetamines, marijuana, opioids, heroin etc.…) per patient report and (7) no herbal medications for pain in the last 1 month prior to surgery per patient report. Urine or blood testing was not used to confirm opioid use pre-operatively. Exclusion criteria included: (1) patients less than 18 yo, (2) non-English speaking and unable to consent, (3) known allergy to ropivacaine, (4) chronic pain conditions, including idiopathic migraine as defined by the ICHD (International Classification of Headache Disorders) II criteria, requiring the use of pain medications or (5) inability to comprehend or adhere to the study protocol (Chart 1).

Chart 1 Study Inclusion and Exclusion Criteria

Inclusion Criteria	1.	Elective pituitary surgery for tumors less than or equal to 2 cm diameter volume within the Sella Turcica and without cavernous sinus invasion
	2.	Male or female patients
	3.	English speaking patients providing informed consent
	4.	Not on chronic pre-op pain medications (non-narcotics) in the last week prior to surgery per patient report
	5.	No opioid pain medications pre-op in the last month before surgery per patient report
	6.	No abuse of recreational drugs (cocaine, methamphetamines, marijuana, opioids, heroin etc.) per patient report
	7.	No herbal medications for pain in the last 1 month prior to surgery

Exclusion Criteria	1.	Patients less than 18 years old
	2.	Non-English speaking and unable to consent
	3.	Allergy to ropivacaine
	4.	Chronic pain conditions, including idiopathic migraine as defined by the ICHD (International Classification of Headache Disorders) II criteria, requiring the use of pain medication
	5.	Inability to comprehend or adhere to the study protocol

After written informed consent, the subjects were randomly assigned to 1 of 2 groups using randomization envelopes in 3 blocks of 20. A “triple mask design” was used: the subjects, healthcare providers (including the anesthesiologist in the operating room, anesthesiologist administering the SION blocks), randomization consent nurse and data collection nurse as well as the statistician were all blinded to the treatment groups assigned.

Intra-operative Block Protocol:

The subjects assigned to Block group (B) would receive the SION blocks with 0.5% ropivacaine with epinephrine 1:200 000 following induction of general anesthesia and the Placebo group (P) would receive the same volume SION blocks using sterile, preservative free normal saline. Following general anesthetic induction and endo-tracheal intubation, supra-orbital and infra-orbital (SION) injections with study medication were performed. Supra-orbital nerve blocks were performed bilaterally using 3 cc (on each side for a total of 6 cc) of the study solution. A percutaneous technique was used to block both bilateral supra-orbital and supra-trochlear nerves. A 27 gauge, 1.5 in needle, attached to a 10-cc syringe was used. Then, the infra-orbital nerves were blocked intra-orally following retraction of the upper lip and using a 27-gauge, 2.54 cm needle attached to a 10-cc syringe inserted anterior to the ipsi-lateral canine tooth that runs along the maxilla. Here, 3 cc of study drug was placed bilaterally for a total of 6 cc. The needles were directed superiorly toward the infra-orbital foramen on the ipsi-lateral side as was described in the "Lynch" method.[8] Correct needle placement was confirmed by palpation of the needle tip near the infra-orbital foramen and by negative aspiration for blood. A wheel of study drug was palpated next to the nose under the inferior orbital rim. As mentioned earlier, the study drug was prepared by an independent physician who was not involved in the data acquisition, operating room care of the patient, or placement of the block. Thus, a total of 12 cc of the study solution was placed per patient in the distribution of the supra-orbital branches of V1 (Trigeminal sensory nerve) and infra-orbital nerve V2 (Trigeminal sensory nerve).

Intra-Operative Anesthetic:

Following a pre-medication with midazolam 1-2 mg IV, anesthesia was induced with lidocaine 1 mg/kg IV, propofol 1-2 mg/kg IV, fentanyl 1 mcg/kg IV, and rocuronium 0.6 mg/kg IV.

The surgeons then administered standard topical intra-nasal anesthesia with lidocaine and epi soaked pledgets on the inner nasal mucosa. Less than 10 cc of 1% lidocaine with epi 1:200 000 was used to ensure hemostasis. Exposure of the pituitary gland was obtained trans-nasally with an endoscope via the sphenoid sinus and then via the sellar floor. Following removal of the sellar floor, the dura was opened, and the pituitary tumor was resected using a series of micro-dissectors and curettes. CSF leaks were then repaired, and fat was placed in the free intra-sellar space. The sellar floor was repaired and the sphenoid sinus and nostrils packed temporarily to close the sellar space. We removed the nasal packings just prior to extubation.

Following induction of anesthesia, the local injection study block drug/placebo was administered, and the patients were maintained with a balanced anesthetic technique using intra-venous agents, inhaled gas and a neuro-muscular relaxant. Desflurane in O2/Air mixture with 80% inspired O2 was administered to provide anesthesia and to maintain the blood pressure within 20% of baseline. Fentanyl was infused at 1 mcg/kg/hr from induction of anesthesia to end of surgery. Dexamethasone 10 mg IV or Hydrocortisone 100 mg IV was administered at the beginning of surgery as directed by the surgeon. An end-tidal CO2 of 30-35 mmHg was maintained. The patients were relaxed with rocuronium as needed to maintain 1-2 twitches by a NMT (neuro-muscular twitch) monitor. On emergence from anesthesia, ondansetron 4 mg IV was administered, and residual muscle relaxation was reversed with neostigmine 0.07 mg/kg and glycopyrrolate 0.01 mg/kg IV.

Post-operatively, a morphine PCA (1mg IV every 6 min lock out time) to a max of 10 mg IV morphine sulfate per hour, without a basal rate was administered. For pain ranked at >4/10, rescue pain medicine of morphine 1 mg IV was administered by the PACU recovery room nurses every 5-10 min until the pain was < 4/10 or acceptable to the patient. Blood pressure was maintained with a systolic BP< 140 mmHg using (labetalol, esmolol, nicardipine). Following intra-operative treatment of nausea with ondansetron and dexamethasone/hydrocortisone, the following escalating rescue algorithm was used for PONV:

1. Additional ondansetron 4 mg IV for 1 dose, then
2. prochlorperazine 5-10 mg IV, then
3. scopolamine patch 1.5 mg topical.[9]

The primary outcome of the study was to compare the total amount of morphine (in mg) used post-operatively (for 6 hours) in the 2 study groups from T0-T6 time from PACU entry (T0) to 6 hours post PACU entry (T6). Study data was collected for 5 data time points: T0 (PACU entry), T1, T2, T4, T6 (1,2,4,6 hours after PACU entry, respectively). Pain scores (P0-P6) were collected using the Wong-Baker FACES Pain Rating Scale at times T0-T6 in the scale (0-10/10) with 10/10 being the worst imaginable pain. Nausea score N0-N6 was collected using the Baxter retching faces (BARF) nausea scale (0-10/10) with 10/10 being the worst nausea imaginable with or without vomiting. Other secondary data collected included Tr (total time in PACU from admission to "eligibility"

for PACU discharge (using the UCSF Modified Aldrete Score), Th (total time from surgery start to eligibility for home discharge), Tn (time from surgery start to last dose of narcotic). Modified UCSF Aldrete PACU score in PACU incorporates individual scores for vital signs, activity, mental status, pain, nausea, bleeding and intake/output. At one-week post-op, patients were contacted by phone and asked about potential study complications.

A research assistant collected all the study data and was blinded to the assigned treatment group.

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Statistics

From Jan 1, 2017 through Dec 31, 2018, 175 patients were screened for the study using the inclusion and exclusion criteria. (Chart 1) Based on clinical experience, we considered an effect size 0.5 to be clinically significant. With this assumption, 64 patients randomized into two equal groups should have provided a statistical power of 0.8 for the main outcome. Of those, 49 patients were enrolled and randomized into the study. Although the original sample size was estimated at 64 patients, study enrollment was stopped after 49 subjects for administrative reasons.

Demographics and opioid consumption results are presented as means with 95% confidence intervals. Comparisons between groups were performed with unpaired t-tests, Mann-Whitney u-tests and Fisher's exact test as appropriate. Parametric data are presented as means (95% confidence interval [95%CI]), while non-parametric data are presented as medians (95%CI). Opioid consumption, pain exposure, and nausea exposure over time were analyzed with a repeated measures mixed effects model. Groups were compared post-hoc at each time point, correcting for multiple comparisons using the two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli to control the false discovery rate. Results with a $p < 0.05$ or a false discovery rate $q < 0.05$ were considered statistically significant. All analyses were performed using Prism 8.4.2 for MacOS (GraphPad Software, Inc, La Jolla, CA, USA).

Results

A total of 49 patients were randomized. Three of the randomized patients subsequently had to be disqualified from the study due to protocol violations. There was no statistically significant difference between groups in demographic variables (Table 1).

Table 1. Patient characteristics

	Block	Placebo	p
Sample size, n	20	26	
Demographic characteristics			
Mean age (years) Sex, n (%)	41.7 (11.8)	48.3 (13.1)	0.08
Male	8 (40.0%)	17 (65.4%)	0.14
Female	12 (60.0%)	9 (34.6%)	0.14
Surgical characteristics Mean BMI (SD) in kg/m2	31.8 (8.8)	29.1 (4.2)	0.17
Mean surgical time (SD) in mins	113 (40)	106 (38)	0.53

Abbreviation: SD, standard deviation

The median (95% CI) total post-operative morphine dose was 0.21 mg/kg (0.19 - 0.35 mg/kg) in the Block group and 0.21 mg/kg (0.12 - 0.23 mg/kg) in the Placebo group ($p = 0.22$). Analyzed over time (Figure 1), there was a significant difference between groups ($p = 0.046$). However, although visually there was a tendency towards higher morphine doses in the Block group, false discovery rate corrected comparisons at each time point revealed no statistically significant differences between groups.

Analysis of pain exposure over time (Figure 2) showed a significant difference between groups ($p = 0.0021$), with false discover rate corrected comparisons at each time point showing a significant difference 1 hour after PACU entry and 2 hours after PACU entry. At 1 hour after PACU entry, the mean pain score was 7 (6 - 8) in the Block group, and 4 (3 - 6) in the Placebo group ($q = 0.006$). At 2 hours after PACU entry, the mean pain score was 6 (5 - 7) in the Block group, and 4 (3 - 5) in the Placebo group ($q = 0.03$).

There was no significant difference between groups in nausea exposure over time (Figure 3). Examining both groups combined, compared to PACU arrival, patients experienced significantly more nausea at 1 hour after PACU entry (mean difference 1.1 [SE 0.4], q = 0.03) and at 4 hours after PACU entry (mean difference 0.9 [SE 0.3], q = 0.03).

The median PACU stay duration was 128 minutes (110 - 158 minutes) in the Block group, and 113 minutes (98 - 143 minutes) in the Placebo group (p = 0.28).

There was no difference in either median time from surgery start to hospital discharge (Block group 1540 minutes [1447 - 1811 minutes] vs Placebo 1703 minutes [1592 - 1821 minutes], p = 0.26), nor median time from surgery start to last in-hospital narcotic dose (Block 1355 minutes [733 - 1467 minutes] vs Placebo 698 minutes [422 - 1657 minutes], p = 0.15). Just prior to hospital discharge, but before the last dose of narcotic, the Block group had significantly higher median pain scores (Block 2 [1 - 4] vs Placebo 1 [0 - 2], p = 0.03).

Discussion

Usually, prolonged hospital admissions following total endoscopic endonasal pituitary surgery result from headache and nausea +/- vomiting. The etiology of their post-operative headache is likely multifactorial but one theory is that stimulation of the peripheral trigeminal (Cranial Nerve number V) fibers in V1 (ophthalmic branch) and V2 (maxillary branch) sensory distribution of the face by the surgical endoscope and surgical trauma may lead to extravasation and release of inflammatory mediators (Substance P (SP), Calcitonin gene-related peptide (CGRP), Vasoactive Intestinal Peptides (VIPs))from the local area via the trigemino-vascular system. This “sterile neuro-genic peri-vascular inflammation” can ultimately cause meningeal blood vessel vaso-dilation, increased cerebral blood flow and migraine type post-op headaches.[2,3,4] It has been shown that repetitive injection of local anesthetics in the distribution of the supra-orbital nerve (SON) V1 and infra-orbital nerve (ION) V2 can decrease the incidence of chronic idiopathic migraine headaches not related to surgery.[5] Thus, potentially local anesthetics injected in the distribution of the supra-orbital (V1) and infra-orbital (V2) nerves were postulated to pre-emptively prevent this sequence of events that ultimately lead to post-operative headache pain after trans-sphenoidal pituitary surgery.

These study results showed that addition of supra-orbital and infra-orbital sensory trigeminal nerve blocks intra-operatively to general anesthesia during trans-sphenoidal, total endo-nasal pituitary surgery do not appear to reduce post-operative pain and thus 6-hour post-op morphine PCA consumption as compared to patients receiving only general anesthesia. In fact, the Placebo group had less postoperative pain and morphine use along with a shorter median PACU stay. Because the standard deviations in both groups were so wide, this effect was not clinically significant. Possible explanations for this unexpected pain and morphine consumption post-op response in the Block group may include:

1. It may be more difficult to accurately execute the supra-orbital V1 and infra-orbital nerve V2 blocks under general anesthesia than expected. The terminal sensory nerve anatomy of patients may vary and so the block, placed using landmarks, may not actually capture all the branches of the trigeminal nerves V1 and V2 that then contribute and eventually trigger the trigemino-vascular effects leading to the post-op migraine headache. As the patients were under general anesthesia, the presence/absence and extent of block numbness was not evaluated prior to surgery. Post-op evaluation of this would have led to unblinding of the patient and data collection nurse, so this was not done. Thus, the two groups showed similar post-operative pain exposure data and morphine use.
2. It is possible that the administration of normal saline solution used in the placebo group may have some analgesic properties such that similar pain exposure and 6-hour post-op morphine use data resulted.
3. Most surprisingly/unexpectedly, there was a tendency for a paradoxically increased pain exposure, morphine usage and median time of PACU stay in the block group. One possible explanation for this could be the influence of another mechanism in addition to the sensitization of the trigeminal ganglion in the production of post-op migraine pain. The spheno-palatine ganglion (SPG), a primarily parasympathetic ganglion, located in the pterygopalatine fossa (posterior to the middle nasal turbinate), is known to communicate directly with the trigeminal ganglion via several branches of the infra-orbital or maxillary V2 nerve (Figure 4.1). Both the sphenopalatine and trigeminal nerve ganglia have been extensively studied in migraine headaches.[10,11,12] Perhaps, through some type of neuromodulation, the parasympathetic nervous system vasodilating effects of the SPG are enhanced if the trigeminal V1 and V2 sensory nerve blocks are performed. This may lead to more cerebral vasculature dilation and brain

inflammatory mediator release (SP, CGRP, VIP) causing slight increase in migraine type post-op headache in the block group (Figure 5.1,6.1). [11]A recent study [13] showed that bilateral SPG blocks as adjuvant to general anesthesia for endoscopic trans-sphenoidal pituitary surgery may decrease post-op pain. Blocking the SPG is more invasive and riskier [14] than the superficial trigeminal verve blocks of V1 and V2. Anesthetic pledgets, blind intra-nasal injections performed by the surgeons and specialized endoscopic guided catheters like the "SphenoCath"[12] performed by interventional radiologists under fluoroscopy, can be used to administer this SPG block.

Perhaps future studies should look at randomized, controlled data using both the trigeminal nerve blocks combined with the sphenopalatine ganglion block as a multi-modal regional adjunct to general anesthesia for trans-sphenoidal pituitary resection.

As there appeared to be little difference in the pain exposure and morphine consumption post-op, the post-op nausea exposure over time did not show a significant difference between the Block and Placebo groups.

The post-operative time to discharge and time to last dose of narcotic from surgery start time for the Block and Placebo groups did not have statistically significant differences. Considering pain on discharge, again the Placebo group had less pain, although the final median pain scores of 1/10 for Placebo and 2/10 for Block did not seem to have clinical significance. However, looking at the individual pain scores, the Block group had a much wider spread of pain data, showing some patients with significant pain on discharge.

Conclusions

In conclusion, the mechanism of the pain response to pituitary surgery via the total endo-nasal endoscopic technique appears to be more complex than expected. Likely, several nerves and ganglia interact via a complex mechanism of neuro-modulation to determine the final post-op migraine headache intensity experienced by the patient. Simple peripheral sensory nerve supra-orbital V1 and infra-orbital V2 nerve blocks in addition to general anesthesia do not decrease pain exposure or 6-hour post-op morphine PCA consumption as compared to general anesthesia alone.

Declarations

Ethics Approval and Consent to Participate

This study was approved on May 24, 2016 by the University of California, San Francisco, USA (UCSF) by the UCSF Institutional Review Board (IRB) and Independent Ethics Committee (IEC). All patients provided informed consent to participate in this trial.

Consent for Publication

All patient data collected has been deidentified in compliance with ethical standards. All manuscript authors have reviewed the final manuscript and given consent for publication.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files. The corresponding author has all available raw data and can share on reasonable request.

Competing Interests

None declared

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Author's Contributions

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Formal Analysis: Litonius, Srejic, Bickler, Talke, Maties, Siegmueller, Hasen, Kunwar, Seth

Investigation: Srejic, Litonius, Bickler, Talke, Maties, Siegmueller, Hasen, Kunwar, Seth, Gibson, Magsaysay, Gibson

Methodology: Srejic, Talke, Bickler, Litonius

Project Administration: Magsaysay, Srejic, Hasen

Validation: Srejic

Writing-original draft: Srejic

Writing-review, editing and final manuscript review: Srejic, Litonius, Bickler, Talke, Maties, Siegmueller, Hasen, Kunwar, Seth, Gibson, Magsaysay, Gandhi

References

1. J. Cousins and P.O. Bridenbaugh. Neural blockade in clinical anesthesia and management of pain. In: L.M. Broadman and L.J. Rice, Editors, *Neural Blockade for Pediatric Surgery (3rd Ed)*, Lippincott-Raven, Philadelphia, PA (1998), pp 605-637.
2. Goadsby PJ, Edvinsson L. The Trigeminovascular system and migraine: studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. *Ann Neurol* 1993; 33;48-56
3. Lauritzen M. Cerebral Blood flow in migraine and cortical spreading depression. *Acta Neurol Scand* 1987; 76:1-40
4. Zagami AS, Goadsby PJ, Edvinsson L. Stimulation of the superior sagittal sinus in the cat causes release of vasoactive peptides. *Neuropeptides* 1990; 16:69-75
5. Ilhan Alp, R. Supraorbital and infraorbital nerve blockade in migraine patients: results of 6-month clinical follow-up. *European Review for Medical and Pharmacological Sciences*, 2013:17:1778-1781
6. Edward R. Mariano, Deborah Watson et al. Bilateral infraorbital nerve blocks decrease postoperative pain but do not reduce time to discharge following outpatient nasal surgery. *Can J Anesth* (2009), 56:584-589
7. Dugald McAdam, Kenji Muro, et al. The use of Infraorbital Nerve Block for postoperative Pain Control after Trans-sphenoidal Hypophysectomy, (Case Report) *Regional Anesthesia and Pain Medicine*, 2005, Vol 30, No 6 (November-December) : pp 572-573
8. Michael T. Lynch, Scott A. Syverud et al. Comparison of Intraoral and Percutaneous Approaches for Infraorbital Nerve Block, *Academic Emergency Medicine* (1994); 1:514-519
9. Brigid C. Flynn, Edward C. Nemergut. Postoperative Nausea and Vomiting and Pain After Trans-Sphenoidal Surgery: A Review of 877 Patients. *Anesth Analg* 2006; 103:162-167
10. Matthew S. Robbins, Carrie E. Robertson, Eugene Kaplan et al. The Sphenopalatine Ganglion: Anatomy, Pathophysiology, and Therapeutic Targeting in Headache, *Headache* (2016); 56:240-258
11. David W. Dodick. A Phase-by-Phase Review of Migraine Pathophysiology, *Headache* (2018); 58:4-16
12. Mohamed Binfalah, Eman Alghawi, Eslam Shosha, et al. Ali. Sphenopalatine Ganglion Block for the Treatment of Acute Migraine Headache, *Pain Research and Treatment,* Volume 2018, Article ID 2516953, 6 pages, https://doi.org/10.1155/2018/2516953
13. Ashgan R. Ali, Sameh A. Sakr, Ahmed Shawky M.A. Rahman. Bilateral Sphenopalatine Ganglion block as adjuvant to general anesthesia during endoscopic trans-nasal resection of pituitary adenoma. *Egyptian Journal of Anaesthesia* (2010); 26,273-280
14. Julius N. Hill, Nathan Gershon, Peggy O Gargiulo. Total Spinal Blockade during Local Anesthesia of the Nasal Passages, *Anesthesiology* (Case Report) (1983); 59, (2):144-146

Figures

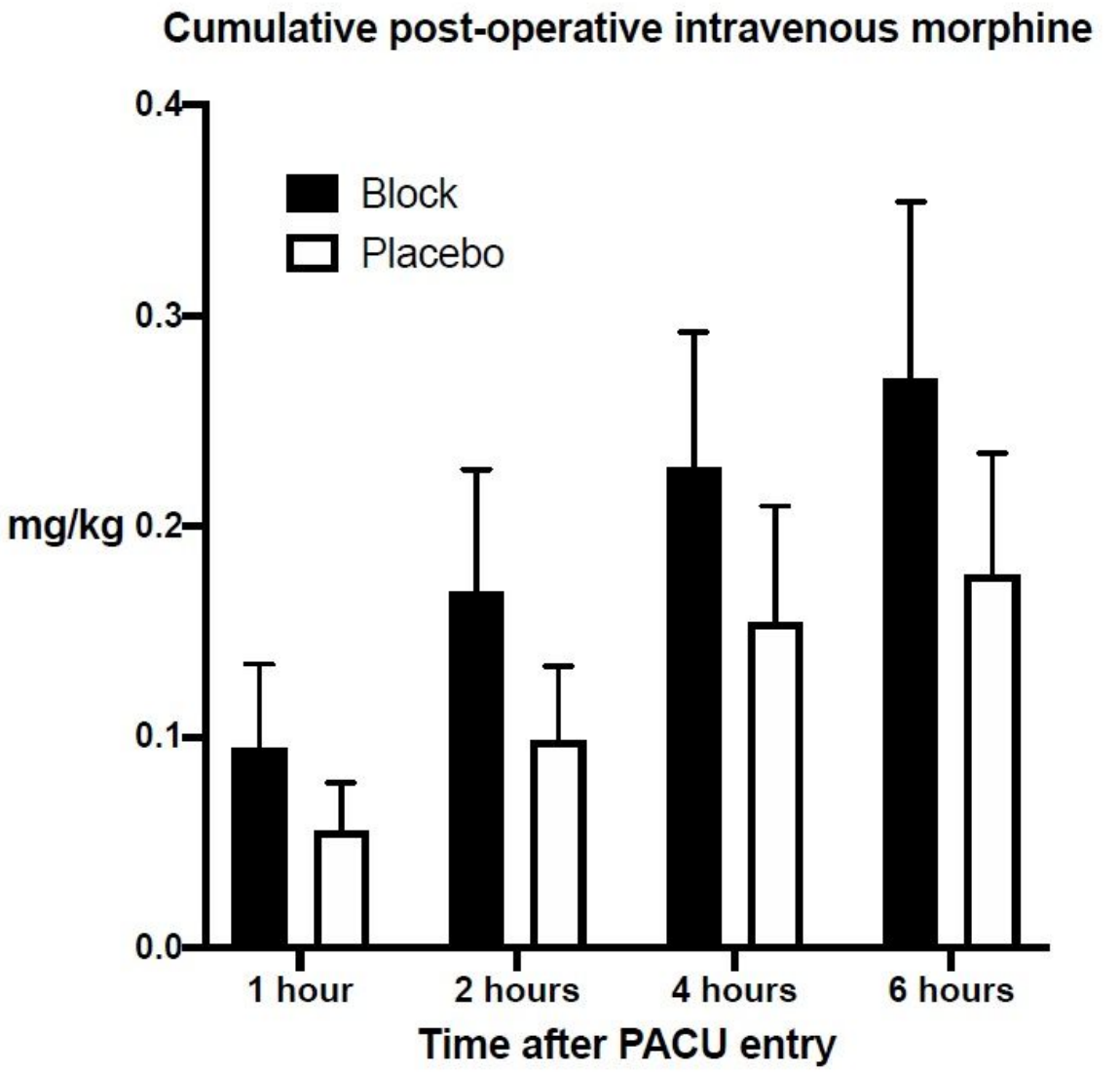
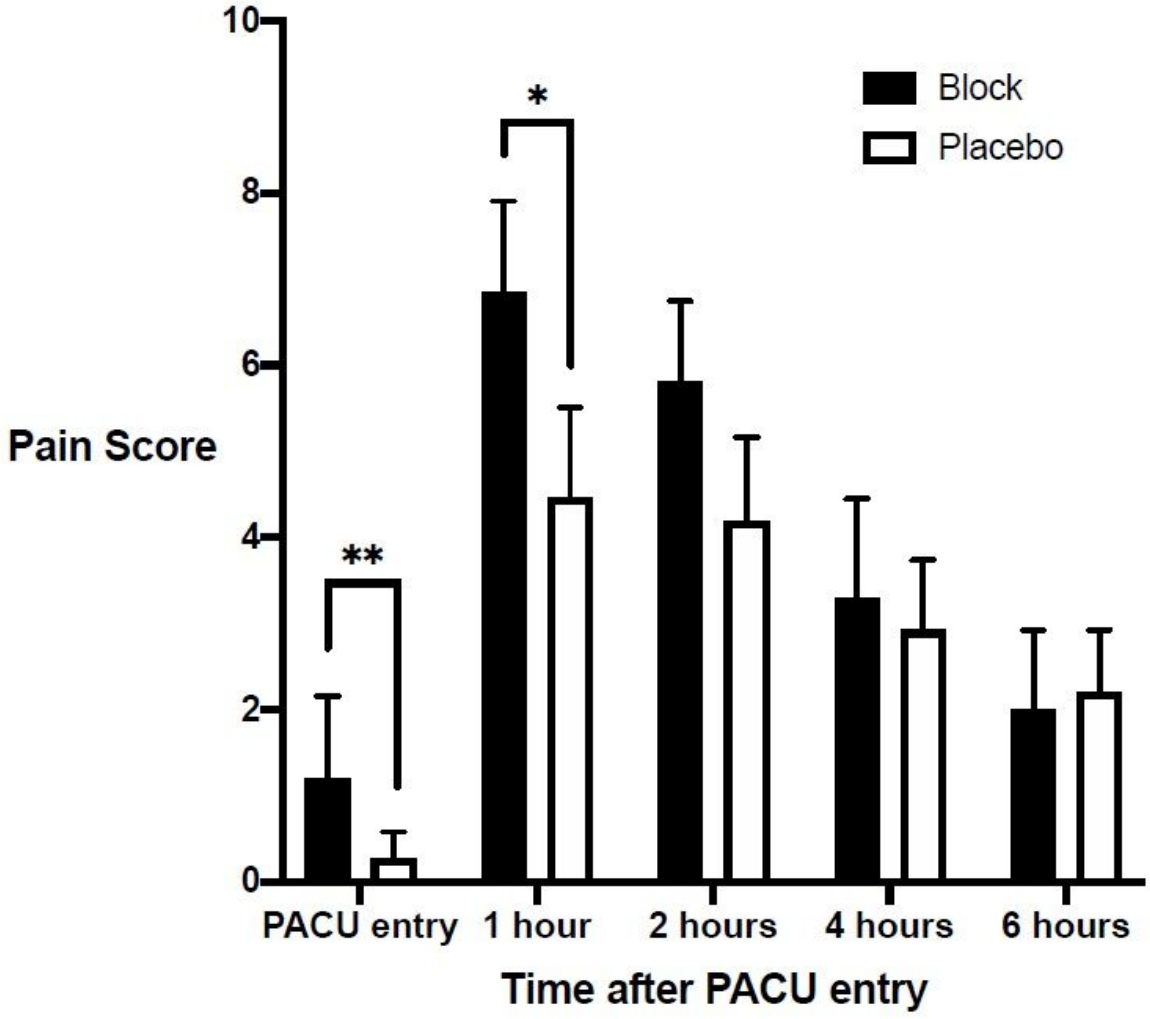


Figure 1

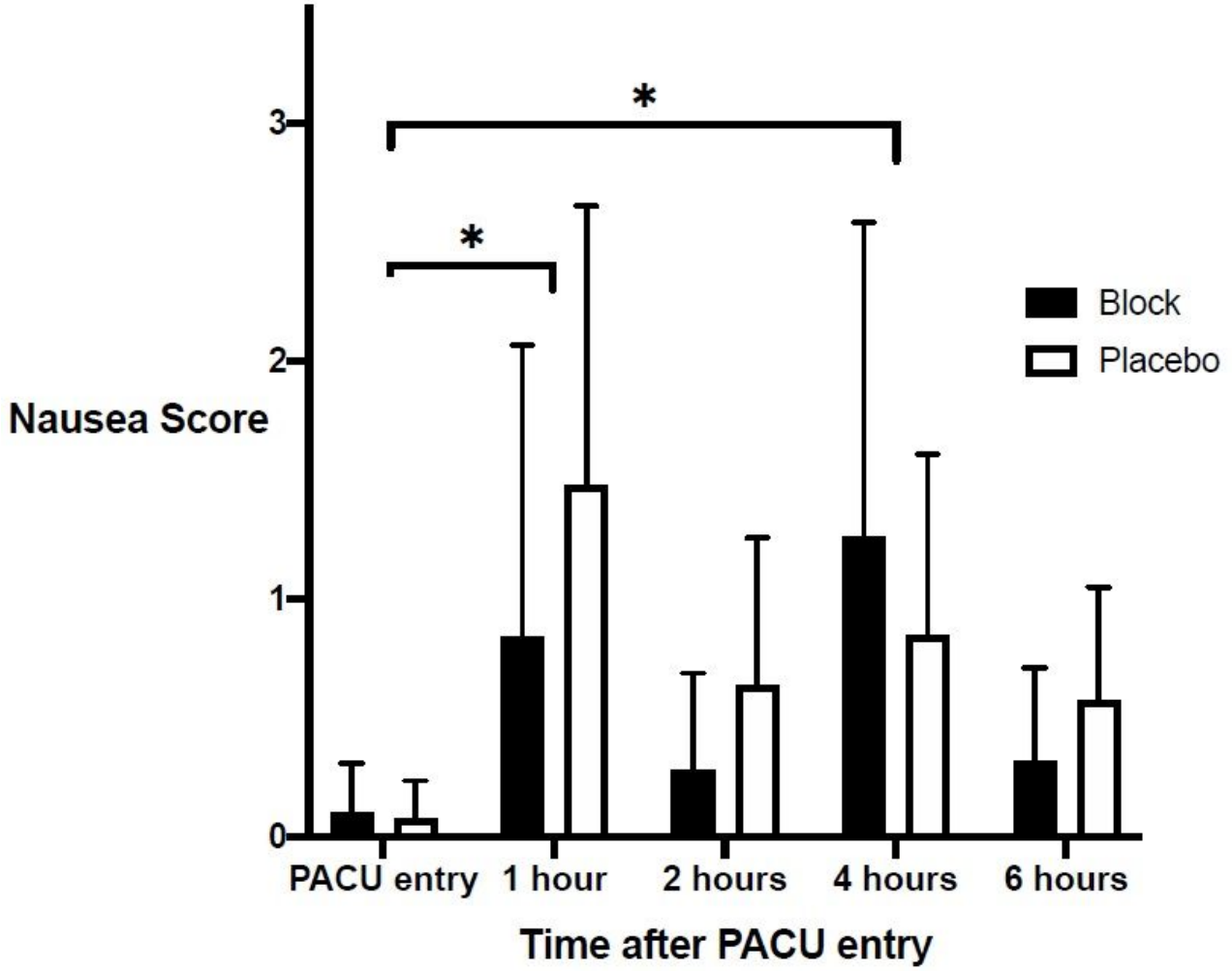
Cumulative Post-operative Intravenous Morphine Consumption in mg/kg



Means displayed as bars. Lines represent 95% confidence intervals.
Abbreviation: PACU, post-anesthesia care unit
* = $p < 0.05$, ** = $p < 0.01$

Figure 2

Pain Exposure by Subjects over Time



Means displayed as bars. Lines represent 95% confidence intervals.
Abbreviation: PACU, post-anesthesia care unit
* = $p < 0.05$, ** = $p < 0.01$

Figure 3

Nausea Exposure by Subjects over Time

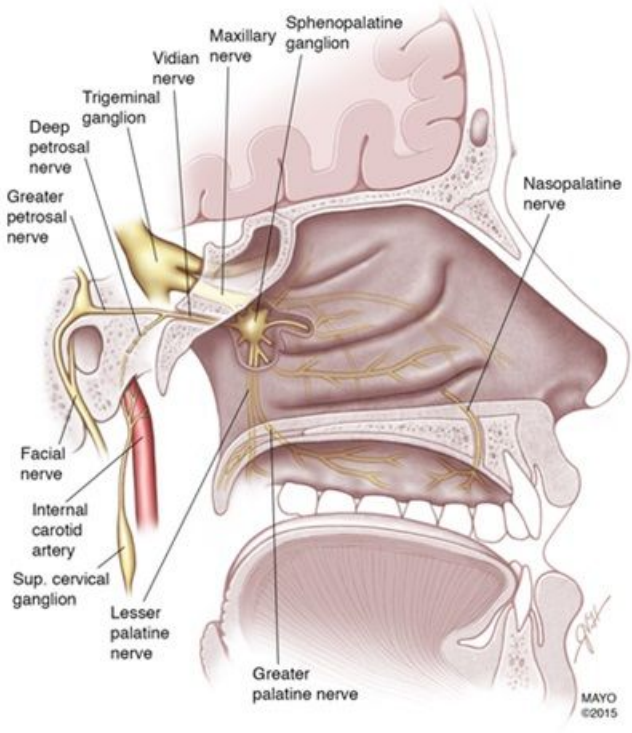


Figure 4

Sagittal View Drawing through the Nasopharynx Demonstrates the Relationship of the Trigeminal Ganglion with the Sphenopalatine Ganglion and its Direct Connections

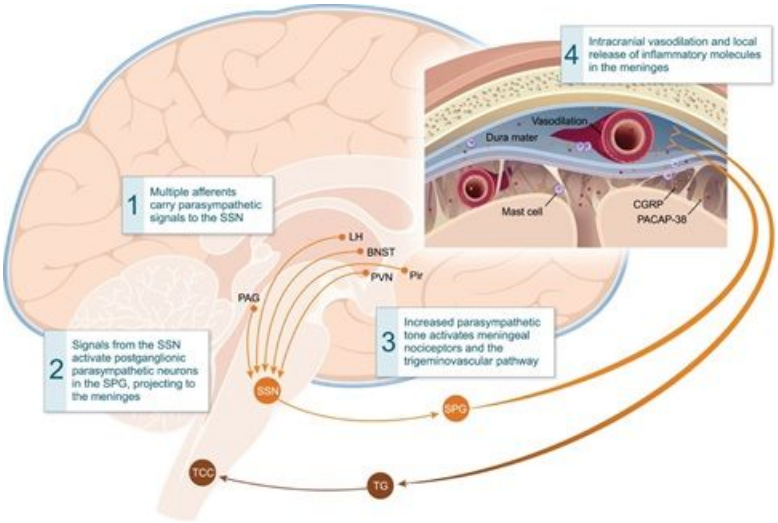


Figure 5

Activation of the Meningeal Receptors by Increased Parasympathetic Tone

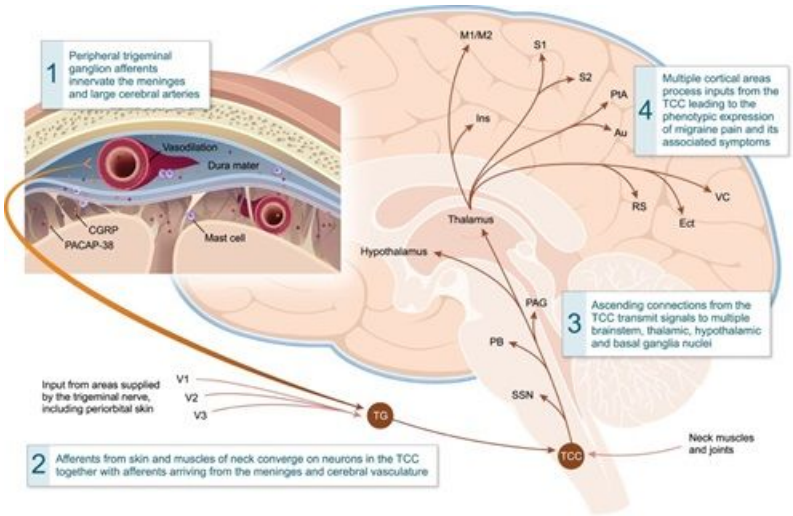


Figure 6

The Triggering of Pain via the Trigemino-Vascular Pathway