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Effects of a sphenopalatine ganglion block on postcraniotomy pain management: a randomized, double-blind, clinical trial

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OBJECTIVE Postcraniotomy pain (PCP) is a common finding after neurosurgical procedures, occurring in as many 87% of patients. The sphenopalatine ganglion (SPG) has a pivotal role in several headache syndromes, and its anesthetic block is currently used in different clinical conditions with benefit. The aim of this study was to evaluate the efficacy of an SPG block (SPGB) via a transnasal approach as adjunctive therapy in reducing pain scores during the postcraniotomy period.

METHODS In this single-center, double-blind, randomized controlled trial, patients undergoing elective surgery with a supratentorial craniotomy were randomly assigned to a scalp block, local anesthetic infiltration of the wound, and systemic analgesia during the first 48 postoperative hours (standard therapy), or to standard therapy as well as an SPGB (experimental therapy). According to the available evidence, assuming a 50% reduction in the incidence of the main outcome in patients with an SPGB (vs standard treatment), 82 patients were needed to achieve 80% statistical power in an intent-to-treat analysis. Pain intensity was recorded during the first 180 postoperative days at selective time points (5 times in the hospital, 3 times by telephone interview) with different pain rating systems (a visual analog scale [VAS], numeric rating scale [NRS], and pain assessment in advanced dementia [PAINAD] scale), together with demographic, clinical, and surgical variables and complications. Heart rate and blood pressure were recorded during surgery. Differences in all variables were evaluated using a paired t-test and confirmed through Wilcoxon matched-pairs signed-rank and Kruskal-Wallis tests.

RESULTS No complications occurred among the 83 patients enrolled. Statistically significant differences were found in the mean VAS score at postoperative days 0 ($p = 0.05$), 2 ($p = 0.03$), and 3 ($p = 0.03$). The PAINAD scale score showed significant differences between groups at postoperative days 1 ($p = 0.006$), 2 ($p = 0.001$), 3 ($p = 0.03$), and 4 ($p = 0.05$). The proportion of patients reporting a VAS score ≥ 3 in the first day after surgery was lower in the SPGB group than in the standard treatment group (71.9% vs 89.5%), although this difference did not reach statistical significance. At postoperative day 180, 5 patients (2 in the control group, 3 in the treatment group) had developed chronic PCP (NRS score ≥ 3).

CONCLUSIONS SPGB is a safe and effective procedure as an adjunctive treatment for PCP management in elective supratentorial craniotomy during the first 4 postoperative days compared with standard therapy. Further studies are needed to better define the clinical impact of SPGB use and its indications.

Clinical trial registration no.: NCT05136625 (ClinicalTrials.gov)

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KEYWORDS postcraniotomy pain; sphenopalatine ganglion block; postsurgical pain; chronic pain; VAS; NRS; PAINAD; RCT; randomized controlled trial

ABBREVIATIONS BP = blood pressure; CH = cluster headache; ERAS = enhanced recovery after surgery; HR = heart rate; IQR = interquartile range; LOS = length of stay; MCID = minimal clinically important difference; NRS = numeric rating scale; NSAID = nonsteroidal anti-inflammatory drug; PAINAD = pain assessment in advanced dementia; PCP = postcraniotomy pain; RCT = randomized controlled trial; SPG = sphenopalatine ganglion; SPGB = SPG block; VAS = visual analog scale.

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Postcraniotomy pain (PCP) is defined as a headache starting within 7 days after a craniotomy, without other clinical explanations[1] (see Table 1 for diagnostic criteria). Between 60% and 84% of patients usually report PCP with an intensity varying from mild to severe. This percentage increases to 87% if the first postcraniotomy day is considered, and decreases by 3% for each year of life.[2] Approximately 5%–10% of patients develop a persistent form of PCP.[2] In these cases, the pain significantly interferes in daily activities such as practicing sports (25%), work (19%–38%), and social activities (8%),[3] and therefore is disabling.

The PCP mechanism is not yet completely understood, but some local and systemic inflammatory and neuropathic factors are known to be involved; both can generate and perpetuate the PCP and facilitate a persistent form. Much evidence supports the central role of the sphenopalatine ganglion (SPG) in the generation of PCP. This pivotal extracranial structure has rich anatomical connections with several afferent and efferent fibers (Fig. 1). Its direct connection to the maxillary branch of the trigeminal nerve may also explain why anesthetic blockade of the SPG (SPG block [SPGB]) is helpful in trigeminal neuralgia and various headache syndromes.[4]

To date, there are no widely shared protocols available for PCP treatment that are based on high-quality, evidence-based data.[2] A complete review of the state-of-the-art prevention and treatment of PCP is beyond the scope of this paper; however, some successful treatments that have been reported are pregabalin,[5] electroacupuncture,[6] anesthetic scalp block,[7] dexmedetomidine,[6,8] parenteral opioids,[7] nonsteroidal anti-inflammatory drugs (NSAIDs),[7] gabapentin,[6,9] and sumatriptan.[10] The study of Patel et al. demonstrated that the administration of triptans, which have been classically used in cluster headache (CH) and migraine, also help in the treatment of PCP. This study highlights the common pathophysiological pathways between PCP and migraine.[10] At the same time, SPGB has proven to be an effective treatment against migraine and CH, trigeminal headache, post–spinal puncture headache, and postoperative headache in nasal endoscopic surgery or paranasal sinus surgery.[4] Padhy et al.[11] studied the effects of SPGB on hemodynamic response at Mayfield skull clamp insertion and concluded that SPGB is an effective and safe technique to attenuate the hemodynamic responses to pain during craniotomy surgeries. However, to date, no data are available on the effect of SPGB on PCP during the postoperative period.

PCP prevention and control is deeply rooted in the neurosurgical application of enhanced recovery after surgery (ERAS) protocols: a patient with optimal pain control regains preoperative function earlier and faster after surgery. To date, several studies have investigated the effect of dedicated ERAS protocols on patients with elective neurosurgical procedures.[12–14] The primary reported outcomes have been length of stay (LOS), postoperative morbidity, surgical complications, nausea and vomiting, duration of urinary catheterization, time to first solid meal, patient satisfaction, and postoperative pain. Even if reported results are variable and the actual body of evidence is insufficient to develop a shared standardized protocol,[13] ERAS neurosurgical investigation is becoming one of the most central topics in the field.

The aim of this study was to evaluate the efficacy of adding SPGB to the standard treatment (scalp block, local anesthetic infiltration of the wound, and systemic analgesia) in the control and prevention of PCP in elective supratentorial craniotomy. Currently, this is the first randomized controlled trial (RCT) to evaluate the clinical effects of SPGB in neurosurgery patients during the postoperative period.

Methods

Study Population and Criteria

We conducted a single-center, double-blind RCT with a superiority design in accordance with the CONSORT guidelines[15] and its pain-specific supplement.[16] We consecutively recruited all adult patients admitted to the neurosurgery department of Sant'Anna University Hospital of Ferrara and treated with an elective supratentorial craniotomy between June 2021 and January 2023. Exclusion criteria included: patients with a deviated septum or turbinate anatomical variation, evaluated by imaging or by anterior rhinoscopy; previous nasal or paranasal sinus surgery; allergy to a local anesthetic; previous episodes of nose bleeding that required medical treatment; psychiatric disorders; abuse of alcohol and/or narcotics; neuroleptic and/or antiepileptic ongoing treatment; SPGB procedure not correctly completed; and previous chronic headache. Informed consent was acquired from each patient before inclusion in the study. Patients were blinded to their treatment, as were the researchers (L.S., A.I.) in charge of postoperative follow-up.

According to the available evidence, the incidence of moderate to severe postcraniotomy headache is 60%.[2] Based on these data and assuming 1) a 50% reduction in the incidence of the main outcome in patients undergoing SPGB compared with standard treatment, and 2) a two-tailed alpha level of 0.05, at least 41 patients per arm (82 in total) were needed to achieve 80% statistical power in an intent-to-treat analysis. The study was approved by the local ethics committee and registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is: NCT05136625.

All eligible patients were randomized with a random number generator from 1 to 100 (Excel function "RANDOM"[17]) using a dichotomic criteria (number ≤ 50 vs ≥ 51). Randomization was performed by a researcher (G.M.) not involved in the follow-up process. The allocation ratio was 1:1 between two groups: 1) the control group, who underwent standard treatment (scalp block, local anesthetic infiltration of the wound, and systemic analgesia during the first 48 hours postoperatively), and 2) the treatment group (SPGB + standard treatment).

Data Collection

Demographic, clinical, and surgical variables were obtained using medical records and diagnostic images. Heart rate (HR) and blood pressure (BP) readings were recorded during surgery at 0, 1, 5, and 10 minutes from the Mayfield closure and at the same time interval from skin incision.

TABLE 1. Diagnostic criteria of PCP

Variable	Acute Headache Attributed to Craniotomy	Persistent Headache Attributed to Craniotomy
Description	Headache of < 3 mos duration caused by surgical craniotomy	Headache of > 3 mos duration caused by surgical craniotomy
Diagnostic criteria	A. Any headache fulfilling criteria C and D	A. Any headache fulfilling criteria C and D
	B. Surgical craniotomy has been performed	B. Surgical craniotomy has been performed
	C. Headache is reported to have developed within 7 days after one of the following: the craniotomy, regaining consciousness following the craniotomy, or discontinuation of medication impairing the ability to sense or report headache following the craniotomy	C. Headache is reported to have developed within 7 days after one of the following: the craniotomy, regaining of consciousness following the craniotomy, or discontinuation of medication impairing the ability to sense or report headache following the craniotomy
	D. Either of the following: headache has resolved within 3 mos after onset, or headache has not yet resolved but 3 mos have not yet passed since its onset	D. Headache persists for > 3 mos after onset
	E. Not better accounted for by another ICHD-3 diagnosis	E. Not better accounted for by another ICHD-3 diagnosis

ICHD-3 = International Classification of Headache Disorders, 3rd edition.
Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalgia.* 2018;38(1):1-211. © International Headache Society, published with permission.

Pain evaluation was performed using the following validated scales: 1) numeric rating scale (NRS; 0 = no pain, 10 = worst possible pain); 2) visual analog scale[18] (VAS; 0 mm = no pain, 10 mm = worst possible pain); and 3) pain assessment in advanced dementia (PAINAD) scale[19,20] (0 = no pain, 10 = intense pain).

PCP was evaluated at 5 in-hospital checkpoints (6 hours after awakening, and at postoperative days 1–4) using different pain score systems (VAS/NRS/PAINAD). The timing of pain evaluation was randomly distributed during the day, but not immediately before or after the administration of scheduled therapy. After hospital discharge (postoperative days 30, 60, and 180), follow-up was performed by telephone interview evaluating only the NRS.

Transnasal SPGB Procedure

The entire transnasal SPGB procedure was performed by a trained surgeon (G.M.) for the patients assigned to the treatment group, after induction of general anesthesia and administration of a bilateral scalp block.[21] The patient was supine with the cervical spine extended. The distance from the opening of the nostril to the mandibular notch,

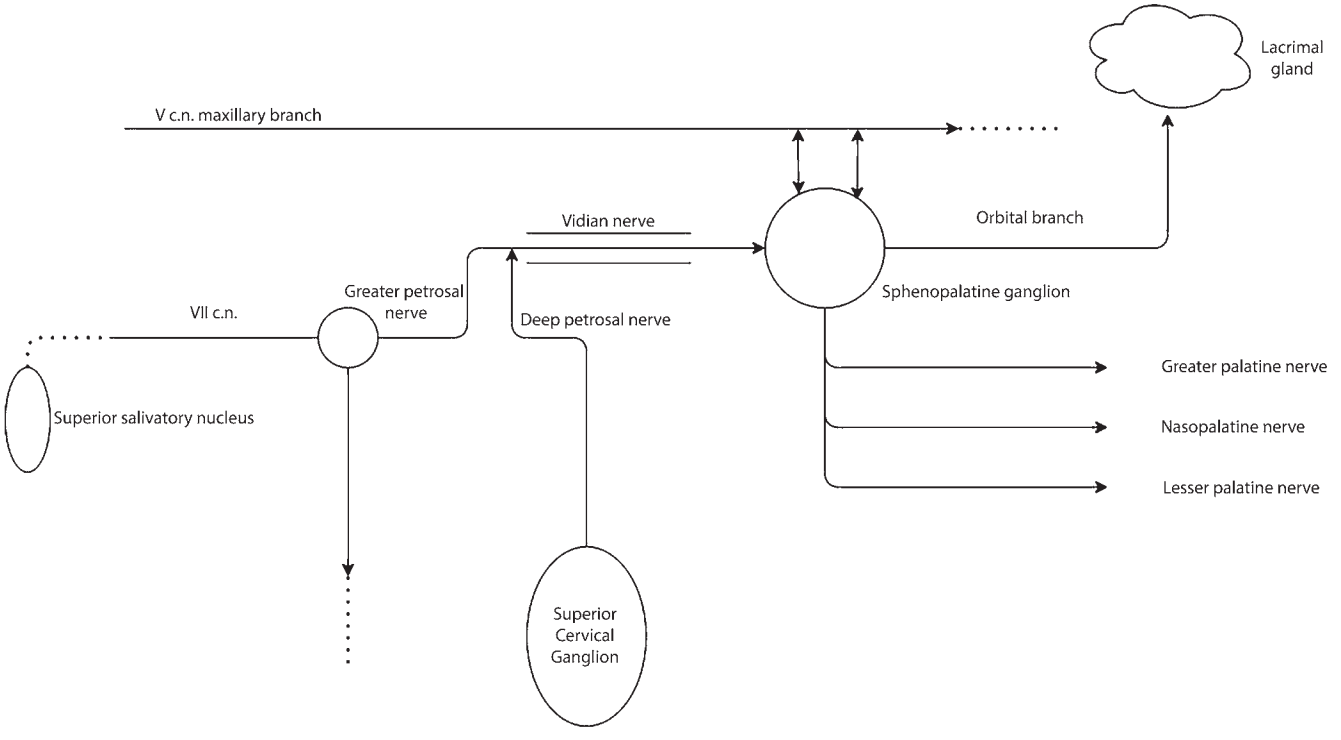

FIG. 1. Anatomical connections of the SPG. c.n. = cranial nerve.

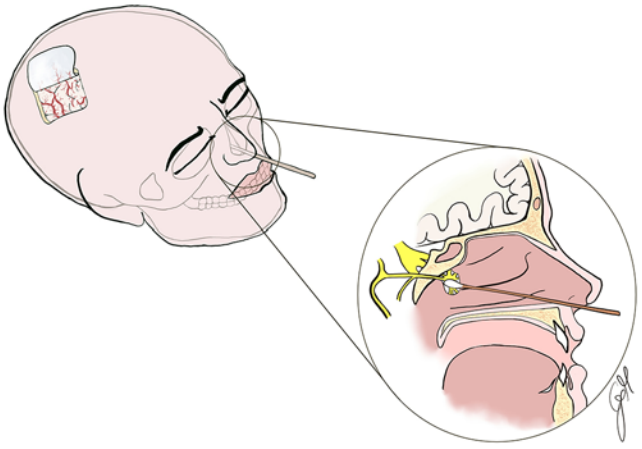

FIG. 2. Illustration of the SPGB technique using a transnasal approach. © Giorgio Mantovani, published with permission.

directly below the zygoma, was measured and used to estimate the depth needed to advance a cotton-tipped applicator.[22] On the side where the craniotomy was going to be performed, the ipsilateral nostril was disinfected by a cotton swab soaked in 0.2% chlorhexidine. After the patients was asleep after general anesthesia, a cotton swab, dipped in a solution of 0.5% levobupivacaine, was applied and kept in place for 10 minutes to perform the SPGB. To reach the SPG, the surgeon sets the inclination of the cotton swabs with an angle of 25° from the palatum durum and passes between the middle and superior nasal turbinates through a superolateral direction, maintaining contact with the lateral wall.[23] Finally, the cotton swab is removed and the Mayfield skull clamp is placed (Fig. 2).

General anesthesia is attained by total intravenous anesthesia using 2 mg/kg of propofol and 0.1 mcg/kg/min of remifentanil; neuromuscular blocks are used only during intubation and avoided for awake procedures. The bilateral scalp block is performed following the usual technique[24] with 0.5% levobupivacaine (2 ml for each injection). Local infiltration of the wound is performed using 1.5% mepivacaine (10 mg total) applied 5–10 minutes before the surgical incision. Postoperative analgesia is performed with administration of paracetamol/acetaminophen (1 g three times a day) and tramadol (1–2 mg/kg twice daily). Chronic PCP is defined as an NRS score ≥ 3 at the last follow-up (postoperative day 180). Complications of the SPGB procedures were reported using the Clavien-Dindo classification of surgical complications.[25]

Statistical Analysis

Continuous parametric and nonparametric variables were described by mean ± standard deviation and by median (interquartile range [IQR]), respectively. The distribution of all continuous variables was assessed using the Shapiro-Wilk test. Differences between groups at baseline and at each time point were assessed using a t-test and Kruskal-Wallis test for normally and nonnormally distributed continuous variables, respectively, and the chi-square test for categorical variables. The efficacy of randomization was verified by comparing the different continuous and categorical variables at baseline using the Wilcoxon rank-sum and Fisher exact tests, respectively. Within each group, the differences in all continuous variables between baseline and 10 minutes after the start of surgery (for BP and HR) and between baseline and postoperative day 4, 30, 60, and 180 days (for VAS, NRS, and PAINAID scales) were evaluated using a paired t-test and confirmed through the Wilcoxon matched-pairs signed-rank test. Differences between groups in the mean changes of each variable (between baseline and each time point) were assessed using a t-test and confirmed using a Kruskal-Wallis test. A two-tailed p value ≤ 0.05 was considered significant for all analyses, which were performed using Stata (version 13.1, StataCorp LLC).

Results

From the 207 craniotomy procedures performed during the study period, 83 patients were enrolled. The primary reasons for study exclusion were urgency/emergency regimen of the surgery (68 cases), ongoing neuroleptic and/or antiepileptic treatment (24 cases), narcotics abuse (13 cases), previous chronic headache (10 cases), psychiatric disorders (8 cases), and the SPGB procedure not correctly completed (1 case, moved to the control group). Patient study flow is shown in Fig. 3.

Demographic and Clinical Characteristics

The mean patient age was 63.7 years, with no statistically significant differences in age between the two groups (p = 0.6). Males represented 49.4% of all patients, with no statistically significant differences in gender between the groups (p = 0.7). Data on craniotomy side, diagnosis, and awake surgery are reported in Table 2. Cardiovascular parameters (mean BP and HR during and after Mayfield closure and skin incision) recorded during intraoperative monitoring did not show any significant statistical differences between the control and treatment groups (Table 3) except for the T10 (10 minutes after Mayfield closure) mean BP, which was lower in the SPGB group (p = 0.03; Table 3).

Postoperative Pain Assessment and Follow-Up

VAS score ≥ 3 on postoperative day 1 was more frequent in the standard treatment group compared with the SPGB group (89.5% vs 71.9%); this difference was statistically significant (p = 0.05). Statistically significant differences were also found in the mean VAS score at postoperative days 0 (p = 0.05), 2 (p = 0.03), and 3 (p = 0.03), with the SPBG group showing lower values.

Mean NRS values were lower in the SPBG group, but no statistically significant differences were found between the two groups. Median postoperative PAINAD scores were also lower in the SPBG group, showing significant statistically differences at postoperative day 1 (p = 0.006), 2 (p = 0.001), 3 (p = 0.03), and 4 (p = 0.05). The randomization process was effective for the baseline characteristic comparison, so that the two arms were sufficiently homogeneous to be compared.

We did not find any significant complications (Clavien-Dindo grade I). One patient in the SPGB group com-

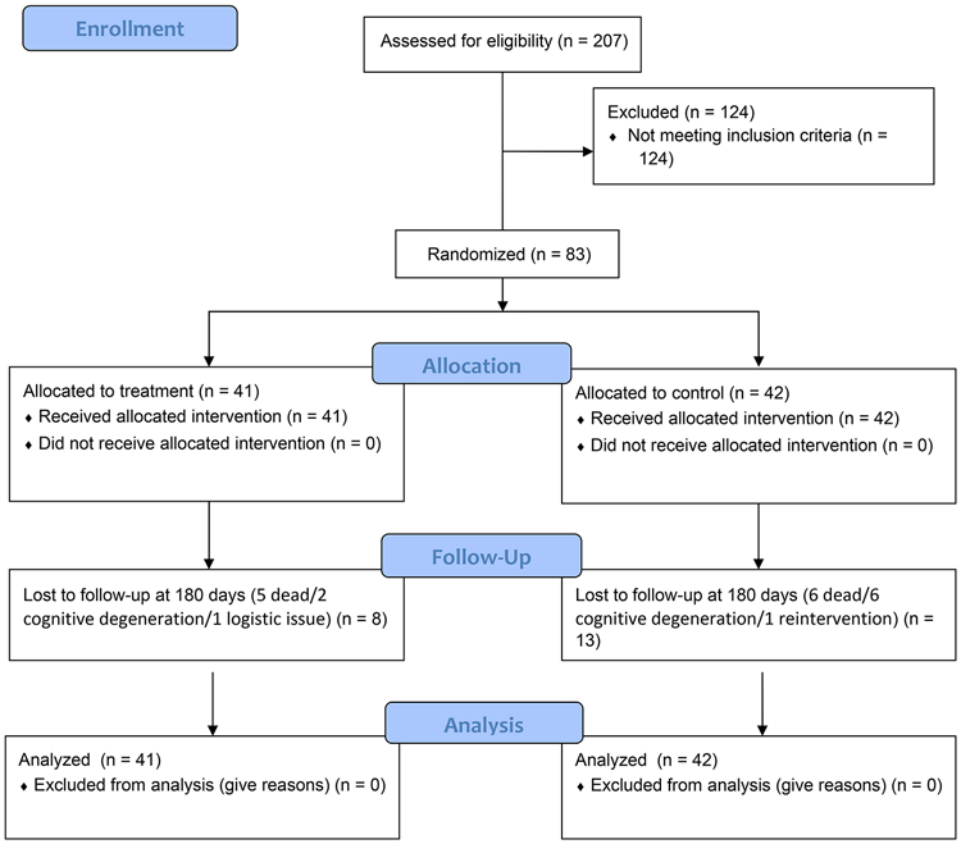

FIG. 3. Patient study flow. Data added to the CONSORT template (from Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ.* 2010;340:c869) under the terms of the Creative Commons Attribution Noncommercial (CC BY-NC 2.0) License (https://creativecommons.org/licenses/by-nc/2.0).

plained of a bitter taste during the first postoperative day, which resolved spontaneously. We did not observe any nose bleeding, nasal pain, or local or systemic allergic reactions. In 1 patient, it was not possible to complete the SPGB procedure because of the presence of anatomical variations of the nasal mucosa not previously detected. Thus, this patient was shifted to the control group. During the follow-up period, 5 patients (2 in the control group, 3 in the treatment group) showed chronic PCP (NRS score ≥ 3 at 180 days).

TABLE 2. Selected demographic and clinical characteristics of the overall sample and according to approach to control PCP

Characteristic	Overall Sample	SPGB Group	Control Group	p Value
No. of patients	83	41	42	
Mean age (SD), yrs	63.7 (12.4)	63.0 (12.3)	64.33 (12.7)	0.6
Male gender, % (n)	49.4 (41)	51.2 (21)	47.6 (20)	0.7
Craniotomy side, % (n)				0.6
Rt	48.2 (40)	48.8 (20)	47.6 (20)	
Lt	45.8 (38)	51.2 (21)	40.5 (17)	
Bilat	6.0 (5)	0.0 (0)	11.9 (5)	
Diagnosis, % (n)				0.7
Neoplastic disease	94.0 (78)	95.1 (39)	92.9 (39)	
Vascular disease	6.0 (5)	4.9 (2)	7.1 (3)	
Awake surgery, % (n)	22.9 (19)	24.4 (10)	21.4 (9)	0.5

Neoplastic disease consisted of meningioma, glioblastoma, low-grade glioma, and metastases. Vascular disease comprised arteriovenous malformation, aneurysm, dural arteriovenous fistula, and cerebral bleeding.

TABLE 3. Selected cardiovascular parameters recorded during intraoperative monitoring, and postoperative outcomes (overall and by treatment group)

Parameter	Overall Sample	SPGB Group	Control Group	p Value*
No. of patients	83	41	42	
Intraop monitoring				
Mean BP during Mayfield closure (SD), mm Hg				
T0–baseline, n = 77†	78.4 (18.4)	77.1 (18.1)	79.7 (18.0)	0.5
T1, n = 76	80.9 (18.9)	79.3 (17.4)	82.4 (20.4)	0.5
T5, n = 78	73.3 (18.1)	70.8 (17.4)	75.7 (18.6)	0.2
T10, n = 78	67.9 (17.6)	63.7 (15.3)	72.2 (18.9)	**0.03**
ΔT0–T10	10.7 (17.0)	13.7 (13.3)	7.7 (19.9)	0.09
Paired t-test p value		<0.001	0.02	
Mean BP after incision (SD), mm Hg				
T0, n = 81	68.4 (13.1)	68.5 (14.8)	68.3 (11.4)	0.9
T1, n = 81	68.4 (13.1)	68.5 (14.8)	68.3 (11.5)	0.9
T5, n = 81	70.0 (13.5)	69.0 (14.2)	71.1 (14.8)	0.5
T10, n = 81	72.3 (12.3)	71.1 (12.9)	73.5 (11.8)	0.4
ΔT0–T10	−4.3 (10.4)	−3.2 (7.4)	−5.5 (12.7)	0.4
Paired t-test p value		0.01	0.01	
Mean HR during Mayfield closure (SD), bpm				
T0, n = 76	70.7 (14.7)	69.4 (13.9)	71.9 (15.5)	0.4
T1, n = 76	72.6 (16.5)	71.5 (14.8)	73.8 (18.1)	0.5
T5, n = 79	67.3 (14.1)	66.1 (12.5)	68.5 (15.6)	0.5
T10, n = 78	67.3 (17.0)	67.1 (18.3)	67.5 (15.9)	0.9
ΔT0–T10	3.5 (12.7)	3.0 (15.4)	4.0 (9.5)	0.10
Paired t-test p value		0.2	0.012	
Mean HR after incision (SD), bpm				
T0, n = 78	63.6 (11.2)	62.5 (10.2)	64.6 (12.2)	0.4
T1, n = 81	64.3 (12.4)	64.4 (12.5)	64.3 (12.5)	0.9
T5, n = 81	63.9 (12.5)	63.5 (12.8)	64.3 (12.4)	0.8
T10, n = 81	62.0 (13.5)	60.2 (14.7)	63.7 (12.3)	0.2
ΔT0–T10	1.7 (7.7)	3.4 (8.4)	0.1 (6.0)	0.12
Paired t-test p value		0.02	0.9	
Postop monitoring				
VAS				
VAS score at 1st postop day ≥3, %	81.4	71.9	89.5	**0.05**
Mean postop VAS score (SD), mm				
0d, n = 67‡	37.1 (30.3)	38.4 (33.3)	36.1 (28.0)	**0.05**
1d, n = 70	27.6 (24.6)	25.5 (23.7)	29.4 (25.6)	0.5
2d, n = 71	18.8 (22.2)	13.9 (19.0)	23.3 (24.1)	**0.03**
3d, n = 62	14.3 (19.1)	9.4 (13.7)	19.6 (22.6)	**0.03**
4d, n = 51	9.8 (14.1)	7.3 (11.7)	13.1 (16.6)	0.14
30d, n = 61	6.0 (9.0)	2.9 (10.4)	7.7 (15.7)	0.3
Preop-postop surgical variation				
ΔVAS0–VAS4	23.6 (24.3)	26.2 (26.9)	20.0 (20.3)	0.9
Paired t-test p value		<0.001	<0.001	
ΔVAS0–VAS30	30.0 (26.9)	33.8 (30.5)	25.8 (22.1)	0.5
Paired t-test p value		<0.001	<0.001	
NRS				
Mean postop NRS score (SD)				
0d, n = 70	4.0 (3.2)	3.9 (3.1)	4.2 (3.9)	0.6

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TABLE 3. Selected cardiovascular parameters recorded during intraoperative monitoring, and postoperative outcomes (overall and by treatment group)

Parameter	Overall Sample	SPGB Group	Control Group	p Value*
Postop monitoring (*continued*)				
NRS (*continued*)				
Mean postop NRS score (SD) (*continued*)				
1d, n = 72	3.1 (2.6)	2.8 (2.4)	3.3 (2.8)	0.5
2d, n = 75	2.2 (2.5)	1.6 (2.0)	2.7 (2.7)	0.06
3d, n = 65	1.7 (2.3)	1.3 (1.9)	2.1 (2.6)	0.3
4d, n = 53	1.1 (1.7)	0.9 (1.6)	1.3 (1.8)	0.3
30d, n = 68	1.1 (2.1)	1.4 (2.4)	0.8 (1.8)	0.4
60d, n = 62	0.9 (2.0)	0.7 (1.9)	1.1 (2.1)	0.4
180d, n = 44	0.7 (1.8)	1.0 (1.2)	0.5 (1.1)	0.6
ΔNRS0–NRS4	2.6 (2.7)	2.8 (2.9)	2.3 (2.4)	0.6
Paired t-test p value		<0.001	0.008	
ΔNRS–NRS30	2.8 (2.8)	2.2 (2.8)	3.4 (2.8)	0.07
Paired t-test p value		<0.001	<0.001	
ΔNRS0–NRS60	3.3 (2.9)	3.0 (2.9)	3.6 (2.8)	0.4
Paired t-test p value		<0.001	<0.001	
ΔNRS0–NRS180	2.6 (2.8)	2.5 (3.3)	2.8 (2.1)	0.8
Paired t-test p value		0.002	<0.001	
PAINAD scale				
Median postop PAINAD scale score (IQR)				
0d, n = 69	1.4 (1.8)	1.1 (1.4)	1.6 (2.0)	0.2
1d, n = 71	0.9 (1.6)	0.4 (0.9)	1.4 (1.9)	**0.006**
2d, n = 73	0.7 (1.5)	0.2 (0.5)	1.1 (1.8)	**0.001**
3d, n = 67	0.4 (0.9)	0.1 (0.5)	0.6 (1.2)	**0.03**
4d, n = 57	0.2 (0.7)	0.0 (0.4)	0.4 (0.9)	**0.05**
30d, n = 65	0.2 (0.6)	0.0 (0.4)	0.2 (0.8)	0.2
ΔPAINAD0–PAINAD4	1.2 (1.6)	1.0 (1.2)	1.4 (1.9)	0.7
Paired t-test p value		<0.001	0.002	
ΔPAINAD0–PAINAD30	1.2 (1.4)	1.1 (1.4)	1.2 (1.5)	0.7
Paired t-test p value		<0.001	<0.001	

Δ = difference; bpm = beats per minute.

Boldface type indicates statistical significance. Paired t-test p values reflect the difference between baseline and postoperative follow-up within each group.

* p values obtained using a t-test or Kruskal-Wallis test for normally and nonnormally distributed continuous variables, respectively; the chi-square test was used for categorical variables.

† T (T0, T1, etc.) = time (in minutes) after surgery or incision.

‡ d (0d, 1d, etc.) = number of days after craniotomy.

Discussion

Our results showed that SPGB is efficient in better controlling PCP in the early postoperative period compared with standard treatment. BP and HR showed a lower trend in treated patients, even if the difference did not reach statistical significance. This result partially confirms the previous findings of Padhy et al.[11] and adds new evidence concerning the role of SPGB in neurosurgical patients.

From the first postoperative day, a clinically relevant and statistically significant benefit was noted in the SPGB group. This finding could be explained by the possible inhibition of the parasympathetic branches to the noxious surgical stimuli. Moreover, the decrease of neurovascular inflammation caused by the SPGB prevented the development of the migranous correlate of PCP. After the 4th day, with the decrease in postoperative neural inflammation, pain indicators appeared to align between the two groups.

PCP has mainly nociceptive origins, coming from the scalp, pericranial muscles, and soft tissue innervated from branches of the cervical plexus and trigeminal nerve.[26] Even so, in the CNS, pain pathways can also be activated by manipulation of the dura mater, especially in the skull base,[26,27] with subsequent inflammation and vasodilatation of the parenchymal and meningeal vessels.[27] Patients mostly feel PCP in the localized area around the inci-

sion site and in the soft tissues surrounding it. The most common clinical form of PCP is a pulsating or pounding pain.[21,26,28,29] However, PCP can clinically begin in many different ways, such as a migraine with pulsating ipsilateral pain and vegetative symptoms, or tension headaches. Additionally, patient positioning during the procedure may lead to tension headaches and neck spasms of muscular origin.[26,30] PCP management has been investigated from different points of view during the last few decades, and several options are currently available that are discussed below. Yet, one of the latest reviews on the topic stated that no protocols are available that are widely shared and based on high-level quality data.[2]

Recently it has been found that pregabalin can attenuate preoperative anxiety, improve sleep quality, and reduce postoperative pain scores and analgesic use.[5] Acupuncture is an ancient analgesic technique, but there is little scientific evidence of its effectiveness; however, acupuncture has shown promising results in reducing PCP.[6] In addition to the local anesthetic injection of the wound, the scalp block inhibits the trigeminal cutaneous branches and the upper three cervical nerves. It is perhaps one of the most widely used analgesic techniques in neurosurgical patients. The major advantage of using scalp blocks is that they provide transitional analgesia without compromising the neurological examination.[7,24,31] A recent systematic review[8] concluded that dexmedetomidine reduces postoperative pain, intraoperative consumption of opioids and hypnotics, the appearance of postoperative nausea and vomiting, and time to extubation. It is also associated with better intraoperative hemodynamic control, without increasing the incidence of hypotension and bradycardia.[8]

Parenteral opioids remain the most efficient drug for managing moderate to severe pain, especially in the postoperative period after major surgery. Unfortunately, opioids have side effects that can adversely affect patient recovery from surgery. For example, nausea, vomiting, decreased gastrointestinal motility leading to constipation, pruritus, respiratory depression, and oversedation can all result in the need for additional pharmacological intervention, and eventually an increased hospital inpatient LOS. Moreover, parenteral opioids compromise the postoperative neurological examination, which is fundamental in neurosurgical settings.[7]

NSAIDs are effective for analgesia but could lead to platelet dysfunction and increased bleeding times. Therefore, their use in neurosurgical patients is usually avoided.[7] Gabapentin reduces pain scores, opioid consumption, and nausea and vomiting during the postoperative period. But gabapentin can cause delayed tracheal extubation and increased postoperative sedation.[6,9]

Many studies during the last decades have focused on the role of SPGB in headache syndromes. The stimulation of the SPG has also been shown to activate cerebral vasodilation and increase cerebral blood flow, in addition to producing lacrimation, photophobia, and rhinorrhea by releasing acetylcholine, vasoactive intestinal peptide, and nitric oxide in the meningeal blood vessels.[4] This activation provokes neurogenic inflammation and activation of trigeminal nociceptors. All these processes contribute to pain and trigger headaches or migraine attacks.[4,27,32,33] Yarnitsky et al. showed that activation of intracranial perivascular nociceptors induces peripheral and central sensitization along the trigeminovascular pathway. These sensitizations mediate intracranial hypersensitivity and the cutaneous allodynia of migraine by sensitizing the central nociceptive neurons in the spinal trigeminal nucleus.[32]

Emerging as a possible adjunctive therapy for PCP, the SPGB procedure simultaneously stops the nociceptive trigeminal afferences, hindering the onset of peripheral and central sensitization along the trigeminovascular pathway,[32] and the parasympathetic efferences of SPG toward the meningeal and parenchymal vessels, which cause the release of inflammatory mediators and the neurovegetative response.[11] The SPGB can be performed in many ways using transnasal, infrazygomatic, or transoral approaches. These are usually applied with sterile needles, cotton swabs, or dedicated tools (SphenoCath and Allevio SPG nerve block catheter). For the transnasal approach, the use of a rigid applicator, such as a cotton swab, improves the efficiency of the block; in some studies, using the cotton swab to apply the local anesthetic has given better results than using an intranasal spray, with 12%–47% more efficacy.[23,34,35] Most adverse events related to SPGB are transient epistaxis and a bitter taste in the mouth. There have been some reported cases of oropharyngeal numbness, ipsilateral nostril and eye burning sensation, nasal discomfort, diplopia, and reduced buccal opening.[36]

We chose the transnasal approach, considering it the safer and easier procedure. Indeed, no complications occurred in the treated patients. However, dedicated training and detailed anatomical knowledge are required to effectively perform this procedure. In our patients, 5 (4.15%) reported an NRS score > 3 (chronic PCP) at postoperative day 180. Other studies reported an incidence rate of 5%–10%.[2] Further dedicated studies are needed to clarify the possible role of SPGB in preventing chronic PCP. Further studies are also warranted to precisely identify the indications for SPGB in a real-world clinical situation with a larger sample size. Several aspects that were not included in this study still require clarification: association with underlying brain pathology, size and type of craniotomy, previous and perioperative therapy, modification of scheduled and on-demand analgesic drugs, and minimal clinically important difference (MCID). Defining the MCID for SPGB in neurosurgery will be of fundamental importance for its inclusion in routine protocols, as this parameter can aid in defining the real impact of the procedure on the clinical course of the patient.

An effective and data-driven approach to the management of postoperative pain is essential to ensure an ERAS approach: pain-free or pain-controlled patients have a faster, more functional, and more satisfactory return to normal activities of daily life. More generally, it has been proven that a high adherence to ERAS protocols in neurosurgery is linked to a reduction in LOS and costs.[37] A recent review by Greisman et al.[38] emphasized that the body of evidence in favor of ERAS practice in neurosurgery is constantly growing. Given this perspective, SPGB could be included in the routine protocol of PCP prevention and control.

Limitations of the Study

A significant number of patients in our sample were affected by primary cerebral malignancies (glioblastoma in most of the cases) and this hindered the quality of the follow-up procedures—declining neurological functions and death prevented us from a complete analysis of the considered outcome at the last follow-up (180 days). Raw data presented in Table 3 (NRS column) show that most patients who did not complete the follow-up period were lost during the 60- to 180-day interval. A larger sample size with different pathologies is required to confirm these results.

SPGB with an intranasal approach remains a blind procedure, so it is not possible to evaluate the percentage of patients who effectively received a functional anesthetic block. To minimize this bias, a precise and previously validated procedure was followed in every case with preoperative imaging evaluation. Patients in whom completion of SPGB was not possible (anatomical variations not previously detected) were shifted to the control group. Use of vasoactive drugs during surgery and previous hypertension could be significant confounding factors of the hemodynamic response to skull pin insertion. Usually, our team does not use noradrenaline in elective surgery, but precise data are not available regarding patient presurgical hypertension.

Typically, with the standard postoperative therapy detailed above, additional rescue doses of analgesic are not required. However, we did not collect specific data on this, which could represent a significant bias. In addition, the perioperative course of patients undergoing craniotomy can be complicated in various ways. Several factors interfered with a full data sampling: 1) some patients were discharged before postoperative day 4, 2) some patients required postoperative intensive care unit monitoring (prolonged sedation), and 3) patients who underwent awake procedures did not have an arterial line for real-time BP measurement, so the corresponding value is missing.

Conclusions

SPGB appears to be safe and effective as an adjunctive treatment for PCP, in conjunction with classical analgesic measures. A measurable clinical benefit was achieved between the 2nd and the 4th postoperative days. At medium (30 days) and long (180 days) follow-up, the two groups showed similar pain scores.

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Disclosures

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: Mantovani, Indaimo, De Bonis, Scerrati. Acquisition of data: Sgarbanti, Indaimo, De Bonis. Analysis and interpretation of data: Indaimo, De Bonis, Flacco. Drafting the article: Mantovani, Sgarbanti, Indaimo, Scerrati. Critically revising the article: Mantovani, Indaimo, Cavallo, De Bonis, Flacco, Scerrati. Reviewed submitted version of manuscript: Mantovani, Flacco. Approved the final version of the manuscript on behalf of all authors: Mantovani. Statistical analysis: Flacco. Administrative/technical/material support: Sgarbanti, Indaimo. Study supervision: Mantovani, Indaimo, De Bonis.

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