A Comparison Between Scalp Nerve Block and Local Anesthetic Infiltration on the Inflammatory Response, Hemodynamic Response, and Postoperative Pain in Patients undergoing Craniotomy for Cerebral Aneurysms: A Randomized Controlled Trial

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Abstract

BACKGROUND:

The purpose of this study was to compare the effects of the scalp nerve block (SNB) and local anesthetic infiltration (LA) with ropivacaine 0.75% on postoperative inflammatory response, intraoperative hemodynamic response, and postoperative pain control in patients undergoing craniotomy.

METHODS:

Fifty seven patients admitted for elective craniotomy for surgical clipping of an cerebral aneurysm. They were randomly divided into three groups: Group S (SNB with 15mL of ropivacaine 0.75%), group I (LA with 15mL of ropivacaine 0.75%) and group C (only received routine intravenous analgesia). The pro-inflammatory cytokines levels in plasma during postoperative 72 hrs, the hemodynamic response to the skin incision, as well as postoperative pain intensity were measured.

RESULTS:

The SNB with 0.75% ropivacaine not only decreased IL-6 level in plasma at 6 hrs after craniotomy, but also decreased plasma CRP level and increased plasma IL-10 level at 12 and 24 hrs after surgery, as compared to LA and routine analgesia. There were significant increases in mean arterial pressure at 2, and 5 mins after the incision and during dura opening in group I and C compared with group S. Group S had a lower postoperative pain intensity, longer duration of time before the first dose of oxycodone, less consumption of oxycodone and lower incidence of PONV during 48 hrs postoperatively than group I and C.

CONCLUSION:

Preoperative SNB attenuated inflammatory response to craniotomy for cerebral aneurysms, as well as blunted hemodynamic response to the scalp incision, and controlled postoperative pain better than LA or routine analgesia.

Background

Moderate to severe postoperative pain after craniotomy has an incidence as high as 80% (1). Uncontrolled postoperative pain may contribute to the rise in intracranial pressure (ICP) as well as hypertension, which may be detrimental, especially for patients with cerebral aneurysms(2).Therefore, postoperative pain control should be a priority for neurosurgical patients.

An increasing number of studies have suggested that the multimodal pain treatment, which combines systemic analgesics and local anesthetics, optimizes pain relief and limits opioids adverse effects(3,4).

For example, scalp nerve block and local anesthetic infiltration of the scalp have been proposed to blunt hemodynamic response to craniotomy, decrease opioid consumption, and reduce postoperative pain perception(5-7). Additionally, both scalp blocks and local anesthetic infiltration were recommended for enhanced recovery after surgery (ERAS) for oncological craniotomies, although the current evidence is not sufficient to create a standardized ERAS protocol for oncological craniotomy (8). However, scalp nerve block or local anesthetic infiltration, which one is more effective for analgesia has not been evaluated in craniotomy for cerebral aneurysms.

Surgery is capable of initiating inflammatory stress response. Surgical stress induces the migration of inflammatory cells that release cytokines, primarily Interleukin(IL)-6, causing a local inflammatory response at injured site. Then, when cytokines subsequently release into human plasma, a systemic inflammation may occur which leads to an increase in C-reacting proteins (CRP), and T- and B-cell activation in the bone marrow and blood (9). Later, compensatory anti-inflammatory cytokines, such as IL-10, are produced that causes a reduction in pro-inflammatory cytokine synthesis(10,11). Accordingly, acute-phase proteins, such as CRP, and cytokines, such as IL-6 and IL-10, are thought to be early measures of inflammatory response induced by surgical trauma. Local anesthetics via a nerve block have been demonstrated to attenuate the local inflammatory response(12). For instance, previous animal experiments have demonstrated that C-fiber blockade may inhibit the peripheral inflammation in the corresponding innervated zone(12,13). Furthermore, in postoperative patients, peripheral nerve blocks have been shown to attenuate the postoperative inflammatory response in knee arthroplasty(14,15). The scalp is densely innervated with C-fibers (unmyelinated) or A-delta fibers (thinly myelinated)(16).

However, as far as we know, no study has attempted to investigate the impacts of the scalp nerve block on inflammatory response in the craniotomies.

Therefore, the goal of this prospective, randomized and controlled study was to compare the impacts of the scalp nerve block and local anesthetic infiltration with ropivacaine 0.75% on postoperative inflammatory response, intraoperative hemodynamic response, as well as pain scores, and oxycodone consumption during the postoperative 48 hrs in patients undergoing craniotomy for cerebral aneurysms.

Methods

Patients

After written informed consent was obtained, 57 adult patients (ASA I or II, aged 18 to 65 years) who were scheduled for an elective craniotomy for surgical clipping of cerebral aneurysm located in the anterior cerebral circulation were included.

We did not enroll patients if they had (1) a difficult surgical anatomy, as well as multiple or giant aneurysms; (2) a previous craniotomy incision; (3) a history of allergy to opioids or local anesthetics; (4) a history of drug dependence and alcohol abuse; or (5) can not understand a visual analog scale (VAS) or

communicate [scheduled to be sedated postoperatively or a GSC (Glasgow coma score) < 14]. The first author (X.Y.) enrolled the patients in the study.

Anesthesia, surgery and postoperative pain relief

The patients included in the current study were anaesthetised by the same anaesthesiologist and operated on by the same surgeon. Patients received 0.03mg/kg IV midazolam as a preanesthetic medication, and prophylaxis of postoperative nausea and vomiting (PONV) was achieved with palonosetron 0.25mg administered in all patients.
Anesthesia and monitoring were standardized for all patients. Electrocardio- graphy, pulse oximetry, non-invasive blood pressure, end-tidal CO2(ETCO2), nasopharyngeal temperature, and bispectral index (BIS) were continuously monitored during anesthesia and were recorded at fixed intervals of 5 min. General anesthesia was induced with propofol 1.5-2.0 mg/kg , sufentanil 0.5-0.8ug/kg. Cis-atracurium 0.2 mg/kg was given to facilitate orotracheal intubation. After intubation, we put the arterial catheter to monitor mean arterial pressure (MAP) and collect blood sample, and an intravenous catheter was placed in the right jugular vein. After intubation，all patient were ventilated mechanically with the tidal volume of 8ml/kg, and the respiratory rate was adjusted according to maintain 35-40mmHg of paCO2 (partial pressure of carbon dioxide in artery). Propofol 4-9 mg/kg/h was infused continuously to maintain anesthesia. The infusion rate of propofol was adjusted to keep the BIS within 40–60. Remifentanil was adjusted according to the degree of surgical manipulation (0.1-0.5 μg/kg/min). If intraoperative MAP and heart rate (HR) increased by more than 20% from baseline, supplemental doses of remifentanil 0.5μg/kg were administered and the infusion rate of remifentanil was increased by 0.05μg/kg/min. If the increased MAP and HR did not respond to higher remifentanil infusion rate, nicardipine or esmolol were given, as appropriate. Considering intraoperative neurophysiologic monitoring, we did not administer additional neuromuscular blocker during the surgery. Normothermia was maintained throughout the case. Volume was replaced by sodium chloride 0.9% and Hydroxyethyl Starch 130/0.4. Patients were extubated after the operation in the post anesthetic care unit (PACU) when awake and in a neurologically stable condition, before being transferred to the neurosurgical intensive care unit (NICU).

All patients were administered oxycodone (0.1mg/kg) at 30mins before the end of surgery. Oxycodone was also used as rescue analgesic during the first 48 hrs postoperatively. Pain was evaluated with visual analogue scale (VAS) scores from 0 to 10 (0 = no pain, 10 = worst pain). If a patient reported a VAS more than 3,

an intravenous injection of oxycodone 2mg was given by a nurse as the rescue analgesia. This dose was administered at 15-minute intervals until VAS was less than 3. Oxycodone consumption during the first 48 postoperative hrs and the time to first rescue requirement were recorded.

Randomization

A randomization list was generated, and patients were assigned consecutively to one of three groups by the third author (R.D.), who was not involved in patient care. The scalp nerve block was performed in the

Group S, the local anesthetic infiltration was performed in the Group I, while patients in Group C only received sufentanil, remifentanil and oxycodone as analgesics during the intraoperative period.

The patients and the second author (J.M.) who followed the hemodynamic response to skin incision, drew the blood samples, as well as recorded postoperative pain scores and rescue analgesic consumptions were blinded in every case.

Scalp nerve block and local anesthetic infiltration

In the group S, the scalp blocks were performed bilaterally with 15mL of 0.75% ropivacaine at 10 mins before the incision by the anesthesiologist using the Pinosky's et al method (17). In the group I, the surgical incision sites were infiltrated with 15 mL of ropivacaine 0.75% at 10 mins before the incision by the neurosurgeon. Neither scalp blocks nor local infiltration was performed in the group C.

Outcome measurements

Patient characteristics, type of aneurysm, duration of anaesthesia and surgery, the total dose of propofol and remifentanil, fluid balance, the number of patients with the use of nicardipine or esmolol were documented.

Plasma levels of CRP, IL-6, and IL-10 were measured pre-, intra- and

postoperative periods, EDTA arterial blood samples were collected to measure the concentrations of CRP, IL-6, and IL-10 in plasma at the following time points: (Baseline) before the induction of anesthesia, (6H) 6 hrs after incision, as well as (12H)12, (24H)24, (48H)48, and (72H)72 hrs postoperatively. After centrifugation, plasma samples were stored at -80 °C until analysis. The detection levels of cytokines and inflammatory mediator in the assays were 0.4ng/mL for CRP, 4 pg/mL for IL-6, and 1 pg/mL for IL-10.

MAP and HR were recorded just before anaesthesia induction(T1), 5 mins after induction(T2), skin incision(T3), 2 mins(T4) and 5 mins(T5) after the incision, during dura opening(T6) and at the end of the surgery(T7).

Postoperative VAS and cumulative oxycodone consumption as well as postoperative pain control related side effects such as postoperative nausea and vomiting (PONV), infection and pruritus were recorded at 2, 4, 8, 12, 24, and 48 hrs after recovery of consciousness. Additionally, the time intervals from patient recovery to the first use of oxycodone and consumption of oxycodone during 48 hrs postoperatively also were recorded.

The primary endpoint of the current study is to compare the effect of the scalp nerve block and local infiltration with ropivacaine 0.75% on postoperative inflammatory response in patients undergoing craniotomy for cerebral aneurysms. The secondary endpoints are to compare the effects of the scalp nerve block and local infiltration on the hemodynamic response to the skin incision, as well as

postoperative pain intensity, cumulative oxycodone consumption and pain control related side effects during the postoperative 48 hrs.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD), the median and interquartile range (IQR, 25–75% percentile) or a number (%). The Kolmogorov–Smirnov method was applied to test the normality and homogeneity of all the variables.

Continuous variables were presented as mean±SD and analysed using One-way ANOVA with the post hoc multiple comparisons (Bonferroni correction) analysis to determine the difference among the groups. Categorical variables were described as numbers (%) and were compared using the chi-square test. Biological data (CRP, IL-6, and IL-10 levels) and hemodynamic data (HR, MAP), were compared among groups and over time using repeated-measures of ANOVA. Non-normally distributed continuous variables, such as pain scores were presented as median and interquartile range (IQR, 25–75 percentile) and were analyzed with nonparametric tests (Kruskal–Wallis test and Mann-Whitney U-test with the Bonferroni correction).

On the basis of previous study (7) and the assumption that a difference of 20% on MAP is clinically relevant, setting α equal to 0.05 and β equal to 0.2, we calculated a sample size of 15 patients per group. Probability values of $P < 0.05$ were considered significant. SPSS statistical software, version 21.0 (SPSS, Inc, Chicago, Illinois, USA) was used for data analysis.

Results

Patient Demographics and Perioperative Characteristics

Fifty-seven patients agreed and were randomized into the study, and 6 patients were excluded from the study after randomization due to unexpected sedation after surgery and delayed extubation (n=5, 1 in group C, 2 in group I and 2 in group S), as well as reoperation(n=1 in group I). Thus, the remaining 51 patients were analyzed (18 in group S, 16 in group I and 17 in group C). The consort diagram showed the flow of participants through each stage of a randomized trial (Figure 1).
Three groups were similar in age, gender, BMI, ASA, type of aneurysm, duration of operation, duration of anesthesia, cumulative dose of propofol, total loss of blood, urine volume and infusion volume. There were significant differences among the study groups (F=205.377; $P<0.001$, Table 1) for the cumulative dose of remifentanil. Patients in group C received a higher cumulative dose of remifentanil (4.59±0.64mg), compared to the group I (3.67±0.38mg) and group S (1.40±0.38mg)($P<0.001$, $P<0.001$, respectively). Patients in group I consumed more remifentanil during the operation than patients in group S ($P<0.001$).

Additionally, 8 patients (47.1%) in group C, 3 patients (18.8%) in group I, and 1 patients (5.6%) in group S used nicardipine during the operation. Nicardipine administration was different among three groups

(*P*=0.017 with fisher's exact test, Table1) and nicardipine was less frequently required in group S than in group C (*P*=0.007, Table 1).

Plasma concentrations of CRP、IL-6, and IL-10

Plasma concentrations of CRP、IL-6, and IL-10 during all time points are displayed in Figures 2. Plasma CRP levels significantly changed with time in three groups (main effect of time: F(3.874, 185.944) = 108.039, P<0.001). In all groups, CRP levels increased during 24 hrs after surgery, reaching maximum values at 24 hrs, and subsequently decreased gradually until 72 hrs after operation (Figure 2A). Additionally, there was no significant interaction between analgesia modal and time on plasma levels of CRP (group-time interaction: F(7.748, 185.944) = 1.43, P =0.069). Although plasma CRP level was not significantly different among the three groups, there was a tendency to lower CRP level in group S, as compared to group C and I at postoperative 12 and 24 hrs (Figure 2A).

The same applied for IL-6 levels, there was a significant difference over time among the three groups in plasma IL-6 values (main effect of time: F(2.238, 107.447) = 303.761, P <0.001). IL-6 values increased during 24 hrs after surgery, reaching peak at 24 hrs and decreased gradually until 72 hrs after operation (Figure 2B). Moreover, there was a significant interaction between analgesia modal and time on plasma levels of IL-6 (group-time interaction: F(4.477, 107.447) =2.47, P=0.043), and patients in Group S had lower IL-6 level at 6 hrs post-operatively compared with those in Group C and I (P=0.001, and P=0.009, respectively) (Figure 2B).

Plasma IL-10 levels significantly changed with time in three groups (main effect of time: F(3.189, 153.067) = 198.014, *P* <0.001). In three groups, IL-10 levels increased during 48 hrs after surgery, reaching maximum values at 12 hrs, and subsequently decreased gradually until 72 hrs after operation (Figure 2C). There was a significant interaction between analgesia modal and time on plasma levels of IL-10 (group-time interaction: F(6.378, 153.067) = 5.107 , *P*<0.01). Furthermore, Patients in Group S had higher IL-10 levels at 12 and 24 hrs post-operatively compared with those in Group C and I (12 hrs: *P*=0.012, and *P*<0.001, 24 hrs: *P*=0.011, and *P*<0.001, respectively) (Figure 2C).

Haemodynamic parameters (HRs and MAPs)

The HRs were significantly lower in the group I and S compared to the group C at T3, T4, T5 and T6 (group-time interaction: F(3.46, 166.075) =86.081, *P*<0.001). Post hoc analysis showed significant differences during skin incision(T3)(*P*=0.03, *P*=0.035, respectively), second (T4)(*P*<0.001, P<0.001, respectively), and fifth min(T5) after incision (P<0.001, P<0.001, respectively) and during dura opening(T6)(P =0.032, P<0.001, respectively).There were no significant differences in HRs between group S and group I at all time points (P>0.05)(Figure 3A).

There were significant differences in MAP among three groups at T3, T4, T5 and T6 (group-time interaction: F(6.995, 167.883) = 24.192, P<0.001). Post hoc analysis showed that the MAPs were significantly lower in the group I and group S compared to the group C during skin incision (T3) (group S vs. group C: P<0.001, group I vs. group C: P<0.001). Additionally, the MAPs in the group S were

significantly lower than those in the group I and group C at second(T4), fifth min(T5) after the incision, and during dura opening(T6)(T4,T5 and T6: group S vs. group I, P<0.001; group S vs. group C, P<0.001). However, there were no significant differences in MAPs between group I and C at T4.T5 and T6 (P>0.05) (Figure 3B).

Postoperative pain scores and oxycodone consumptions

The VAS scores were significantly lower in the Group S than those in the Group C and group I at 2,4,8,12, 24 and 48 hrs postoperatively (*P*<0.001, respectively). However, the group I just had the lower VAS score, compared to group C at 2 hrs after surgery (*P*=0.026) (Figure 4).
The time intervals from patient recovery to the first use of oxycodone in group I and S were significantly longer than those in group C [5.75(3.58-9.28) and 9.85 (7.93-14.83) vs. 1.5(0.8-3.65) hrs, *P*=0.009, and *P*<0.001, respectively]. In addition, the first use of oxycodone in group S was significantly longer than those in group I (*P*=0.018)(Figure 5A).

Oxycodone consumption during 48 postoperative hours was significantly higher in group C and I than those in group S (27±9.6 and 22.06±12.24 vs. 5.01±4.3mg, *P*<0.001, *P*<0.001, respectively). There was no significant difference in oxycodone consumption between group I and C (*P*=0.386)(Figure 5B).

Pain control related adverse events during the study period

Adverse events during 48 hrs after surgery, such as respiration depression, cutaneous pruritus, subcutaneous haematomas, scalp infection, and local anesthetic toxicity were not observed. However, the incidence of PONV was significantly different among the three groups (*P*=0.017, Table 2.). Five patients (29.4%) in group C, 4 patients (25%) in group I and 2 patients (11.1%) in group S suffered from PONV, and PONV occurred less frequently in Group S than Group C (*P*=0.012, Table 2). There were no significantly differences in the incidence of fever and dizziness among groups (*P*=0.721, *P*=0.462, respectively, Table 2).

Discussion

This prospective, randomized and controlled study demonstrated that the scalp nerve block with 0.75% ropivacaine had a modest preventive effect on postoperative inflammation demonstrated by a lower IL-6 concentrations in plasma at 6 hrs after craniotomy for cerebral aneurysms, and reduced CRP level and increased IL-10 level at postoperative 12 and 24 hrs, as well as scalp nerve block blunted hemodynamic response to skin incision better than local anesthetic infiltration or routine anesthesia. Additionally, both the scalp nerve block and local anesthetic infiltration decreased the remifentanil consumption during the operation compared to the control, and scalp nerve block group had a lower postoperative pain intensity, longer duration of time before the first dose of oxycodone, less consumption of oxycodone and lower incidence of PONV during 48 hours postoperatively than local anesthetic infiltration group and control group.

Neurogenic inflammation is a process in which substances released by sensory nerve terminals produce inflammation in their target tissue(18). The main trigger of neurogenic inflammation is the activation of primary afferents giving rise

to dorsal root reflexes in the spinal cord(19). Blocking the nerve through local anesthetics can reduce the release of substances such as substance P and calcitonin gene–related peptide, and block neural transmission at the site of tissue injury, thereby alleviating the neurogenic inflammatory response(20), although the exact mechanisms are still largely unclear.

Therefore, it is possible that in the current study, the reduced concentrations of pro-inflammatory cytokines CRP and IL-6, as well as the increased concentration of anti-inflammatory cytokine IL-10 in plasma, as compared to local anesthetic infiltration and routine analgesia, were related to the local anti-inflammatory effects of scalp nerve block. It is possible that scalp nerve block has a more sufficient deafferentation effect than local anesthesic infiltration to prevent the development of peripheral and systemic inflammation. Again, there is also evidence suggesting that inflammation and pain are related(21). In the current study, patients in scalp nerve block group had a lower postoperative pain intensity, and a longer duration of time before the first dose of oxycodone than patients in local anesthetic infiltration and routine analgesia group, supporting our findings that scalp nerve block inhibited craniotomy-induced inflammation.

Effects of neuraxial blockade with local anesthetics on postoperative inflammatory response was still controversial. For example, a previous study have suggested that a combined continuous lumbar plexus and sciatic nerve blocks with ropivacaine 0.2% contributed to the attenuation of the postoperative inflammatory response, demonstrated by decreased CRP and IL-6 concentrations in plasma at postoperative 24 and 48 hrs (14). Other clinical study using more extensive nerve blocks, such as epidural analgesia, have also indicated attenuated ex vivo pro- inflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10 production after visceral surgery(22). However, Moore and co-workers have found that the circulating CRP and IL-6 response to pelvic surgery was unaffected by extradural analgesia(23). This is in contrast with the present study where the scalp nerve block inhibited CRP and IL-6. Such discrepancies could originate from the technique of nerve block, the type of surgery, and probably the assay used to measure of inflammatory mediator concentration (i.e., ex vivo or in vivo assays).

Of note is that, in our study, scalp nerve block just had an modest anti- inflammatory effects. Previous studies have indicated the impacts of remifentanil on the systemic inflammation. For example, remifentanil have been indicated to reduce plasma IL-6 levels on the seventh day after abdominal surgery(24). It has also been demonstrated to inhibit the exaggerated inflammation after cardiac surgery with cardiopulmonary bypass(25). In the present study, we found that patients in scalp nerve block group consumed less remifentanil during the operation than patients in local anesthetic infiltration group and routine analgesia group. Therefore, remifentanil requirements may be a confounding factor which hampered the interpretation of the effects of different analgesic modalities on the inflammatory response caused by craniotomy. Furthermore, our study might have been underpowered because of the small study

group size, which could also explain the modest anti-inflammatory properties of scalp nerve block. Collectively, our findings suggested a potential anti-inflammatory effect of scalp nerve block with 0.75% ropivacaine, pending further investigations.

Acute increases in MAP and HR could be deleterious for neurosurgical patients with cerebral aneurysm, given that acute arterial hypertension and tachycardia may result in ruptured cerebral aneurysms. In the current study, we found that scalp nerve block blunted hemodynamic response to skin incision and dura opening better than local anesthetic infiltration or routine anesthesia. These results are in line with the study of Geze et al (7), in which scalp nerve block with 0.5% bupivacaine has been shown to be better in blunting the haemodynamic response to strong nociceptive stimulus, such as head pinning, than local infiltration or routine analgesia(7). However, the effects of local infiltration in promoting intraoperative hemodynamic stability in patients undergoing craniotomy have also been reported in the previous studies (26-28). Our study is inconsistent with these studies. The discrepancy may be explained by different local anesthetic (bupivacaine vs. ropivacaine), time point and nociceptive stimulus.

Both scalp nerve block and local infiltration have been demonstrated to reduce the VAS scores and opioid requirements after surgery. For example, Meta-analysis of scalp blocks has demonstrated not only a significant reduction in VAS scores at 2, 4, 6 and 8 hrs after operation, with the most significant mean reduction occurring at 1 hr after surgery, but also decrease opioid requirements over the first 24 hrs postoperatively. However, few studies have compared the effects of scalp nerve block and local infiltration on postoperative pain control. In the current study, we found that scalp nerve block group had a lower postoperative pain intensity, longer duration of time before the first dose of oxycodone, less consumption of oxycodone and lower incidence of PONV during 48 hrs postoperatively than local infiltration group and control group. Our study is consistent with the study of Hwang et al (29) showing that scalp blocks with 0.75% levobupivacaine effectively lowered postoperative pain and PCA consumption in patients undergoing frontoparietal craniotomy for aneurysm clipping at 72 hrs postoperatively as compared to routine analgesia. In our study, the beneficial result of the scalp block seemed to last longer than expected duration of action. This phenomenon could be explained by preemptive analgesia(30), which commences before surgery and continues in the postoperative period, preventing the establishment of peripheral and central sensitization, since we performed the scalp block prior to scalp incision(31).

It is noteworthy that in our study, PONV occurred less frequently in scalp nerve block group than local infiltration group and control group. It is possible that the lower incidence of PONV in scalp nerve block group was related to less intraoperative remifentanil consumption and postoperative oxycodone requirement.

The current studies have several limitations. First, 0.75% ropivacaine (15 mL, 112.5 mg) was used for scalp nerve block and local infiltration, but the plasma concentration was not measured, although the maximum recommended dose of ropivacaine is 225 mg with or without epinephrine(32). Furthermore, in our study, no patient developed side effects related to local anesthetic toxicity. Second, we did not apply

isotonic sodium chloride for scalp nerve block or local infiltration in the control group. Thus, we could not rule out the effects of injection stress. Third, in the present study, we just focused on the effects of different analgesic modality on systemic inflammatory response, but not local inflammatory response at the site of tissue injury. Finally, in the current study, we just evaluated the effect of the ropivacaine scalp block on acute pain after craniotomy (48 hrs postoperatively), but not chronic postcraniotomy headache. These limitations indicate the need for further investigations.

Conclusions

In conclusion, the present study shows that scalp nerve block with 0.75% ropivacaine attenuated inflammatory response to craniotomy for cerebral aneurysms, as well as blunted hemodynamic response to the scalp incision, and control postoperative pain better than local anesthetic infiltration or routine anesthesia. Scalp nerve block should be considered in conjunction with general anaesthesia for aneurysm clipping. Scalp nerve block might exert potential anti-inflammatory effect in neuroanaesthesia, pending further investigations.

Declarations

(1) **Ethics approval and consent to participate**

This study was approved by the research ethics committee of Zhongnan Hospital of Wuhan University (No.2016013) and written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03073889, Principal investigator: Xi Yang, Date of registration: 2017.03.08). The study was conducted at Zhongnan Hospital of Wuhan University, Wuhan, China, between March 2017 and February 2018. The CONSORT recommendations for reporting randomized trials were followed.

(2)Consent for publication:Not Applicable

(3)Availability of data and materials

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

(4)Competing interests: The authors declare no conflict of interest.

(5)Funding

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(6) Authors' contributions

Each author's individual contribution to the manuscript:

1.Xi Yang: This author helped to enroll the patients in the study and test the samples of patients.

2.Jing Ma: This author helped to record the experiment data and gather specimens.

3.Rui Dong: This author helped to group the patients.

4.Yayuan Lu, Lei Chen and Ke Li: These authors helped to analyse the data.

5.Mian Peng and Zongze Zhang: These authors helped to design experiments and write the manuscript.

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Tables

Table 1 Patient Demographics and Perioperative Characteristics

Characteristic	Group C(n=17)	Group I(n=16)	Group S(n=18)	P values
Age (years)	54.41±6.62	55.19±5.94	55.94±5.14	NS
Gender (M/F)	4/13	4/12	6/12	NS
BMI(kg/m^2)	22.48±1.30	22.54±0.80	22.51±0.90	NS
ASA (I/II)	7/10	8/8	8/10	NS
Type of aneurysm (number%)				NS
Middle cerebral artery	11（64.6%）	12（75%）	13（72.2%）	
Anterior communicating artery	2（11.8%）	0	1（5.6%）	
Posterior communicating artery	2（11.8%）	2（12.5%）	3（16.6%）	
Anterior cerebral artery	2（11.8%）	2（12.5%）	1（5.6%）	
Duration of operation (min)	169.41±44.75	161.88±36.69	155.56±40.94	NS
Duration of anesthesia(min)	252.94±42.65	248.44±36.96	240.28±41.53	NS
Total dose of propofol(mg)	1854.65±375.03	1820.88±233.17	1716.33±206.67	NS
Total dose of remifentanil(mg)	4.59±0.64	3.67±0.38	1.40±0.38	0.000*
Total loss of blood(ml)	370.59±161.11	393.75±166.21	305.56±93.76	NS
Urine volume(ml)	1135.29±337.16	1218.75±335.10	1055.56±261.72	NS
Infusion volume(ml)				
Crystalloids(ml)	1361.76±644.58	1468.75±618.30	1147.22±269.24	NS
Colloids(ml)	1161.76±264.30	1109.38±240.98	1111.11±213.90	NS
Number of use of nicardipine(%)	8（47.1%）	3（18.8%）	1（5.6%）	0.017#
Number of use of esmolol(%)	0	0	0	NA

Values are expressed as mean±SD or number of patients(%).

Group C: control group, *Group I*: local anesthesic infiltrationgroup, *Group S:* scalp nerve block group.

The differences among groups were not significant except for the consumption of remifentanil and the use of nicardipine.

#*P*<0.05 for Group I and Group S compared with group C. **P* < 0.05 among three groups.

Abbreviations: ASA = American society of Anaesthesiologists, NA = not applicable, NS = not significant

Table 2 Pain control related adverse events during the study period (48 hrs after surgery)

	GroupC（n=17）	GroupI（n=16）	GroupS（n=18）	P values
Fever	1(5.9%)	2(12.5%)	1(5.6%)	NS
Nausea and Vomit*	5(29.4%)	4(25%)	2(11.1%)	0.017*
Dizziness	1(5.9%)	0	1(5.6%)	NS
Respiration depression	0	0	0	NA
Cutaneous pruritus	0	0	0	NA
Subcutaneous haematomas	0	0	0	NA
Scalp infection	0	0	0	NA
Local anesthetic toxicity	0	0	0	NA

Values are given as number of patients(%).

Group C, control group; *Group I*, local anesthesic infiltration group; *Group S*, scalp nerve block group.

* $P < 0.05$ comparison among three groups.

Abbreviations: NA = not applicable, NS= not significant

Figures

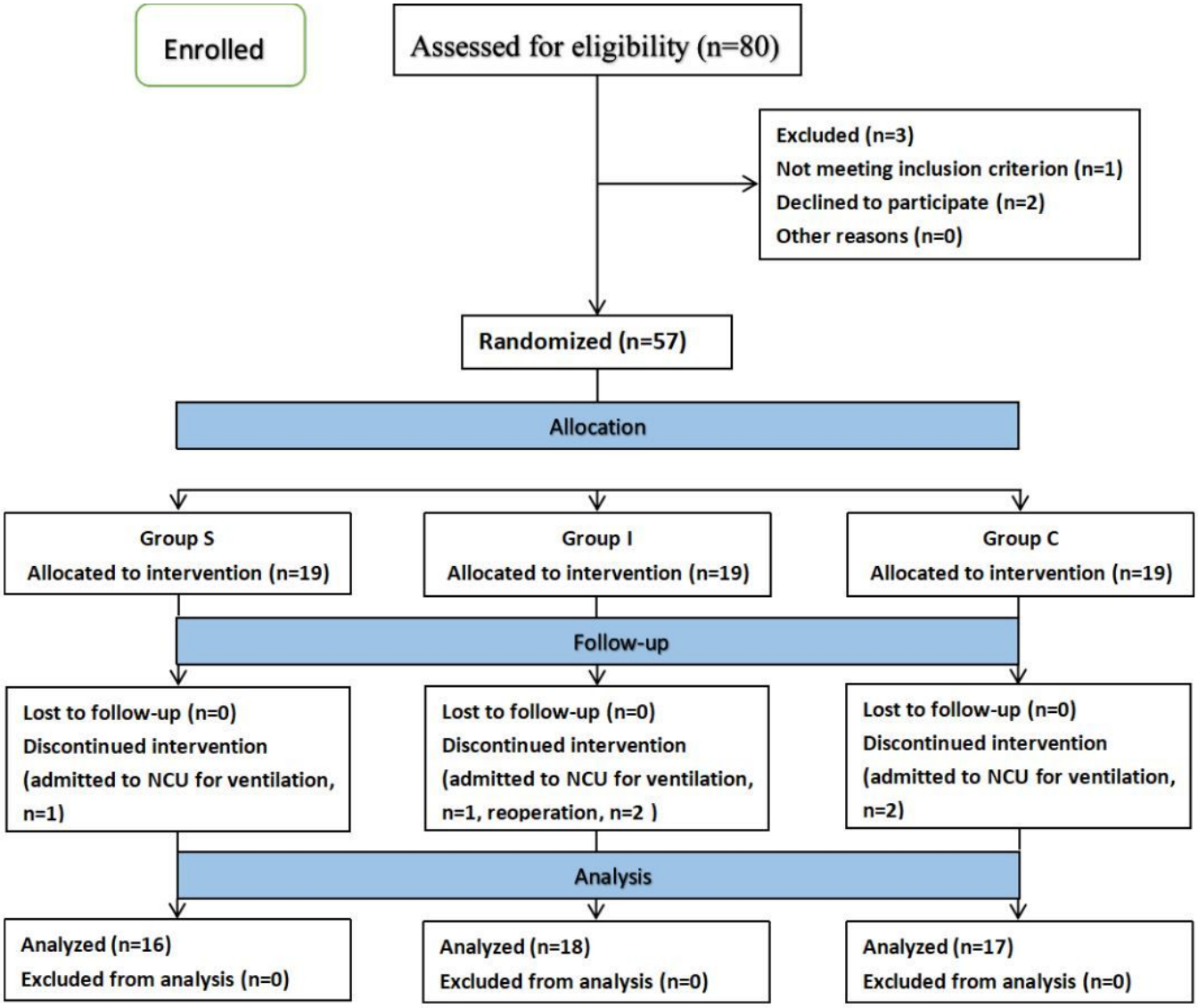

Figure 1

CONSORT flow diagram

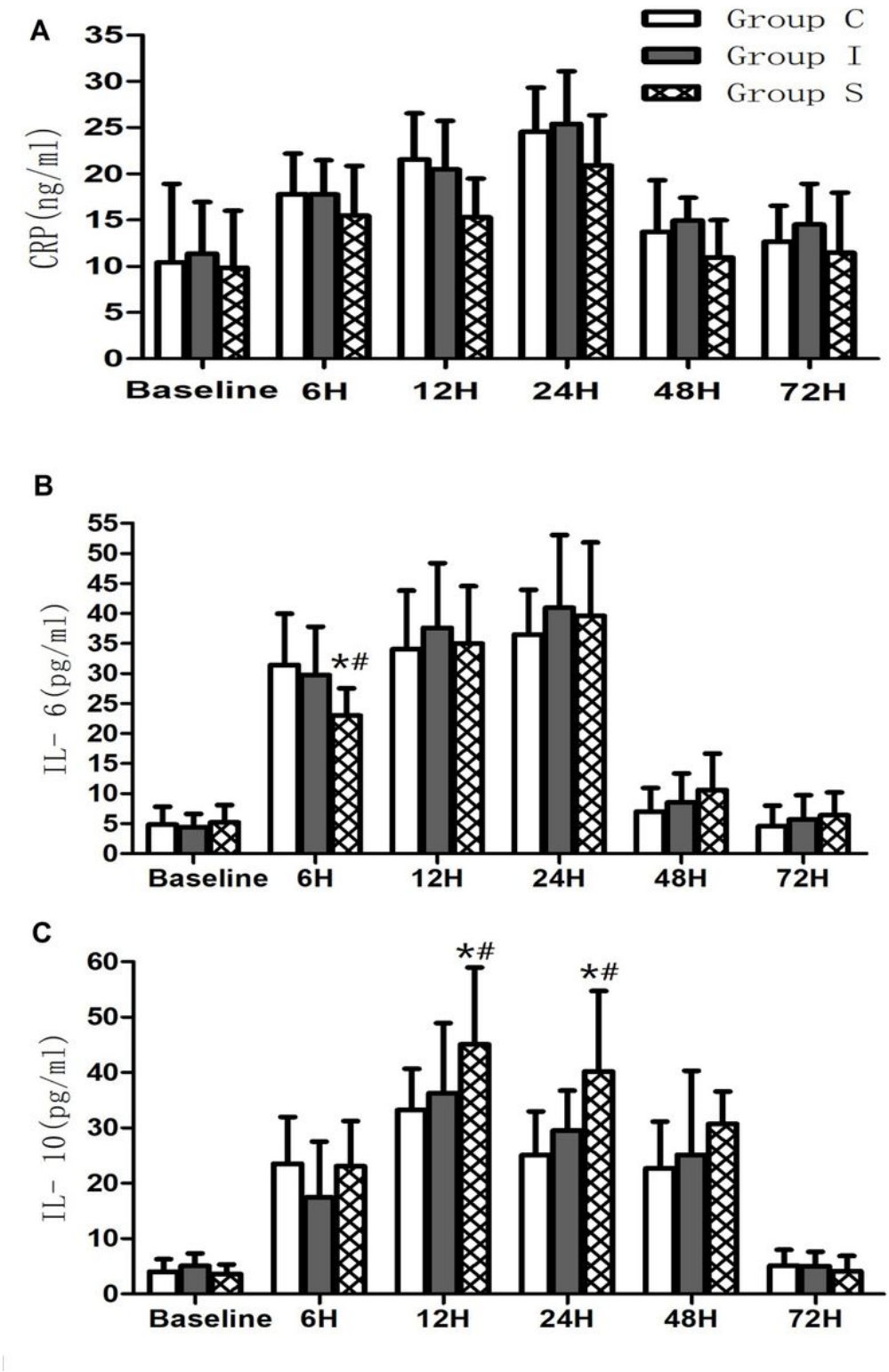

Figure 2

Concentrations of (A) C-reactive protein (CRP), (B) interleukin-6 (IL-6), and (C) interleukin-10 (IL-10), preoperatively (Pre-op), and postoperatively, at 6, 12, 24, 48 and 72 hrs, in the three groups studied. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. *P<0.05, compared to group C, #P<0.001, compared to group I.

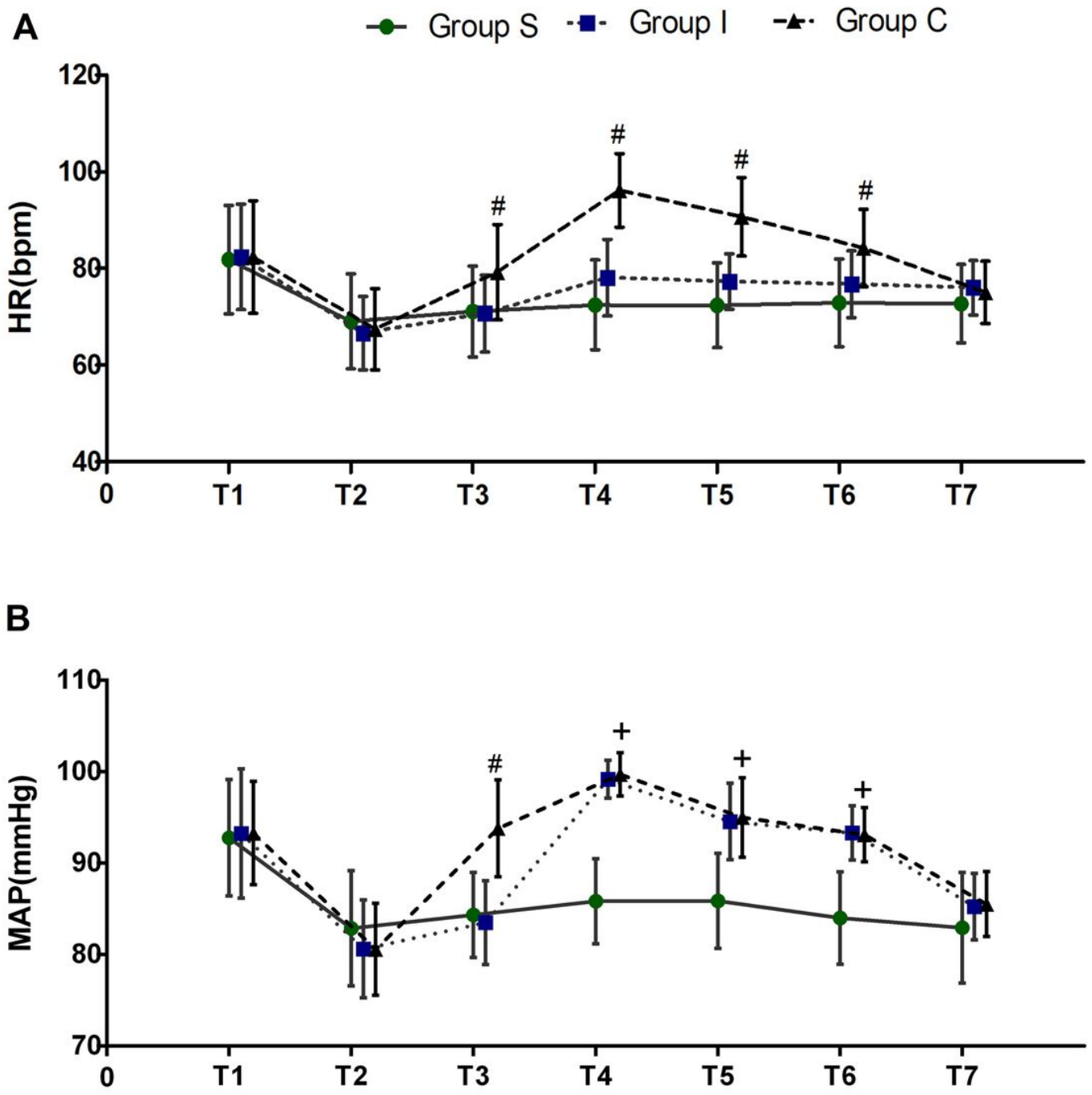

Figure 3

Comparison of HR and MAP changes during surgery. T1: before anaesthesia induction, T2: 5 mins after induction, T3: skin incision, T4: 2 mins after the incision, T5: 5 mins after the incision, T6: during dura opening, and T7: the end of the surgery. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. #P<0.05, for group C compared with group I and S, +P<0.001 for group I and C compared with group S.

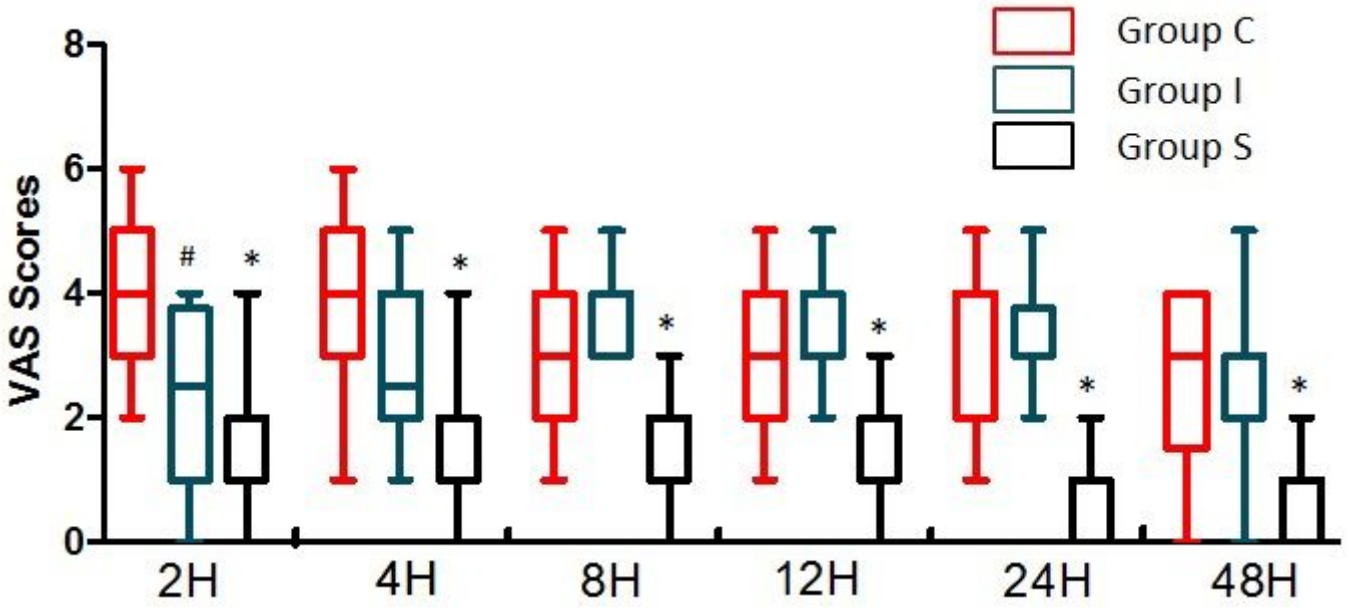

Figure 4

Comparison of VAS scores postoperatively for three groups. Group C: control group, Group I: local anesthesic infiltration group, Group S: scalp nerve block group. #P<0.05, Compared to group C, *P<0.001 for group S compared with group I and C.

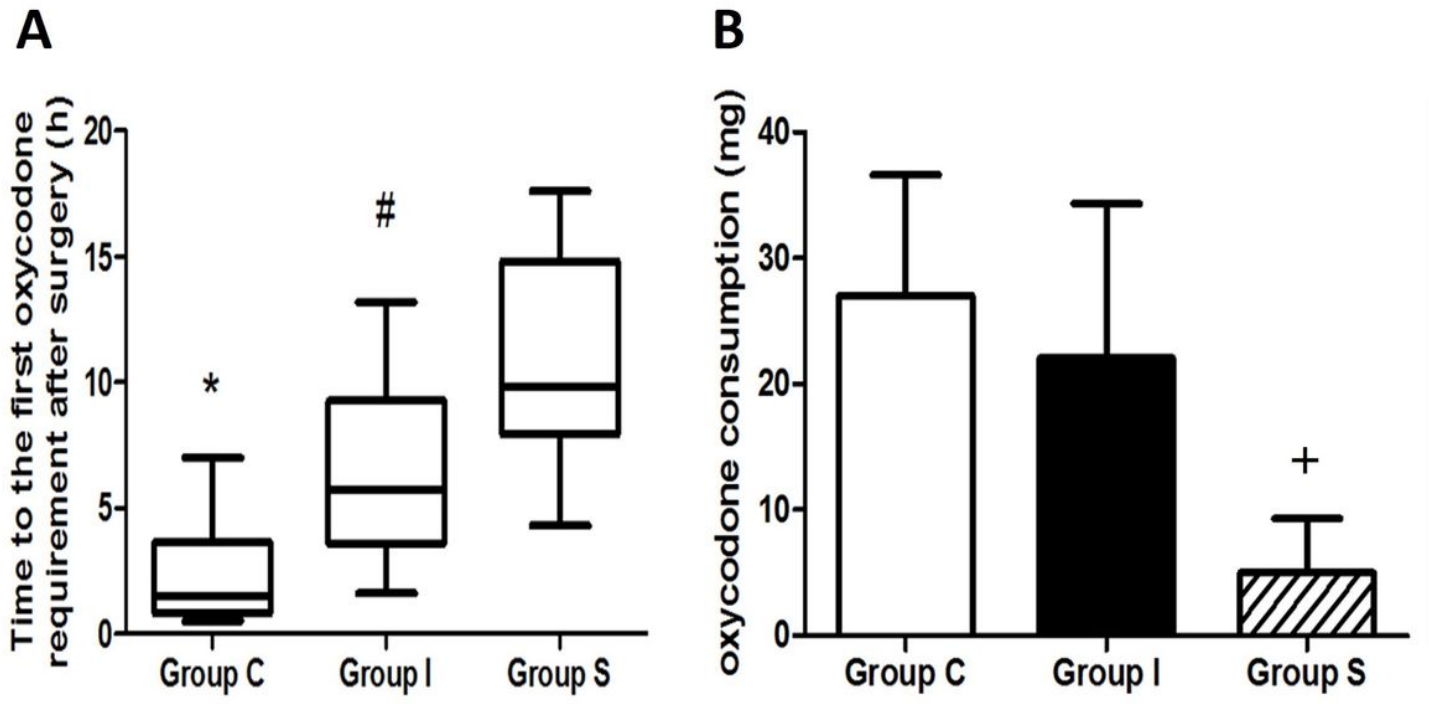

Figure 5

Comparison of (A) the first time patients requested rescue analgesia and (B) oxycodone consumption during the first 48 postoperative hrs. Group C: control group, Group I: local anesthesic infiltration group,

Group S: scalp nerve block group. *P<0.01 for group C compared with group I and S, #P<0.05 for group I Compared with group S, +P<0.001 for group S Compared with group C and I.