Influence of levobupivacaine regional scalp block on hemodynamic stability, intra- and postoperative opioid consumption in supratentorial craniotomies: a randomized controlled trial

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Conflict of interest statement

Vincent Bonhomme has received funds and research support from Orion Pharma, as well as honoraria from Medtronic. He is the Editor-in-Chief of the Acta Anaesthesiologica Belgica. The other authors have no conflict of interest to disclose.

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Abbreviated title

Scalp block for supratentorial craniotomy

Author's individual contribution to the manuscript

Michele Carella: This author performed data acquisition, data analysis, and wrote the manuscript.
Gabriel Tran: This author participated to the writing of the protocol and conception of the study, performed data acquisition and analysis, and reviewed the manuscript.
Vincent Bonhomme: This author performed statistical analysis of recorded data, and reviewed the manuscript.
Colette Franssen: This author wrote the protocol and designed the study, performed data acquisition, participated to data analysis, and reviewed the manuscript.

Previous presentations

This work has already been presented in part at the Graduation Day of the Society for Anesthesia and Resuscitation of Belgium, held in Brussels on May 25, 2019. It has also been presented in part at the annual congress of the French Society of Anesthesia and Resuscitation (SFAR), held in Paris on September 19-21, 2019.

Abstract

Background: The anesthetic management of supratentorial craniotomy necessitates tight intraoperative hemodynamic control. This type of surgery may also be associated to substantial postoperative pain. We aimed at evaluating the influence of regional scalp block (SB) on hemodynamic stability during the noxious events of supratentorial craniotomies and total intravenous anesthesia, its influence on intraoperative anesthetic agents' consumption, and its effect on postoperative pain control.

Methods: Sixty patients scheduled for elective craniotomy were prospectively enrolled. Patient, anesthesiologist, and neurosurgeon were blind to the random performance of SB with either levobupivacaine 0.33% (Group SB, n=30) or the same volume of saline (Group CO, placebo group, n=30). General anesthesia was induced and maintained using target-controlled infusions of remifentanil and propofol that were adjusted according to hemodynamic parameters and State Entropy of the electroencephalogram (SE), respectively. Mean arterial pressure (MAP), heart rate (HR), SE, and propofol and remifentanil effect-site concentrations (Ce) were recorded at the time of SB (Baseline), and 0, 1, 3, and 5 minutes after skull-pin fixation (SP), skin incision (SI), craniotomy (CR), and dura-mater incision (DM). Morphine consumption and postoperative pain intensity (0-10 visual analogue scale, VAS) were recorded 1, 3, 6, 24 and 48 hours after surgery. Propofol and remifentanil overall infusion rates were also recorded. Data were analyzed using two-tailed Student unpaired t-tests, two-way mixed-design ANOVA and Tukey's HSD tests for post-hoc comparisons as appropriate.

Results: Demographics and length of anesthetic procedure of Group CO and SB were comparable. SP, SI and CR were associated with a significantly higher MAP in Group CO than in Group SB, at least at one of the time points of recording surrounding those noxious events. This was not the case at DM. Similarly, HR was significantly higher in Group CO than in Group SB during SP and SI, at least at one of the points of recording, but not during CR and DM. Propofol and remifentanil Ce and overall infusion rates were significantly higher in Group CO than in Group SB, except for propofol

Ce during SP. Postoperative pain VAS and cumulative morphine consumption were significantly higher in Group CO than in Group SB.

Conclusions: In supratentorial craniotomies, SB improves hemodynamic control during noxious events, and provides adequate and prolonged postoperative pain control as compared to placebo.

Glossary of terms

ANOVA: Analysis of variance
ASA: American Society of Anesthesiologists
Baseline: Time of scalp block performance
Ce: Effect-site concentration
CONSORT: Consolidated Standards of Reporting Trials
CR: Craniotomy
DM: Dura mater incision
G: Gauge
GCS: Glasgow coma scale
Group CO: Control group
Group SB: Intervention group
HR: Heart rate
ICH-GCP: International Conference on Harmonisation-Good Clinical Practice
IV: Intravenous
MAP: Mean arterial blood pressure
MD: Mean difference
ME: Main effect
NCT: National Clinical Trial
PCA: Patient-controlled analgesia
Propo: Propofol
Remi: Remifentanil
SB: Scalp bloc
SD: Standard deviation
SE: State entropy of the electroencephalogram
SI: Skin incision
SME : Simple main effect
SP: Skull-pin fixation
t+1: One minute after time 0
t+3: Three minutes after time 0
t+5: Five minutes after time 0
t0: Time 0
Tukey's HSD: Tukey's honestly significant difference
VAS: Visual analogue scale
WBI: Within-between interaction

Key Points Summary

Question: Is scalp block effective at improving hemodynamic stability and postoperative pain control in patients receiving total intravenous anesthesia for supratentorial craniotomies?

Findings: As compared to placebo, scalp block strongly attenuates hemodynamic responses to skull pin insertion, skin incision, and craniotomy, lowers intraoperative opioid and hypnotic agent requirements, and provides good quality postoperative pain control with low opioid consumption in patients undergoing intravenous anesthesia for supratentorial craniotomies.

Meaning: Scalp block can be considered as a useful add-on to total intravenous anesthesia for the perioperative anesthetic management of those patients.

Introduction

During supratentorial craniotomies, skull pin fixation, skin incision, bone-flap removal and dura-mater incision are the strongest noxious stimuli [1]. Their occurrence may cause increases in blood pressure, even during deep general anesthesia. The elevation of blood pressure may not only provoke an abrupt increase of intracranial pressure with potential adverse effects on cerebral perfusion [2], but favor bleeding in an injured parenchyma with fragile hemostasis. Pain after surgery may also have the same consequences. Attenuating nociception perioperatively is therefore of fundamental importance, in order to minimize hemodynamic variations.

The multimodal approaches to intraoperative anti-nociception and postoperative pain treatment, combining systemic analgesic medications and local anesthetic agents, optimize pain relief and limit the adverse effects of opioids [3,4]. Scalp infiltration or regional scalp block (SB) has been proposed to be part of this type of multimodal approach to prevent hemodynamic responses to noxious stimulation during craniotomy and to prevent postoperative pain [5–7]. It has been used for chronic subdural hematomas drainage [8], treatment of chronic neuralgias of the great occipital nerve [9,10], and awake craniotomies [11] successfully. SB necessitates the subcutaneous infiltration of local anesthetic agents at several points over the scalp surface, which is highly vascularized. Local anesthetic agents with low toxicity, such as levobupivacaine, are therefore preferred [12].

In this study, we primarily aimed at evaluating the influence of levobupivacaine regional SB on blood pressure stability during the main noxious events of supratentorial craniotomies in patients receiving general anesthesia as compared to the absence of such a block. The secondary endpoints were the evaluation of the influence of SB on heart rate, intraoperative and postoperative opioid consumption, and postoperative pain. Our primary hypothesis was that SB would improve intraoperative hemodynamic stability, and secondary hypothesis that it would allow requiring less opioids to achieve similar postoperative pain levels.

Methods

This prospective, randomized, placebo-controlled, blinded study was approved by our local Ethics Review Board (Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège; President: Prof. V. Seutin; Committee number: 707) under the study number 2016/235-B707201629458, and registered in the ICH-GCP-Clinical Trials Registry under the number NCT02880566 and registry URL https://ichgcp.net/it/clinical-trials-registry/NCT02880566 on August 1st, 2016 (Principal Investigator: Colette Franssen). A written informed consent was obtained before inclusion into the study. This study adheres to the applicable CONSORT guidelines and was performed in accordance with the most recent version of the Helsinki Declaration. Data acquisition occurred between October 21, 2016 and December 18, 2019 at the University Hospital of Liege, Liege, Belgium.

Patient recruitment and assignment to groups

Sixty-four ASA physical status 1, 2 and 3 patients scheduled to undergo elective supratentorial intracranial surgery and to receive general anesthesia were prospectively screened for possible inclusion. Only patients whose surgery was planned in the supine position with an estimated time length between 90 and 360 minutes were approached. Exclusion criteria included refusal of the patient, and contraindications to the performance of SB such as known allergy to used medications or local infection. Other exclusion criteria included age >75 or <18 years, obesity (body mass index >35 $Kg.m^{-2}$), emergency craniotomies, chronic pain (persistent or recurrent pain lasting longer than 3 months) or fibromyalgia, drug addiction (illicit substances and opioid regular use), chronic alcohol abuse, treatment with corticosteroids for more than 6 months, uncontrolled systemic arterial hypertension, severe kidney or liver diseases, mental disorders or serious neurological diseases, and cardiomyopathies or sustained cardiac arrhythmias (permanent paroxystic atrial fibrillation or other sustained supraventricular rhythmic anomalies). Should major intraoperative hemorrhage occur (necessitating blood transfusion), data would be excluded from further analyses. After exclusion of 4 screened patients because of patient refusal (n=2) or not meeting the inclusion criteria (n=2), 60 patients were randomly assigned to one of two groups (Figure 1). Randomization occurred through a

computer-generated randomization list. Patient, anesthesiologist, and neurosurgeon were blind to group assignment. Groups differed according to the performance of a regional SB with either levobupivacaine 0.33% (Group SB) or the same volume of saline (Group CO, placebo group).

Anesthesia protocol

All patients received oral premedication, at least 90 minutes before induction of general anesthesia (hydroxyzine 50mg, alprazolam 0.5mg, and atropine 0.5mg). General anesthesia was performed using standard monitoring including 5-lead ECG, pulse oximetry, non-invasive blood pressure with adapted cuff size, end-tidal CO_2, and spectral entropy (SE, M-Entropy® module, GE-Healthcare, Finland). Following anesthesia induction, a continuous invasive blood pressure monitoring was initiated through a radial or brachial 20-G arterial catheterization, as well as urine output through bladder catheterization.

After 3-5 minutes of pre-oxygenation with 100% oxygen, anesthesia was induced and maintained using a target-controlled infusion system (Orchestra® Base Primea, Fresenius Kabi, France) delivering remifentanil (Minto model [13]) and propofol (Marsh model [14]). Neuromuscular blockade was achieved using a single 0.2 $mg.Kg^{-1}$ intravenous (IV) bolus of cisatracurium upon loss of consciousness.

Ventilation was mechanically controlled after endotracheal intubation to achieve a partial pressure of end-tidal CO_2 between 4.0 and 4.7 kPa.

Propofol effect-site concentration (Ce) was adjusted by steps of 0.5-1 $\mu g.mL^{-1}$ to maintain SE within the 40-60 range constantly. Remifentanil Ce was adjusted according to heart rate (HR) and man arterial blood pressure (MAP). Increases of HR and/or MAP over or below 20% of baseline values prompted an increase or a decrease in remifentanil Ce by steps of 0.5-1 $ng.mL^{-1}$ until stabilization within the ±20% range. Baseline values were defined as 3 minute-averaged values immediately before the performance of SB. Severe intraoperative hypo- or hypertension episodes (MAP decreases or increases of more than 30% from baseline, or absolute value <60 or >120 mmHg) were treated

using 3 mg IV boluses of ephedrine or 1 mg IV boluses of nicardipine, respectively. Episodes of bradycardia <40 $b.min^{-1}$ were treated using 0.5 mg IV boluses of atropine.

Recovery from anesthesia and tracheal tube removal occurred early after the end of surgery to allow for precocious neurological examination.

Prevention and treatment of postoperative nausea and vomiting was insured by a continuous infusion of alizapride (0.15 $mg.mL^{-1}$ solution in normal saline at a rate of 42 $mL.h^{-1}$ for 24 hours), and 4 mg IV boluses of ondansetron every 8 hour if necessary.

To insure postoperative analgesia, 1g of paracetamol was administered to each patient IV at the end of surgery, before skin closure. In addition, the patients were equipped with a patient-controlled analgesia (PCA) device containing a morphine solution and connected to the IV line (parameters: 0.5 mg boluses, 5-minute refractory time, and 25 $mg.4h^{-1}$ maximum dose). All patients had been informed on the adequate PCA use the day before surgery.

Regional scalp block

SB was performed by the anesthesiologist after induction of general anesthesia, once all equipment and catheters had been placed, during stable and steady-state anesthetic conditions. Thirty mL syringes were prepared by a nurse, who was not participating to patient anesthetic management and data recording or analysis, according to the computer-generated randomization list. For Group SB patients, the syringe was containing 30 mL of 0.33% levobupivacaine (10 mL of normal saline added to 20 mL of 0.5% levobupivacaine). For Group CO patients, the syringe was containing 30 mL of normal saline. An interval of at least 20 minutes was left between the end of SB performance and skull-pin fixation.

An adapted Pinosky technique was used to perform SB [15]. A 23-G needle was introduced with a 45° angle into the skin, and penetrated deeply to the outer margin of the skull. The needle was then gradually withdrawn while injecting the study solution. This was done at several points over the scalp: 1) the supra-orbital and supra-trochlear nerves bilaterally, at their emergence from the orbit above the eyebrow (2x2 mL), 2) the auriculo-temporal nerves bilaterally, anterior to the ear and 1cm above the

tragus transverse plane (2x2 mL), 3) the post-auricular branches of the greater auricular nerves over the mastoid process area, 2cm posterior to the ear on the tragus transverse plane (2x2 mL), 4) the zygomatico-temporal nerve, 2cm posterior to the lateral epicanthus on the tragus transverse plane (2x2 mL) 5) the greater, lesser and third occipital nerves along the superior nuchal line, halfway between the occipital protuberance and the mastoid process (2x7 mL). The whole content of the syringe was used for each patient. Surgeons were not performing any additional skin infiltration along the incision line.

Recorded parameters and events of interest

The following parameters were recorded at Baseline and 0 (immediately before, t0), 1 (t+1), 3 (t+3) and 5 (t+5) minutes after the below-defined noxious events of interest: MAP, HR, propofol and remifentanil Ce, and SE. Noxious events of interest were skull pin fixation (SP), skin incision (SI), craniotomy (CR), and dura-mater incision (DM). During those events, recorded data corresponded to a single measurement at each of the defined time points. At Baseline, recorded data were means of 3 consecutive measurements made immediately before SB. The parameters were recorded by a blind observer.

Pain intensity was blindly evaluated on a 0 to 10 visual analogue scale (VAS) and morphine consumption was recorded 1, 3, 6, 24, and 48 hours after surgery.

The overall consumption of propofol ($mg.Kg^{-1}.min^{-1}$) and remifentanil ($\mu g.Kg^{-1}.min^{-1}$), delay between SB and SP (minutes), as well as total duration of the procedure (from the beginning of anesthesia induction to tracheal tube removal, minutes) were also recorded.

Sample size calculation and statistical analyses

The primary endpoint of the study was the comparison of the evolution of MAP over the different time points of interest between groups. Secondary endpoints were identical comparisons for HR, postoperative pain scores, and related opioid consumption, and between-group comparisons in intraoperative propofol and remifentanil total consumption.

Statistical analysis was achieved using the IBM® SPSS® Statistics software (version 26, IBM Corporation), Datasim© (Version 1.1, Bradley DR, Bates College, Lewiston, ME, USA), and Microsoft® Excel® 2016 (Microsoft Corporation). Normality of distributions was tested by calculating the skewness of distributions and Kurtosis tests. We chose an intention-to-treat approach for data analysis, meaning that any existing data for a given patient were analyzed, including those of patients with protocol violation. Data existing before randomization were not submitted to hypothesis testing and are reported as count (%) and absolute between-group difference (%) for proportions, and as mean (range) and between-group standardized difference for continuous data. Other non-repeated measure data were compared between groups using two-tailed Student unpaired t-tests or Mann-Whitney U tests as appropriate. MAP, HR, SE, propofol and remifentanil Ce, and VAS were compared using two-way mixed-design ANOVA and Tukey's HSD tests for post-hoc comparisons. The assumption of sphericity was assessed using the Mauchly's test, and the Huynh and Feldt epsilon was calculated to adjust the degrees of freedom for the within-between interaction, main effect (ME) of time, or simple main effect (SME) of time testing. The equality of covariance matrices was tested using the Box test, and the equality of error variances using the Levene's test. A two-tailed P-value <0.01 was considered statistically significant for the primary endpoint, and <0.05 for the other endpoints.

Sample size calculation was performed using the G*Power software (version 3.1.9.2, Franz Faul, Kiel University, Germany). Considering the two-factor mixed design (2 groups, 4 repeated measures) at 5 noxious events of interest, a total sample size of 52 was necessary to achieve a power of 0.8 at detecting a within-between interaction medium effect size f=0.2, at a 0.01 α threshold, and assuming a 0.5 within-subject correlation.

Results

Demographic characteristics

As indicated in Figure 1, 64 patients were assessed for eligibility to be included in the study. Two of them were not meeting the inclusion criteria, and 2 of them declined to participate, leading to a total number of 60 patients for randomization. They were separated into two groups of equal size (n=30). There were perioperative data loss for technical reasons (n=4), incomplete data on post-operative morphine consumption (n=4), surgery exceeding 360 minutes (n=1) and an immediate postoperative complication (n=1, 10/15 Glasgow Coma Score in the post-anesthesia care unit, restart of sedation, tracheal intubation, and admission to the intensive care unit). The data from those patients were included in the analyses when existing. Group SB and Group CO were comparable in terms of demographic characteristics, type of surgery, length of the anesthetic procedure, baseline MAP, and baseline HR (Table 1).

Hemodynamics

SP and SI were associated with a significantly higher increase in MAP in Group CO than in Group SB, 1, 3, and 5 minutes after the event of interest [mean difference (MD)=20.5, 19.3, and 14.5 mmHg at SP and 20.4, 16.6, and 14.5 mmHg at SI; within-between interaction (WBI) $p<0.0001$ for SP and SI; group SME at t+1, t+3, and t+5: p at least<0.001 for all time points at SP and SI]. At CR, MAP was globally significantly higher in Group CO than in Group SB [MD=8.9, 8.4, 7.9, and 6.1 mmHg at t0, t+1, t+3, and t+5; group ME p=0.0014], with no significant change over time. This was not the case at the time of DM, where no significant between-group difference in MAP could be observed (group ME p=0.0136).

Similarly, HR increased slightly but significantly higher in Group CO than in Group SB at SP and SI (MD=7.6, 6.8, and 4.2 $b.min^{-1}$ at t+1, t+3, and t+5 at SP, and 7.1, 5.2, and 3.1 $b.min^{-1}$ at SI; WBI: p=0.0021 and <0.0001 at SP and SI; group SME at t+3 and t+5: p=0.0052 and 0.017 at SP, and p=0.0074 and 0.0492 at SI), but not at CR and DM.

Anesthetic agents

Propofol Ce was significantly higher in Group CO than in Group SB during SP at t+5 (MD=0.3 $\mu g.mL^{-1}$). During SI, CR, and DM, propofol Ce was globally significantly higher in Group CO than in Group SB (MD between 0.2 and 0.3 $\mu g.mL^{-1}$). All studied noxious events necessitated significantly higher remifentanil Ce in Group CO than in Group SB (SP: MD=1.0, 1.3, and 1.3 $ng.mL^{-1}$ at t+1, t+3, and t+5; SI: MD=1.0, 1.5, 1.6, and 1.5 $ng.mL^{-1}$ at t0, t+1, t+3, and t+5; CR and DM: MD between 1.1 and 1.3 $ng.mL^{-1}$) (Figure 2B). SP and SI triggered a significant increase in remifentanil Ce after t0 in Group CO (from 2.7 to 3.8, and from 3.4 to 4.0 $ng.mL^{-1}$ at SP and SI). The overall consumption rate of propofol and remifentanil were both significantly higher in Group CO than in Group SB (MD=0.02 $mg.Kg^{-1}.min^{-1}$ and 0.05 $\mu g.Kg^{-1}.min^{-1}$) (Table 1).

Entropy

SE was globally significantly higher in Group CO than in Group SB during SP and SI (MD=1.0, 4.8, 5.7, and 2.7 at t0, t+1, t+3, and t+5 during SP; MD=2.2, 5.2, 5.6, and 3.9 at t0, t+1, t+3, and t+5 during SI), but the difference was not clinically relevant (less than 10 units) (Figure 2C). No between-group statistically significant difference in SE was found at CR and DM.

Vasoactive medications

Only 7 patients received ephedrine, in the amount of 6 mg in total, 3 in Group CO and 4 in Group SB. Four patients received 1 mg nicardipine, 3 in Group CO and 1 in Group SB. No patient received atropine.

Postoperative pain scores and morphine consumption

Pain VAS was significantly globally higher in Group CO than in Group SB during the postoperative period (MD=3, 3, 2, 2, and 2 at H1, H3, H6, H24, and H48; group ME: $p<0.0001$) (Figure 3). The cumulative morphine consumption was significantly higher in Group CO than in Group SB at H48 postoperative (MD=12 mg; $t_{(48)}=4.89$, $p<0.001$).

Discussion

The main findings of our study are that a complementary approach to general anesthesia with a loco-regional technique provides good intraoperative hemodynamic stability during elective supra-tentorial craniotomies, allows sparing hypnotic and anti-nociceptive anesthetic agent consumption, and improves pain control during the first postoperative 48 hours as compared to placebo.

In the absence of regional anesthesia, strategies to control hemodynamic variations in response to noxious stimulation usually involve deepening of anesthesia through an increase in opioid and/or hypnotic anesthetic agent concentrations [16], or the use of cardio- and vasoactive medications [17,18]. Hemodynamic control then may occur at the cost of too deep anesthesia or episodes of hypotension/bradycardia. Too deep anesthesia may have deleterious consequences on patient outcome, as cumulative deep hypnotic time is known to be linked to increased postoperative morbidity and mortality [19–21], and as high remifentanil concentrations may lead to tolerance [22], postoperative hyperalgesia [23], and chronic pain [24]. We observed only a few hypotension episodes requiring the administration of vasoactive medications in both groups, and no alarming bradycardia. The same was observed for hypertension episodes, with very few administrations of nicardipine. Hence, good hemodynamic control was achieved in both groups, although with less anesthetic agents in Group SB. SB can therefore be seen as an efficient add-on to general anesthesia for controlling the 'hyper' side of hemodynamic variations.

Other authors have already demonstrated a beneficial effect of SB at controlling hemodynamic variations during skull pin fixation [15,25,26] and skin incision [27]. In our study, we looked at other potentially noxious events than SP and SI. Not surprisingly, it appears that the most intense noxious stimuli were SP and SI. Both events required a substantial increase in propofol and remifentanil concentrations in Group CO after the initiation of noxious stimulation, but not in Group SB. Despite these increases, the blood pressure response to the stimulus was not abolished in Group CO, while HR remained reasonably stable. Later on during surgery, CR and DM did not require any increase in anesthetic agent concentrations in each of the studied group, but, overall, these concentrations were

significantly higher in Group CO than in Group SB. This probably means that craniotomy and dura-mater incision do not add relevant noxious intensity to the underlying one when surgery has started. We are confident that our results are not linked to inadequate depth of anesthesia in Group CO. By guiding propofol administration with SE, comparable and recommended depths of the hypnotic component of anesthesia were achieved in both groups (SE between 40 and 60). Although SE was significantly higher in Group CO than in Group SB in some instances, the observed mean difference was never higher than 6 units, which is not clinically relevant. In Group CO, MAP and HR were higher (maximum mean difference of 20 mmHg and 7 b.min-1) but moderately, and hemodynamic control was still acceptable. Hence, at comparable depth of the hypnotic component of anesthesia, SB is efficient at providing anti-nociception and hemodynamic control, while moderately reducing the needed amount of anesthetic agents, and particularly the one of remifentanil (1 $ng.mL^{-1}$ Ce reduction) as compared to propofol (0.1 to 0.3 $\mu g.mL^{-1}$ Ce reduction). The overall mean difference in remifentanil rate was 0.05 $\mu g.Kg^{-1}.min^{-1}$, which is not huge but substantial. In both groups, remifentanil rate was much lower than the 0.2 $\mu g.Kg^{-1}.min^{-1}$ recommendation to avoid hyperalgesia [28].

SB has also beneficial postoperative effects. Our study clearly demonstrates lower pain scores (in the range of 2 to 3 units) and lower morphine consumption in Group SB during the first 48 postoperative hours (12 mg less cumulative morphine). As already shown by others, this has the potential of reducing postoperative nausea and vomiting [29] and surgical stress response [27]. We did not study those endpoints specifically. Our nausea and vomiting prevention was efficient in both groups. One may object that, due to the remifentanil very short half-life and our shy preemptive analgesic administration at the end of the procedure (paracetamol only), patients of Group CO were exposed to the risk of high immediate postoperative pain, and that we were actually comparing an intervention (SB) with almost nothing. However, post-craniotomy pain is deemed to be of moderate intensity [30] and all patients were equipped with a morphine PCA, allowing them to titrate analgesic administration themselves. As shown in Figure 3, immediate postoperative mean VAS was 5 in Group

CO, which corresponds to moderate intensity pain. Hence, while paracetamol alone led to moderate immediate postoperative pain, SB and paracetamol provided much better pain scores without the need of other medications. Other postoperative analgesic regimens may probably also be equally efficient at relieving patients without side effects. Interestingly, the beneficial effect of SB in terms of postoperative analgesia was observed up to 48 hours after surgery, although the duration of the block itself is estimated to be of at least 6 hours when levobupivacaine is used without epinephrine [31]. A beneficial effect of skin local anesthesia on early postoperative pain has already been shown by others [32], but we are not aware of studies demonstrating an analgesic effect up to 2 days after surgery. This long lasting effect could be related to a preemptive control of nociception, an immunomodulatory effect, and/or a prevention of central sensitization. This has already been advocated by others, and can also probably be achieved using other techniques such as multimodal analgesia [28,33,34]. An eventual beneficial effect of SB on chronic post-craniotomy headaches should be the object of a specifically designed study.

Our choice of using levobupivacaine was guided by its relatively short onset time as compared to ropivacaine, long effect duration as compared to lidocaine, and advantageous security profile as compared to racemic bupivacaine [35]. Differential advantages of one local anesthetic agent over others would merit dedicated studies.

Our study has limitations. First, patient installation, location of skull pins, and scalp territories concerned by incision were highly variable. SB might have not covered the entire region of surgical aggression and this may have introduced bias. However, we are confident in achieving the largest possible sensory scalp block through our modified Pinosky technique [15]. As compared to the original technique, we additionally targeted the zygomatico-temporal nerve, and the third occipital nerves. Therefore, all known sensory nerve branches of the scalp were blocked [36]. Second, our results were obtained in a patient population of variable age, physical characteristics, and co-morbidities, all of them undergoing supratentorial craniotomies and receiving total IV anesthesia. They should be transposed to specific patient populations, to other types of craniotomies, and to other types of general

anesthesia techniques with caution. Third, one may question whether guiding propofol administration using SE, and remifentanil administration using MAP and HR might have introduced bias. SE is known as a reliable tool to assess the depth of the hypnotic component of anesthesia, and guide hypnotic agent administration, including during intracranial neurosurgery. The gold-standard for guiding anti-nociception administration has long been HR and blood pressure, even if more recent monitors of the autonomic nervous system have been proposed. Although not perfect, the advantage of using specific parameters to guide a pharmacodynamic component of anesthesia is the possibility of overcoming pharmacokinetic inter-individual variability to achieve comparable effects. Insofar as propofol and opioids display strong interactions, using SE only for guiding anesthetic agents' administration would have exposed to the risk of achieving the same SE value with highly variable propofol and remifentanil combinations [37]. In that case, the propofol and remifentanil sparing effect of SB could have been missed. The same is true if we had used hemodynamic parameters only to guide anesthetic agents' administration. Fourth, our study was powered to detect a significant within-between interaction, not for several other outcomes, time points of interest, and between-group post-hoc comparisons. We may therefore have missed some significant effects. However, our significant results are strong and allow drawing meaningful conclusions. Fifth, we did not measure levobupivacaine plasma concentrations in our patients, to rule out the risk of toxicity with our SB technique. Thirty mL (100 mg) of 0.33% levobupivacaine in adult patients is within the usually recommended dose range (between 1 and 2.5 $mg.Kg^{-1}$ [12,38–40]), and the risk of toxicity was low.

Conclusions

Considering the ease of execution and the safety of the technique, SB can be proposed as a complement to routine total IV general anesthesia for intraoperative hemodynamic control, opioid sparing, and postoperative pain control optimization. However, our study does not bring any evidence of a more favorable clinical outcome when using SB as compared to other anesthetic techniques.

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Tables

Table 1: Demographic characteristics of Group CO and Group SB.

	Group SB (n=30)	Group CO (n=30)	Statistics
Gender [male/female, n (% males)]	13/17 (43)	13/17 (43)	Abs. diff. (%): 0
ASA score [I/II/III, n (% total)]	3/25/2 (10/83/7)	7/23/0 (23/77/0)	Abs. diff. (%): -13/6/7
Type of surgery [supratentorial mass lesion/ aneurysm clipping/ arteriovenous malformation, n (% total)]	25/4/1 (83/13/4)	28/2/0 (93/7/0)	Abs. diff. (%): -10/6/4
Age [years; mean (range)]	57 (22-78)	57 (30-78)	St. diff.: -0.02
Body mass index [$Kg.m^{-2}$; mean (range)]	26 (19-34)	27 (19-35)	St. diff.: -0.14
Baseline MAP [mmHg; mean (range)]	72 (53-92)	76 (61-119)	St. diff.: -0.40
Baseline HR [$b.min^{-1}$; mean (range)]	59 (46-76)	60 (42-82)	St. diff.: -0.04
Delay between SB and SP [minutes; mean (range, SD)]	23 (13-45; 7)	25 (15-40; 7)	$t_{(58)}$=1.22 p=0.23 Mean diff.=2.2 (95% CI: -1.4 – 5.8)
Length of anesthesia [minutes; mean (range, SD)]	194 (104-306; 54)	190 (115-447; 77)	Mann-Whitney U=296 p=0.34 Median diff.=15.0 (95% CI: -15.0 – 49.0)
Propo consumption [$mg.Kg^{-1}.min^{-1}$; mean (range, SD)]	0.09 (0.06-0.12; 0.02)	0.11 (0.07-0.15; 0.02)	$t_{(49)}$=3.67 p<0.001 Mean diff.=-0.02 (95% CI: -0.03 - -0.01)
Remi consumption [$\mu g.Kg^{-1}.min^{-1}$; mean (range, SD)]	0.09 (0.06-0.12; 0.02)	0.13 (0.11-0.16; 0.01)	$t_{(49)}$=10.25 p<0.001 Mean diff.=-0.05 (95% CI: -0.05 - -0.04)

Footnote: ASA score=American Society of Anesthesiology physical status score; Abs. diff.=absolute difference; St. diff.=standardized difference (mean difference/pooled standard deviation); Mean. diff.=mean difference; Median diff.=median difference; 95% CI=95% confidence interval; $t_{(df)}$=two-tailed unpaired t test with degrees of freedom; Baseline MAP or HR=mean arterial blood pressure or

heart rate at the time of the performance of SB; SB=scalp block performance; SP=skull-pin insertion; Propo consumption=overall propofol consumption during the procedure; Remi consumption=overall remifentanil consumption during the procedure.

Legend of figures

Figure 1: CONSORT flow chart of patient enrollment, group allocation, follow-up, and data analysis.

Figure 2: Intraoperative hemodynamic parameters [mean arterial blood pressure (MAP) and heart rate (HR); A], propofol and remifentanil effect-site concentrations (Propo and Remi Ce; B) and state entropy (SE; C) at the noxious events of interest. Numerical data [mean(SD)] are provided in the tables below each graph. In those tables, N indicates the sample size in each group according to the intention-to-treat approach. t0, t+1, t+3, and t+5=0, 1, 3, and 5 minutes after the noxious event of interest; SP=skull-pin insertion; SI=surgical skin incision; CR=bone flap removal; DM=dura-mater incision; Diff. (99% CI) and Diff. (95% CI)=between-group mean difference (SB – CO) and 99 or 95% confidence interval. Results of statistical analysis (two-way mixed design ANOVA and Tukey's HSD for post-hoc comparisons) are summarized in the tables by symbols: *=significantly lower in Group SB than in Group CO, when considering a single time point; **=globally significantly lower in Group SB than in Group CO; +=significantly higher than at t0 in a single group; †=globally significantly higher than at t0, both groups pooled. For the sake of clarity, only pertinent statistical results are provided. Complete statistical results can be found in Appendix 1.

Figure 3: Visual analogue pain scores (VAS) and cumulative morphine consumption (mg) at postoperative hour 1, 3, 6, 24, and 48 (H1, H3, H6, H24, and H48). Numerical data [mean(SD)] are provided in the tables below each graph. Results of statistical analysis (two-way mixed design ANOVA and Tukey's HSD for post-hoc comparisons) are summarized in the tables by symbols: *=significantly lower in Group SB than in Group CO at H48; **=globally significantly lower in Group SB than in Group CO. For the sake of clarity, only pertinent statistical results are provided. Complete statistical results can be found in Appendix 1.

Figure 1

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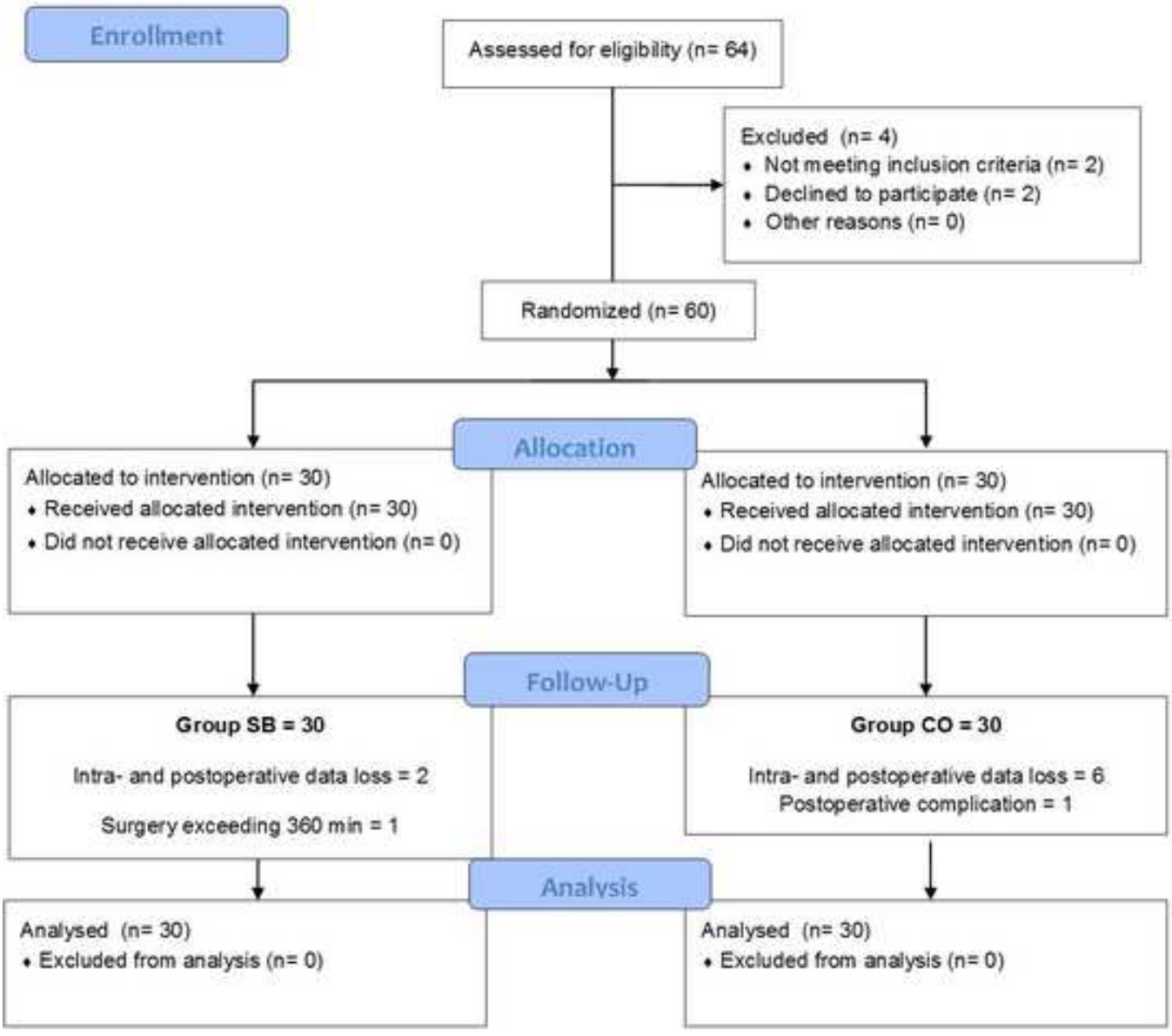

Figure 2A

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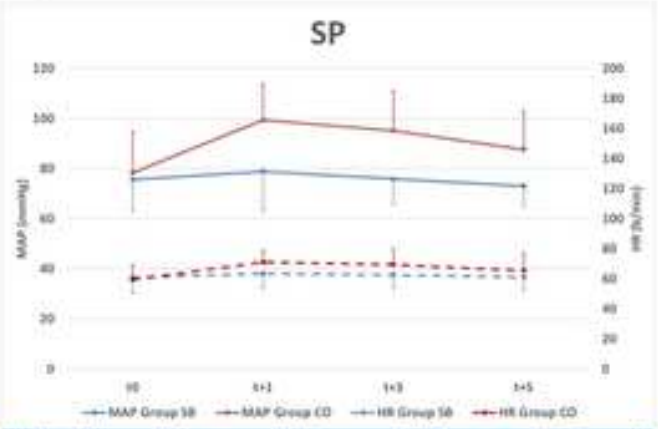
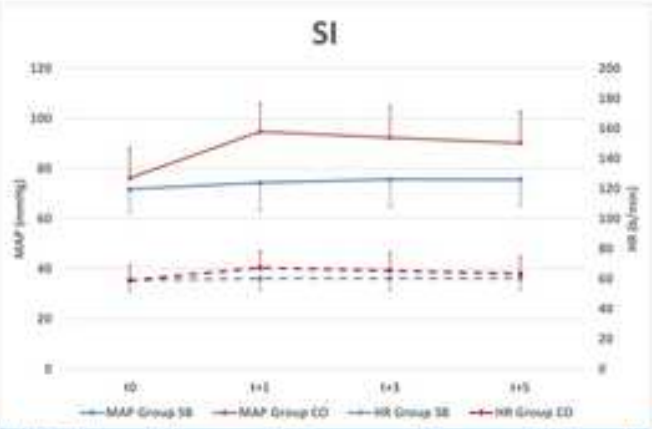
A) Hemodynamics

SP



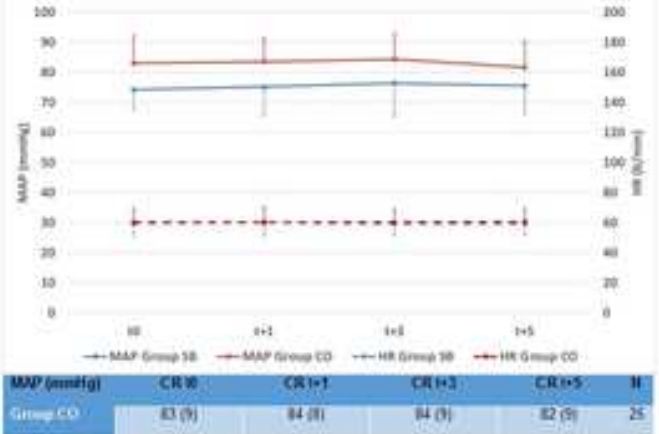
MAP (mmHg)	SP t0	SP t+1	SP t+3	SP t+5	N
Group CO	78 (16)	99 (14)+	95 (16)+	88 (15)+	26
Group SB	76 (13)	79 (16)*	76 (10)*	73 (8)*	28
Diff. (95% CI)	-2.8 (-13.3; 7.7)	-20.5 (-31.4; -9.6)	-19.3 (-28.9; -9.6)	-14.5 (-23.4; -5.6)	
HR (b min⁻¹)	SP t0	SP t+1	SP t+3	SP t+5	N
Group CO	59 (9)	71 (8)+	69 (11)+	66 (11)+	26
Group SB	61 (10)	63 (10)*	63 (9)*	61 (9)	28
Diff. (95% CI)	1.4 (-4.0; 6.8)	-7.6 (-12.6; -2.6)	-6.8 (-12.3; -1.4)	-4.2 (-9.9; 1.4)	

SI



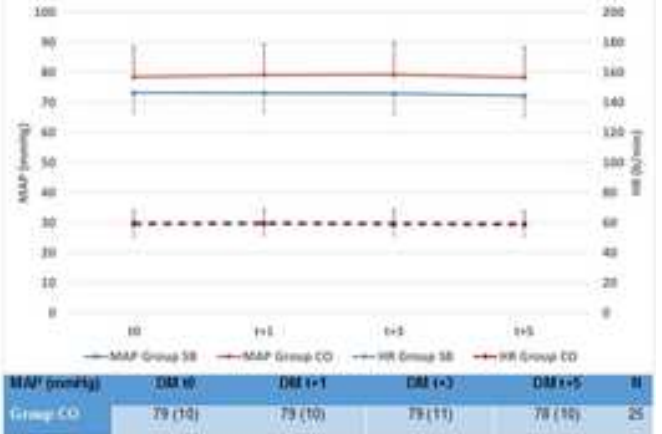
MAP (mmHg)	SI t0	SI t+1	SI t+3	SI t+5	N
Group CO	76 (12)	95 (11)+	92 (12)+	90 (13)+	25
Group SB	72 (10)	74 (11)*	76 (11)*	76 (11)*	28
Diff. (95% CI)	-4.4 (-12.4; 3.5)	-20.4 (-28.6; -12.1)	-16.6 (-25.3; -7.9)	-14.5 (-23.0; -6.0)	
HR (b min⁻¹)	SI t0	SI t+1	SI t+3	SI t+5	N
Group CO	59 (10)	67 (11)+	65 (11)+	63 (12)+	25
Group SB	59 (8)	60 (8)*	60 (8)*	60 (8)	28
Diff. (95% CI)	0.2 (-4.7; 5.2)	-7.1 (-12.4; -1.8)	-5.2 (-10.6; 0.2)	-3.1 (-8.5; 2.4)	

CR



MAP (mmHg)	CR t0	CR t+1	CR t+3	CR t+5	N
Group CO	83 (9)	84 (8)	84 (9)	82 (9)	25
Group SB**	74 (6)	75 (10)	76 (11)	76 (9)	27
Diff. (95% CI)	-8.9 (-14.7; -3.0)	-8.4 (-15.9; -1.0)	-7.9 (-15.3; -0.5)	-6.1 (-12.9; 0.7)	
HR (b min⁻¹)	CR t0	CR t+1	CR t+3	CR t+5	N
Group CO	60 (9)	60 (10)	60 (9)	60 (9)	25
Group SB	60 (9)	60 (9)	60 (9)	61 (9)	27
Diff. (95% CI)	-0.5 (-5.5; 4.6)	0.1 (-5.3; 5.5)	0.7 (-4.3; 5.7)	1.1 (-4.1; 6.2)	

DM



MAP (mmHg)	DM t0	DM t+1	DM t+3	DM t+5	N
Group CO	79 (10)	79 (10)	79 (11)	78 (10)	25
Group SB	73 (7)	73 (6)	73 (7)	72 (7)	27
Diff. (95% CI)	-5.3 (-11.6 – 1.0)	-6.0 (-12.3 – 0.2)	-6.2 (-13.0 – 0.5)	-6.1 (-12.5 – 0.3)	
HR (b min⁻¹)	DM t0	DM t+1	DM t+3	DM t+5	N
Group CO	59 (9)	59 (10)	59 (10)	59 (9)	25
Group SB	60 (10)	60 (9)	60 (9)	60 (9)	27
Diff. (95% CI)	1.5 (-3.8; 6.8)	1.3 (-4.0; 6.7)	1.6 (-3.7; 6.9)	1.3 (-3.7; 6.4)	

Figure 2B

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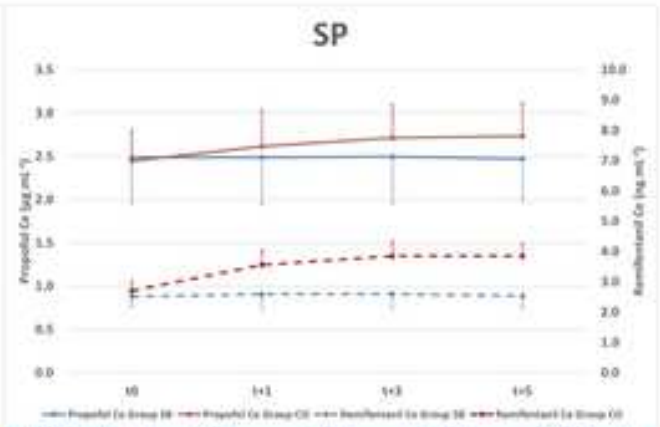
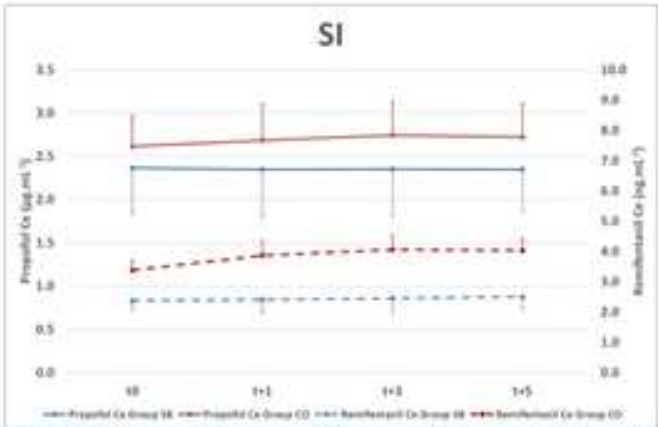
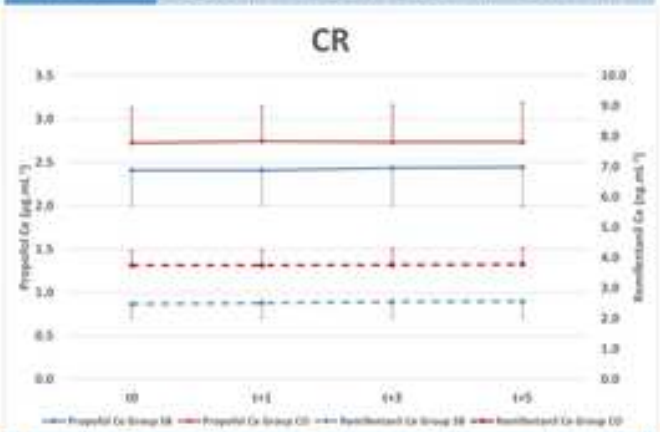
B) Propo and remi Ce



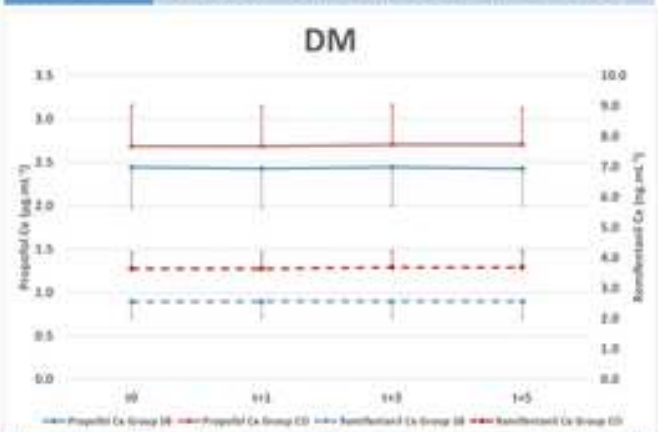
Propo Ce (µg mL⁻¹)	SP t0	SP t+1	SP t+3	SP t+5	N
Group CO	2.4 (0.4)	2.5 (0.4)+	2.7 (0.4)+	2.7 (0.4)+	26
Group SB	2.5 (0.5)	2.5 (0.5)	2.5 (0.5)	2.5 (0.5)*	28
Diff. (95% CI)	0.0 (-0.2; 0.3)	-0.1 (-0.4; 0.1)	-0.2 (-0.5; 0.0)	-0.3 (-0.5; 0.0)	
Remi Ce (ng mL⁻¹)	**SP t0**	**SP t+1**	**SP t+3**	**SP t+5**	**N**
Group CO	2.7 (0.5)	3.6 (0.5)+	3.8 (0.5)+	3.8 (0.5)+	26
Group SB	2.5 (0.3)	2.6 (0.5)*	2.6 (0.5)*	2.5 (0.4)*	28
Diff. (95% CI)	-0.2 (-0.4; 0.0)	-1.0 (-1.2; -0.7)	-1.3 (-1.5; -1.0)	-1.3 (-1.6; -1.1)	



Propo Ce (µg mL⁻¹)	SI t0	SI t+1	SI t+3	SI t+5	N
Group CO	2.6 (0.4)	2.7 (0.4)	2.7 (0.5)	2.7 (0.5)	25
Group SB**	2.4 (0.4)	2.3 (0.4)	2.4 (0.4)	2.3 (0.4)	26
Diff. (95% CI)	-0.2 (-0.5; 0.0)	-0.3 (-0.6; -0.1)	-0.4 (-0.6; -0.1)	-0.4 (-0.6; -0.1)	
Remi Ce (ng mL⁻¹)	**SI t0**	**SI t+1**	**SI t+3**	**SI t+5**	**N**
Group CO	3.4 (0.6)	3.9 (0.5)+	4.1 (0.6)+	4.0 (0.6)+	25
Group SB	2.4 (0.4)*	2.4 (0.5)*	2.5 (0.5)*	2.5 (0.5)*	26
Diff. (95% CI)	-1.0 (-1.3; -0.7)	-1.5 (-1.7; -1.2)	-1.6 (-1.9; -1.3)	-1.5 (-1.8; -1.2)	



Propo Ce (µg mL⁻¹)	CR t0	CR t+1	CR t+3	CR t+5	N
Group CO	2.7 (0.5)	2.7 (0.5)	2.7 (0.5)	2.7 (0.5)	25
Group SB**	2.4 (0.4)	2.4 (0.4)	2.4 (0.4)	2.4 (0.5)	27
Diff. (95% CI)	-0.3 (-0.6; -0.1)	-0.3 (-0.6; -0.1)	-0.3 (-0.5; 0.0)	-0.3 (-0.5; 0.0)	
Remi Ce (ng mL⁻¹)	**CR t0**	**CR t+1**	**CR t+3**	**CR t+5**	**N**
Group CO	3.7 (0.6)	3.7 (0.5)	3.8 (0.5)	3.8 (0.5)	25
Group SB**	2.5 (0.5)	2.5 (0.5)	2.5 (0.5)	2.6 (0.5)	27
Diff. (95% CI)	-1.3 (-1.6; -1.0)	-1.2 (-1.5; -0.9)	-1.2 (-1.5; -0.9)	-1.2 (-1.5; -0.9)	



Propo Ce (µg mL⁻¹)	DM t0	DM t+1	DM t+3	DM t+5	N
Group CO	2.7 (0.4)	2.7 (0.4)	2.7 (0.4)	2.7 (0.4)	25
Group SB**	2.4 (0.5)	2.4 (0.5)	2.4 (0.5)	2.4 (0.4)	27
Diff. (95% CI)	-0.2 (-0.5; 0.0)	-0.3 (-0.5; 0.0)	-0.3 (-0.5; 0.0)	-0.3 (-0.5; 0.0)	
Remi Ce (ng mL⁻¹)	**DM t0**	**DM t+1**	**DM t+3**	**DM t+5**	**N**
Group CO	3.6 (0.7)	3.6 (0.7)	3.7 (0.7)	3.7 (0.7)	25
Group SB**	2.6 (0.5)	2.6 (0.5)	2.6 (0.5)	2.6 (0.5)	27
Diff. (95% CI)	-1.1 (-1.4; -0.8)	-1.1 (-1.4; -0.7)	-1.1 (-1.5; -0.8)	-1.1 (-1.5; -0.8)	

Figure 2C

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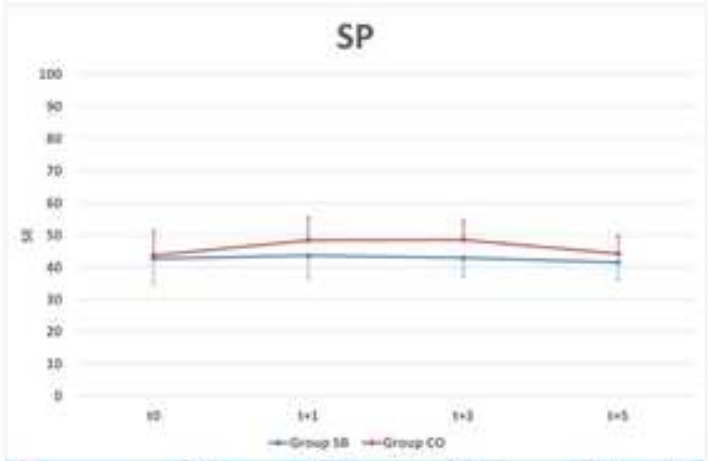
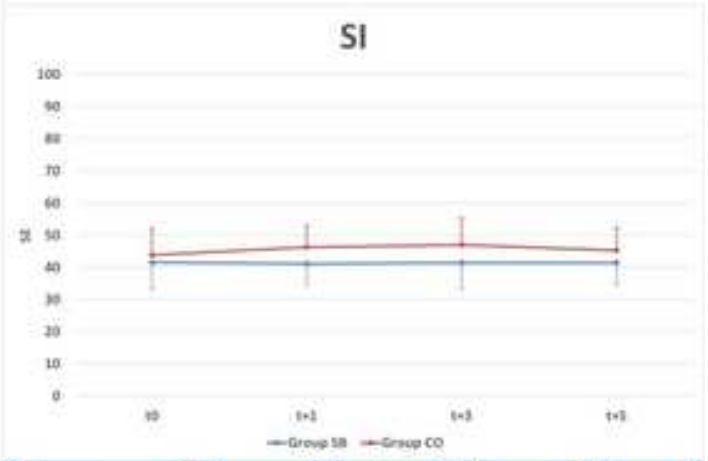
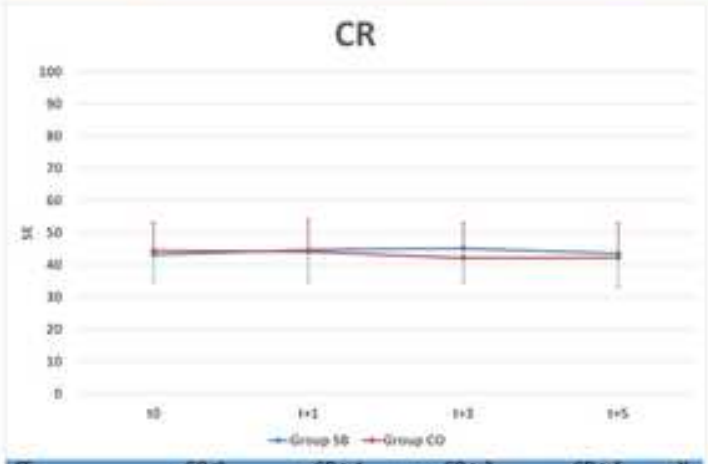
C) SE



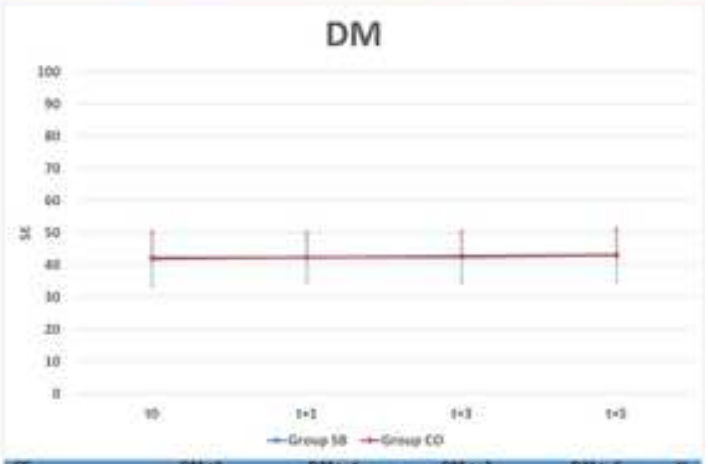
SE	SP t0	SP t+1	SP t+3	SP t+5	N
Group CO	44 (5)	48 (7)†	49 (7) †	44 (4)	25
Group SB**	43 (8)	44 (7) †	43 (6) †	42 (6)	26
Diff. (95% CI)	-1.0 (-4.7; 2.6)	-4.8 (-8.9; -0.8)	-5.7 (-9.2; -2.1)	-2.7 (-5.5; 0.2)	



SE	SI t0	SI t+1	SI t+3	SI t+5	N
Group CO	44 (7)	46 (6)	47 (7)+	45 (7)	25
Group SB**	42 (8)	41 (7)*	41 (8)*	41 (7)*	26
Diff. (95% CI)	-2.2 (-6.6; 2.1)	-5.2 (-8.6; -1.8)	-5.6 (-9.7; -1.4)	-3.9 (-7.6; -0.1)	



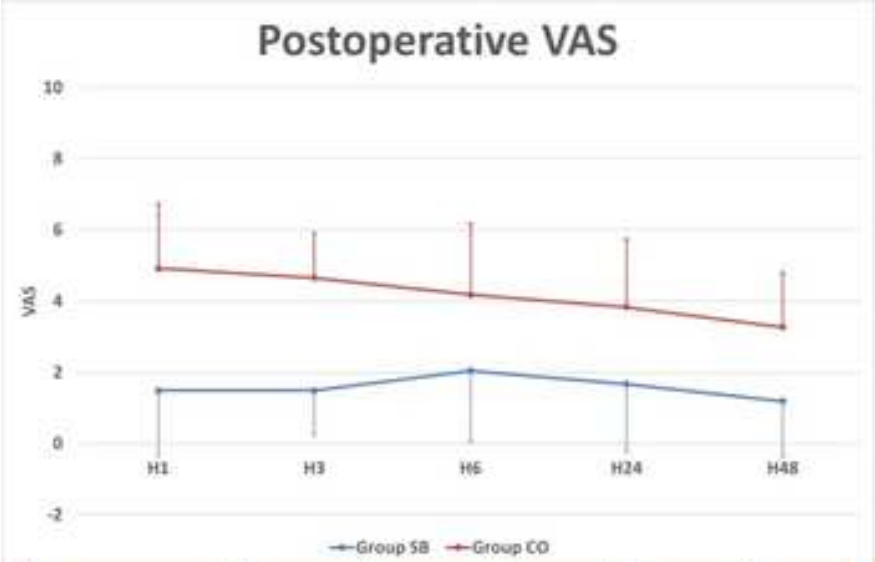
SE	CR t0	CR t+1	CR t+3	CR t+5	N
Group CO	44 (6)	44 (5)	42 (4)	42 (5)	25
Group SB	43 (9)	45 (10)	45 (11)	44 (11)	27
Diff. (95% CI)	-1.3 (-5.4; 2.8)	0.5 (-3.9; 4.9)	3.0 (-1.6; 7.5)	1.2 (-3.3; 5.8)	



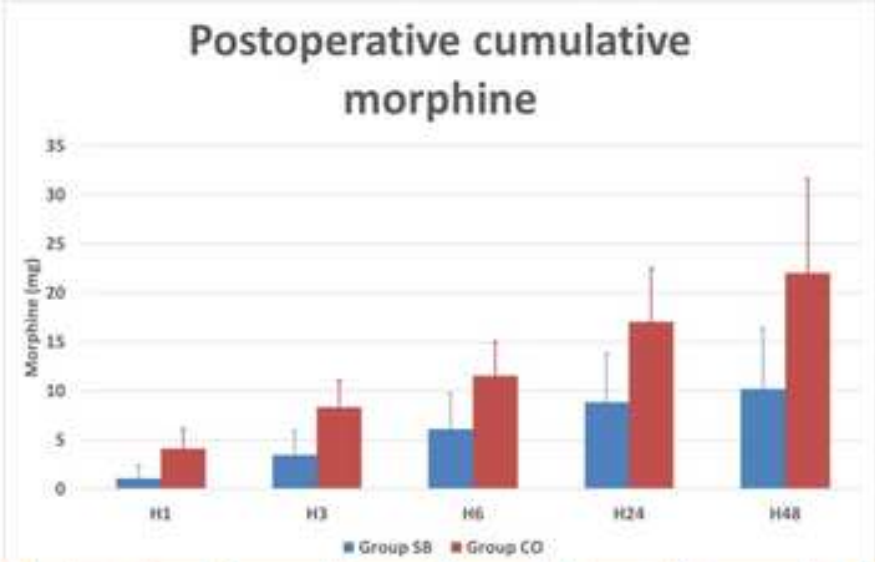
SE	DM t0	DM t+1	DM t+3	DM t+5	N
Group CO	42 (5)	42 (5)	42 (5)	43 (6)	25
Group SB	42 (9)	42 (8)	43 (8)	43 (8)	27
Diff. (95% CI)	0.3 (-3.5; 4.2)	-0.1 (-3.7; 3.6)	0.3 (-3.5; 4.2)	0.2 (-3.8; 4.1)	

Figure 3

Click here to access/download;Figure;figure3_corrected.jpg



VAS	H1	H3	H6	H24	H48	N
Group CO	5 (2)	5 (2)	4 (2)	4 (2)	3 (2)	23
Group SB**	1 (2)	1 (1)	2 (2)	2 (2)	1 (2)	27
Diff. (95% CI)	-3 (-5; -2)	-3 (-4; -2)	-2 (-3; -1)	-2 (-3; -1)	-2 (-3; -1)	



Morphine (mg)	H1	H3	H6	H24	H48	N
Group CO	4 (2)	8 (3)	12 (3)	17 (5)	22 (10)	23
Group SB	1 (1)	3 (2)	6 (4)	9 (5)	10 (6)*	27
Diff. (95% CI)					-12 (-16; -7)	

Appendix 1: Complete results of the two-way mixed design ANOVA's and Tukey's HSD tests for post-hoc comparisons.

Part I: Intraoperative data.

A = group effect, B = time effect, AB = interaction between group and time, a1 = Group SB, a2 = Group CO, b1 = t0, b2 = t1, b3 = t3, b4 = t5. AB11 = Group SB at t0, etc …

MAP = mean arterial pressure, HR = heart rate, Ce propo = propofol effect-site concentration, Ce remi = remifentanil effect site concentration, SE = State Entropy of the electroencephalogram.

aov = ANOVA, simple a at b = simple main effect of Group at Time, etc …, hsd a at b1 = Tukey's HSD tests of Group at t0, etc …

SP = skull pin insertion, SI = skin incision, CR = craniotomy, DM = dura-mater incision.

Source = source of variance, SS = sum of squares, df = degrees of freedom, Epsilon = Huynh and Feldt epsilon, Corrected df = corrected degrees of freedom when the assumption of sphericity was not met, MS = mean square, F = F value.

Statistically significant results are highlighted in bold. The P threshold for statistical significance was set at 0.01 for the primary endpoint (MAP) and 0.05 for the other variables.

Results:

MAP at SP
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	10989.4240	1		1.0000	10989.4240	20.0917	<0.0001
B	4698.4510	3	0.7210	2.1630	2172.1919	22.4393	<0.0001
AB	**2645.6910**	**3**		**2.1630**	**1223.1581**	**12.6356**	**<0.0001**
S/A	28442.1130	52		52.0000	546.9637		
BxS/A	10887.9940	156		112.4760	96.8028		
Total	57435.0370	215		169.8020			

simple a at b

Source	SS	df	MS	F	p
A at b1	103.7950	1	103.7950	0.5489	0.4596
A at b2	**5679.2680**	**1**	**5679.2680**	**30.0352**	**< 0.0001**
A at b3	**5001.4370**	**1**	**5001.4370**	**26.4505**	**< 0.0001**
A at b4	**2850.6150**	**1**	**2850.6150**	**15.0757**	**0.0001**
Pooled	39330.1070	208	189.0870		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	P
B at a1	453.7190	3	0.7210	2.1630	209.7638	2.1669	0.1193
B at a2	**6890.4230**	**3**		**2.1630**	**3185.5862**	**32.9080**	**<0.0001**
BxS/A	10887.9940	156		112.4760	96.8028		

hsd b at a2
Tukey's HSD test on k=4 means with df=156
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	P	SE
AB21 vs AB22	**12.8200**	**156**	**<0.01**	**1.6384**
AB21 vs AB23	**10.2600**		**<0.01**	**1.6384**
AB21 vs AB24	**5.6300**		**<0.01**	**1.6384**
AB22 vs AB23	2.5600		> 0.05	1.6384
AB22 vs AB24	**7.1800**		**<0.01**	**1.6384**
AB23 vs AB24	**4.6200**		**<0.01**	**1.6384**

MAP at SI
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	10340.9860	1		1.0000	10340.9860	25.3182	<0.0001
B	3925.3970	3	0.7180	2.1540	1822.3756	37.4653	<0.0001
AB	**1835.3210**	**3**		**2.1540**	**852.0525**	**17.5169**	**<0.0001**
S/A	20830.4670	51		51.0000	408.4405		
BxS/A	5343.4900	153		109.8540	48.6417		
Total	41998.2030	211		166.1620			

simple a at b

Source	SS	df	MS	F	p
A at b1	261.0390	1	261.0390	2.0345	0.1553
A at b2	**5474.1510**	**1**	**5474.1510**	**42.6655**	**< 0.0001**
A at b3	**3657.6600**	**1**	**3657.6600**	**28.5078**	**< 0.0001**
A at b4	**2783.4570**	**1**	**2783.4570**	**21.6942**	**< 0.0001**
Pooled	26173.9570	204	128.3040		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	274.2920	3	0.7180	2.1540	127.3408	2.6179	0.0775
B at a2	**5486.4260**	**3**		**2.1540**	**2547.0873**	**52.3642**	**<0.0001**
BxS/A	5343.4900	153		109.8540	48.6417		

hsd b at a2
Tukey's HSD test on k=4 means with df=153
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**15.6700**	**153**	**< 0.01**	**1.1819**
AB21 vs AB23	**13.6700**		**< 0.01**	**1.1819**
AB21 vs AB24	**11.8400**		**< 0.01**	**1.1819**
AB22 vs AB23	2.0000		> 0.05	1.1819
AB22 vs AB24	3.8200		< 0.05	1.1819
AB23 vs AB24	1.8300		> 0.05	1.1819

MAP at CR
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**3165.6030**	**1**		**1.0000**	**3165.6030**	**11.3948**	**0.0014**

B	110.4180	3	0.751	2.2530	49.0093	2.4880	0.0877
AB	57.1870	3		2.2530	25.3826	1.2886	0.2797
S/A	13890.5700	50		50.0000	277.8114		
BxS/A	2219.0240	150		112.6500	19.6984		
Total	19441.6730	207		168.1560			

MAP at DM
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	1819.9450	1		1.0000	1819.9450	6.5429	0.0136
B	22.6640	3	0.6330	1.8990	11.9347	1.1046	0.2960
AB	7.0490	3		1.8990	3.7120	0.3435	0.5592
S/A	13907.6850	50		50.0000	278.1537		
BxS/A	1025.9180	150		94.9500	10.8048		
Total	16783.3800	207		149.7480			

HR at SP
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	1000.9800	1		1.0000	1000.9800	3.1273	0.0829
B	1596.9120	3	0.6380	1.9140	834.3323	23.9481	<0.0001
AB	**667.2260**	**3**		**1.9140**	**348.6029**	**10.0061**	**0.0021**
S/A	16644.0200	52		52.0000	320.0773		
BxS/A	3467.4770	156		99.5280	34.8392		
Total	23304.5000	215		156.3560			

simple a at b

Source	SS	df	MS	F	p
A at b1	26.3620	1	26.3620	0.2726	0.6021
A at b2	**772.8470**	**1**	**772.8470**	**7.9930**	**0.0052**
A at b3	**625.8040**	**1**	**625.8040**	**6.4723**	**0.0117**
A at b4	243.1950	1	243.1950	2.5152	0.1143
Pooled	20111.4970	208	96.6900		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	117.9200	3	0.6380	1.9140	61.6092	1.7684	0.1866
B at a2	**2146.2180**	**3**		**1.9140**	**1121.3260**	**32.1857**	**<0.0001**
BxS/A	3467.4770	156		99.5280	34.8392		

hsd b at a2
Tukey's HSD test on k=4 means with df=156
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**12.5200**	**156**	**< 0.01**	**0.9246**
AB21 vs AB23	**10.7700**		**< 0.01**	**0.9246**
AB21 vs AB24	**6.5300**		**< 0.01**	**0.9246**

AB22 vs AB23	1.7500		> 0.05	0.9246
AB22 vs AB24	**5.9900**		**< 0.01**	**0.9246**
AB23 vs AB24	**4.2400**		**< 0.05**	**0.9246**

HR at SI
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	754.1460	1		1.0000	754.1460	2.2767	0.1375
B	685.9560	3	0.7100	2.1300	322.0451	21.1817	<0.0001
AB	**391.3900**	**3**		**2.1300**	**183.7512**	**12.0858**	**<0.0001**
S/A	16893.4300	51		51.0000	331.2437		
BxS/A	1651.6000	153		108.6300	15.2039		
Total	20321.8250	211		164.8900			

simple a at b

Source	SS	df	MS	F	p
A at b1	0.7340	1	0.7340	0.0081	0.9285
A at b2	**665.2570**	**1**	**665.2570**	**7.3180**	**0.0074**
A at b3	**355.7600**	**1**	**355.7600**	**3.9135**	**0.0492**
A at b4	123.7860	1	123.7860	1.3617	0.2446
Pooled	18545.0300	204	90.9070		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	26.5750	3	0.7100	2.1300	12.4765	0.8206	0.4429
B at a2	**1050.7710**	**3**		**2.1300**	**493.3197**	**32.4469**	**<0.0001**
BxS/A	1651.6000	153		108.6300	15.2039		

hsd b at a2
Tukey's HSD test on k=4 means with df=153
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**12.8400**	**153**	**< 0.01**	**0.6571**
AB21 vs AB23	**10.1000**		**< 0.01**	**0.6571**
AB21 vs AB24	**6.7600**		**< 0.01**	**0.6571**
AB22 vs AB23	2.7400		> 0.05	0.6571
AB22 vs AB24	**6.0900**		**< 0.01**	**0.6571**
AB23 vs AB24	3.3500		> 0.05	0.6571

HR at CR
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	6.2270	1		1.0000	6.2270	0.0187	0.8918
B	4.5540	3	0.9790	2.9370	1.5506	0.6423	0.5276
AB	17.0930	3		2.9370	5.8199	2.4107	0.0933
S/A	16670.5190	50		50.0000	333.4104		
BxS/A	354.5270	150		146.8500	2.4142		

Total	17053.4950	207		203.7240			

HR at DM
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	107.7780	1		1.0000	107.7780	0.3084	0.5812
B	8.1490	3	0.8860	2.6580	3.0658	1.9397	0.1478
AB	0.7650	3		2.6580	0.2878	0.1821	0.8337
S/A	17474.7410	50		50.0000	349.4948		
BxS/A	210.0620	150		132.9000	1.5806		
Total	17801.5190	207		189.2160			

Ce propo at SP
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	1.0730	1		1.0000	1.0730	1.3722	0.2468
B	0.6650	3	0.5380	1.6140	0.4120	8.2412	0.0052
AB	**0.7130**	**3**		**1.6140**	**0.4418**	**8.8360**	**0.0039**
S/A	40.6610	52		52.0000	0.7819		
BxS/A	4.1960	156		83.9280	0.0500		
Total	47.2590	215		140.1560			

simple a at b

Source	SS	df	MS	F	p
A at b1	0.0210	1	0.0210	0.0972	0.7555
A at b2	0.2130	1	0.2130	0.9861	0.3218
A at b3	0.6450	1	0.6450	2.9861	0.0855
A at b4	**0.9070**	**1**	**0.9070**	**4.1991**	**0.0417**
Pooled	44.8570	208	0.2160		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	0.0065	3	0.5380	1.6140	0.0040	0.0810	0.7767
B at a2	**1.3709**	**3**		**1.6140**	**0.8494**	**16.9878**	**0.0001**
BxS/A	4.1963	156		83.9280	0.0500		

hsd b at a2
Tukey's HSD test on k=4 means with df=156
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**5.1400**	**156**	**< 0.01**	**0.0322**
AB21 vs AB23	**8.2500**		**< 0.01**	**0.0322**
AB21 vs AB24	**8.8500**		**< 0.01**	**0.0322**
AB22 vs AB23	3.1100		> 0.05	0.0322
AB22 vs AB24	**3.7100**		**< 0.05**	**0.0322**
AB23 vs AB24	0.6000		> 0.05	0.0322

Ce propo at SI
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**5.9760**	**1**		**1.0000**	**5.9760**	**8.6962**	**0.0048**
B	0.1020	3	0.6260	1.8780	0.0543	1.8151	0.1811
AB	0.1550	3		1.8780	0.0825	2.7582	0.1001
S/A	35.0470	51		51.0000	0.6872		
BxS/A	2.8660	153		95.7780	0.0299		
Total	44.1330	211		151.5340			

Ce propo at CR
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**4.9850**	**1**		**1.0000**	**4.9850**	**6.4276**	**0.0144**
B	0.0150	3	0.5270	1.5810	0.0095	1.1346	0.2900
AB	0.0180	3		1.5810	0.0114	1.3616	0.2468
S/A	38.7780	50		50.0000	0.7756		
BxS/A	0.6610	150		79.0500	0.0084		
Total	44.4580	207		133.2120			

Ce propo at DM
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**3.4780**	**1**		**1.0000**	**3.4780**	**4.5136**	**0.0386**
B	0.0100	3	0.5850	1.7550	0.0057	0.5841	0.4468
AB	0.0100	3		1.7550	0.0057	0.5841	0.4468
S/A	38.5280	50		50.0000	0.7706		
BxS/A	0.8560	150		87.7500	0.0098		
Total	42.8810	207		142.2600			

Ce remi at SP
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	46.8560	1		1.0000	46.8560	72.0052	<0.0001
B	13.1950	3	0.7650	2.2950	5.7495	63.5315	<0.0001
AB	**10.7420**	**3**		**2.2950**	**4.6806**	**51.7207**	**<0.0001**
S/A	33.8380	52		52.0000	0.6507		
BxS/A	10.8000	156		119.3400	0.0905		
Total	114.5860	215		176.9300			

simple a at b

Source	SS	df	MS	F	p
A at b1	0.5010	1	0.5010	2.3302	0.1284
A at b2	**12.6430**	**1**	**12.6430**	**58.8047**	**< 0.0001**
A at b3	**21.1760**	**1**	**21.1760**	**98.4930**	**< 0.0001**
A at b4	**23.2770**	**1**	**23.2770**	**108.2651**	**< 0.0001**
Pooled	44.6380	208	0.2150		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	0.1460	3	0.7650	2.2950	0.0636	0.7030	0.4972
B at a2	**23.7910**	**3**		**2.2950**	**10.3664**	**114.5493**	**<0.0001**
BxS/A	10.8000	156		119.3400	0.0905		

hsd b at a2
Tukey's HSD test on k=4 means with df=156
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**16.6200**	**156**	**< 0.01**	**0.0516**
AB21 vs AB23	**22.2100**		**< 0.01**	**0.0516**
AB21 vs AB24	**22.2100**		**< 0.01**	**0.0516**
AB22 vs AB23	**5.5900**		**< 0.01**	**0.0516**
AB22 vs AB24	**5.5900**		**< 0.01**	**0.0516**
AB23 vs AB24	< 0.0001		> 0.05	0.0516

Ce remi at SI
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	103.0140	1		1.0000	103.0140	114.0971	<0.0001
B	5.1750	3	0.6810	2.0430	2.5330	30.9589	<0.0001
AB	**2.9650**	**3**		**2.0430**	**1.4513**	**17.7378**	**<0.0001**
S/A	46.0460	51		51.0000	0.9029		
BxS/A	8.5250	153		104.1930	0.0818		
Total	165.3150	211		160.2790			

simple a at b

Source	SS	df	MS	F	p
A at b1	**13.1400**	**1**	**13.1400**	**49.0299**	**< 0.0001**
A at b2	**27.9110**	**1**	**27.9110**	**104.1455**	**< 0.0001**
A at b3	**34.2350**	**1**	**34.2350**	**127.7425**	**< 0.0001**
A at b4	**30.6930**	**1**	**30.6930**	**114.5261**	**< 0.0001**
Pooled	54.5710	204	0.2680		

simple b at a

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	p
B at a1	0.2253	3	0.6810	2.0430	0.1103	1.3479	0.2643
B at a2	**7.9147**	**3**		**2.0430**	**3.8741**	**47.3464**	**<0.0001**
BxS/A	8.5255	153		104.1930	0.0818		

hsd b at a2
Tukey's HSD test on k=4 means with df=153
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
AB21 vs AB22	**10.4200**	**153**	**< 0.01**	**0.0472**

AB21 vs AB23	**14.4900**		**< 0.01**	**0.0472**
AB21 vs AB24	**13.8100**		**< 0.01**	**0.0472**
AB22 vs AB23	**4.0700**		**< 0.05**	**0.0472**
AB22 vs AB24	3.3900		> 0.05	0.0472
AB23 vs AB24	0.6800		> 0.05	0.0472

Ce remi at CR
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**79.3040**	**1**		**1.0000**	**79.3040**	**74.0757**	**<0.0001**
B	0.1050	3	0.5410	1.6230	0.0647	2.7530	0.1009
AB	0.0290	3		1.6230	0.0179	0.7604	0.3858
S/A	53.5290	50		50.0000	1.0706		
BxS/A	1.9070	150		81.1500	0.0235		
Total	134.8780	207		135.3960			

Ce remi at DM
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**63.1230**	**1**		**1.0000**	**63.1230**	**43.8756**	**<0.0001**
B	0.0250	3	0.3540	1.0620	0.0235	1.2639	0.2660
AB	0.0170	3		1.0620	0.0160	0.8595	0.3581
S/A	71.9340	50		50.0000	1.4387		
BxS/A	0.9890	150		53.1000	0.0186		
Total	136.0870	207		106.2240			

SE at SP
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**641.7850**	**1**		**1.0000**	**641.7850**	**6.6247**	**0.0131**
B	**414.4730**	**3**	**0.9860**	**2.9580**	**140.1193**	**6.7864**	**0.0015**
AB	169.4730	3		2.9580	57.2931	2.7749	0.0657
S/A	4747.0100	49		49.0000	96.8778		
BxS/A	2992.6350	147		144.9420	20.6471		
Total	8956.2940	203		200.8580			

hsd b
Tukey's HSD test on k=4 means with df=147
Critical values are: q(.05)=3.68 and q(.01)=4.5

Comparison pair	q	df	p	SE
B1 vs B2	**4.4700**	**147**	**p < 0.05**	**SE = 0.6318**
B1 vs B3	**4.0400**		**p < 0.05**	**SE = 0.6318**
B1 vs B4	0.4700		p > 0.05	SE = 0.6318
B2 vs B3	0.4200		p > 0.05	SE = 0.6318
B2 vs B4	**4.9400**		**p < 0.01**	**SE = 0.6318**
B3 vs B4	**4.5200**		**p < 0.01**	**SE = 0.6318**

SE at SI

aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**939.0700**	**1**		**1.0000**	**939.0700**	**5.7610**	**0.0201**
B	68.9680	3	0.9530	2.8590	24.1231	1.7324	0.1805
AB	90.2510	3		2.8590	31.5673	2.2670	0.1073
S/A	8313.2410	51		51.0000	163.0047		
BxS/A	2030.3060	153		145.8090	13.9244		
Total	11433.5610	211		203.5270			

SE at CR
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	38.3690	1		1.0000	38.3690	0.1863	0.6679
B	57.1560	3	0.8290	2.4870	22.9819	1.2729	0.2837
AB	122.3490	3		2.4870	49.1954	2.7247	0.0695
S/A	10296.6450	50		50.0000	205.9329		
BxS/A	2245.1560	150		124.3500	18.0551		
Total	12758.2640	207		180.3240			

SE at DM
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	2.1000	1		1.0000	2.1000	0.0139	0.9068
B	28.5290	3	0.8350	2.5050	11.3888	0.7858	0.4580
AB	1.4130	3		2.5050	0.5641	0.0389	0.9618
S/A	7580.6070	50		50.0000	151.6121		
BxS/A	1815.2840	150		125.2500	14.4933		
Total	9427.9570	207		181.2600			

Part II: Postoperative data.

A = group effect, B = time effect, AB = interaction between group and time, a1 = Group SB, a2 = Group CO, b1 = H1, b2 = H3, b3 = H6, b4 = H24, b5 = H48. AB11 = Group SB at H1, etc …

VAS = visual analogue pain score.

aov = ANOVA, simple a at b = simple main effect of Group at Time, etc …, hsd a at b1 = Tukey's HSD tests of Group at H1, etc …

Source = source of variance, SS = sum of squares, df = degrees of freedom, Epsilon = Huynh and Feldt epsilon, Corrected df = corrected degrees of freedom when the assumption of sphericity was not met, MS = mean square, F = F value.

Statistically significant results are highlighted in bold. The P threshold for statistical significance was set at 0.05.

VAS
aov

Source	SS	df	Epsilon	Corrected df	Corrected MS	F	Corrected p
A	**418.1340**	**1**		**1.0000**	**418.1340**	**106.4507**	**<0.0001**

B	31.5530	4	0.9670	3.8680	8.1574	2.1821	0.0916
AB	21.1210	4		3.8680	5.4604	1.4607	0.2268
S/A	188.5420	48		48.0000	3.9280		
BxS/A	694.0630	192		185.6640	3.7383		
Total	1351.0760	249		242.4000			