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Impact of subcutaneous infiltration of 0.5% bupivacaine on post-operative C-reactive protein serum titer after craniotomy surgery

Reza Shariat Moharari[1], Saber Amin Zade [2], Farhad Etezadi [3]
Atabak Najafi[4], Mohammad Reza Khajavi[5], Mohammad Shirani Bidabadi[6]
Hadieh Moradi Tabriz[7]

Department of Anesthesiology Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran.

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Abstract

Background: Tissue injuries may provoke neuro-hormonal response which in turn may lead to release of inflammatory cytokines. We hypothesize that block of afferent sensory pathways by infiltration of 0.5% bupivacaine in the scalp may decrease neuro-hormonal response in the neurosurgical patient.

Methods: After obtaining informed consent, forty ASA physical statuses I, II, or III patients between the ages of 18 and 65 years were enrolled randomly into two equal groups to receive either 20 ml of 0.5% bupivacaine (group A) or 20 ml of 0.9% normal saline as a placebo (group B) in the site of pin insertion and scalp incision. As the primary outcome we checked serum C-reactive protein (CRP) levels before implementation of noxious stimulus, 24h, and 48h after the end of surgery to compare these values between groups. In addition, mean arterial pressure (MAP) and heart rate (HR) were checked at baseline (after the induction of anesthesia), one minute after pin fixation and 5, 10, and 15 minute after skin incision and the recorded values were compared between groups.

Results: No significant difference was found between serum CRP levels of the two groups. Comparison of mean HR between groups shows no significant difference. The mean of MAP was significantly lower in the group A in comparison with the group B ($p< 0.001$).

Conclusion: The results of this study confirm that 0.5% bupivacaine scalp infiltration before skull-pin holder fixation and skin incision could not decrease post-operative C-reactive protein level.

Keywords: Craniotomy, C-reactive protein, Neuro-hormonal response, Inflammatory response.

Introduction

Noxious stimulus during neurosurgical procedures such as insertion of cranial pins, scalp incision can result in sudden increases in blood pressure and heart rate (1). Also, many neuro-hormonal responses may be induced following tissue injuries. Release of some cytokines, particularly interleukin-6 may lead to systemic production of acute phase proteins (2). Therefore, the concen-

1. Associate Professor of Anesthesiology, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. moharari@tums.ac.ir
2. Resident of Anesthesiology, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. aminzadehsaber@yahoo.com
3. (**Corresponding author**), Assistant Professor of Anesthesiology Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. etezadi@tums.ac.ir
4. Associate Professor of Anesthesiology, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. nadjafia@tums.ac.ir
5. Associate Professor of Anesthesiology, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. khajavim@tums.ac.ir
6. Assistant Professor of neurosurgery, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. drmshirani@yahoo.com
7. Assistant Professor of pathology, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran. hmoradi@razi.tums.ac.ir

tration of these proteins such as C-reactive proteins (CRP), fibrinogen, and α 2 macroglobulin will increase following stress of surgical trauma. It has been well demonstrated that scalp block offers beneficial effects on hemodynamic responses in patients undergoing the insertion of skull clamp and scalp incision (2). On the other hand, one study showed that CRP as an unspecific indicator of inflammatory process will be increased after elective craniotomy for microsurgery of intracranial tumors (3). Given the above mentioned facts, we hypothesized that local blockade of pain pathways in the site of noxious stimulus may reduce the extent of inflammatory response after the craniotomy surgeries. So, we designed this study to evaluate the effect of bupivacaine scalp infiltration before pin insertion and scalp incision on changes in serum CRP level as a nonspecific biomarker of inflammatory response after elective craniotomy for intracranial supratentorial tumors. Furthermore, we note subsequent intra-operative hemodynamic parameters to define probable effect of our intervention on hemodynamic response.

Methods

After approval of the study by Ethics committee of the deputy of research of anesthesiology department of our university, the informed consent was obtained from all patients who were scheduled for elective craniotomy for supra-tentorial intracranial tumors. This study was registered at IRCT website and the registration ID obtained as: "IRCT201111138087N1". Forty ASA physical statuses I, II, or III patients between the ages of 18 and 65 years were enrolled in this prospective study and divided into two equal groups. By means of a double-blind, randomized construct, on the basis of a sealed envelope technique, patients were scheduled to receive subcutaneous infiltration of either 20 ml of 0.5% bupivacaine (group A) or 20 ml of 0.9% normal saline as a placebo (group B) in the site of pin insertion and scalp incision. Patients who had history of head trauma, repeat craniotomy, documented allergy to bupivacaine were excluded from the study. Both solutions were prepared in a similar coverage and in a sterile fashion by a member of the anesthesia team. The anesthesiologist, surgeon, and patients were blinded to the type of solutions which were infiltrated. Before preparing and draping of cranium, and skull fixation, the pin and skin incision sites were infiltrated subcutaneously by the neurosurgeon. Standard monitoring consisted of electrocardiography, pulse oximetry, noninvasive blood pressure were used during anesthesia and the recovery period. An arterial catheter was inserted into right radial artery for continuous BP monitoring and blood sampling.

After establishment of intravenous (IV) access, a similar induction protocol was followed for all patients. Premedication included midazolam (0.04mg/kg), fentanyl (2μg/kg). As induction agent, IV sodium thiopental (4mg/kg) was used. For achievement of muscle relaxation, IV atracurium (0.5mg/kg) was injected. For maintenance of anesthesia, a mixture of propofol and alfentanil infusion (400mg propofol+1mg alfentanil were mixed) prepared and titrated during the anesthesia period (4). After induction of anesthesia, for all patients, the infusion of mannitol (1g/kg) titrated within 20 minutes and dexamethasone 8mg IV were given. For intraoperative fluid replacement therapy normal saline was used in both groups. Administration of blood or other blood products was according to the ASA guidelines and was at the discretion of anesthesiologist caring for the patients. All surgeries were done by a single neurosurgeon that was blinded to the study.

For measurement of serum CRP level which was our primary objective, three blood samples were collected at baseline, (before induction of anesthesia) 24 and 48 hours after the surgery. Serum CRP level was measured by high sensitivity quantitative ELISA assay (Diagnostics Biochem Canada kit). As the secondary objective, measurement of heart rate (HR) and the

Table1. Demographic and surgical data of patients.

variables	bupivacaine(n =20)	saline (n = 20)	P value
Age (y)	48.2±11.2	47.5± 18.4	0.185
Male/Female	12/8	13/7	0.512
ASA status I	4	3	0.313
ASA status II	7	6	0.118
ASA status III	9	11	0.195
Time interval from LA infiltration to incision (min)	13.4±1.2	14.2±0.6	0.283
Type of surgery		Supra-tentorial tumors	
Duration of surgery (min)	180±17	175±24	0.752

LA = local anesthetic, ASA = American society of anesthesiologists

mean arterial pressure (MAP) were made at baseline (after the induction of anesthesia), one minute after pin fixation and 5, 10, and 15 minute after skin incision and the recorded values were compared between groups. Furthermore, any sign or symptom or paraclinical evidence of infection during the study period was noted (fever, hypothermia, tachycardia, hypotension, tachypnea, leukocytosis, positive blood culture, thrombocytopenia, development of metabolic acidosis, etc.).

Statistical Analysis

Data are presented as means ± standard deviation (SD) for continuous variables. For statistical analysis, SPSS software (SPSS for Windows 18.0; SPSS Inc., Chicago, IL, USA) was used. According to the study of Mirzayan MJ et al, sample size was calculated (20 in each group) for estimating statistical significant difference between groups with power of 80%. Two tailed tests applied for all comparisons. Pearson's cross-correlation analysis was performed to determine interrelations among CRP measurements. Sphericity assumption was checked by Mauchly test before comparisons. Because of multiple measurements of serum CRP levels along the study time we used repeated- measures analysis of variance (ANOVA). A p value less than 5% was considered significant.

Results

Forty patients were enrolled in the study, 20 in each group. No significant demographic differences were identified between the two groups (Table 1). Daily blood samples were collected from all patients before anesthesia and during the first 2 days after surgery, none of the patients experienced a clinically apparent infection following the surgery but, the serum CRP levels increased in both groups after the surgery. Mean values of serum CRP levels were compared and no significant difference was found between groups (p=0.435) (Table 2).

The comparison of mean HR between groups throughout the time intervals of pre-pin fixation to 15 minute post-incision showed no significant difference (p=0.362). The mean of MAP was significantly lower in the group A in comparison to group B ($p < 0.001$). The comparison of mean HR and MAP between groups is shown in figure 1.

Discussion

This prospective, randomized clinical trial demonstrates that local anesthetic scalp infiltration before skull-pin holder fixation and skin incision may decrease serum CRP level during postoperative period in patients who undergo craniotomy surgery, but it isn't statistically significant.

Local infiltration with epinephrine-containing lidocaine solution is routinely used in neurosurgical operations to reduce bleeding on the scalp incision and obtund the hemodynamic response to the pain from incision. But in two studies it was shown that this intervention could not decrease blood catecholamine metabolites following surgery (2, 5).

C-reactive protein increases following routine neurosurgical procedures despite

Table 2. Comparison of CRP serum levels between groups during the study.

	saline (n = 20) (mean±SE)	bupivacaine (n=20) (mean±SE)	p-value (between group)
$CRP_{0\ (n\ g/ml)}$	1372.85±221.97	1207.70±185.037	0.571
$CRP_{1\ (n\ g/ml)}$	3134.06 ± 452.1	2419.65 ± 398.4	0.243
$CRP_{2\ (n\ g/ml)}$	2585.21 ± 429.7	2398.95 ± 663.4	0.815
P-value (within group)	0.2407	0.9533	0.435*

*P-value for time & group interaction, SE = standard error, CRP = C-reactive protein

absence of any clinical or laboratory signs of infection and it reaches to a peak level during the first 48 h after surgery (3).

It was shown that cytokine response to surgery may be affected by several factors, including the type of surgery (e.g., laparoscopy vs. laparotomy), magnitude of surgical injury, duration of operation, and the degree of postoperative pain (6,7, 8). It is supposed that type of anesthesia may have not impact on occurrence of postoperative inflammatory response. For example, it was found that the cytokine production in cardiac surgery was not affected by type of anesthesia (thoracic analgesia combined with inhalation anesthesia or high dose opioid anesthesia) (9).

In this study we did not find a significant decrease in serum CRP levels after performing the pain reducing intervention; it may be because of little impact of our intervention on the extent of inflammation during the neurosurgical procedures. Of course, some more specific biomarkers such as interleukin 1 (IL1), interleukin 6 (IL6), and neutrophil gelatinase - associated lipocalin (NGAL) have been used by investigators in order to follow the extent of inflammatory reactions in different groups of patients (10, 11). We are concerned that if we had used those novel biomarkers, a different result might have been obtained. Anyway, according to our results, we can suggest that the extent of inflammation may be basically dependent on the extent of tissue injury during the surgical procedures. In the other hand, the analgesic effect of infiltrated local anesthetic is not long-lasting and after disappearance of its effects, it may be supposed that ominous process of pain and inflammation evolve. Although in early phase after local anesthetic block, we observed reductive effect of pain control on the MAP of the patients in the group A.

However, Buyukkocak et al. have shown

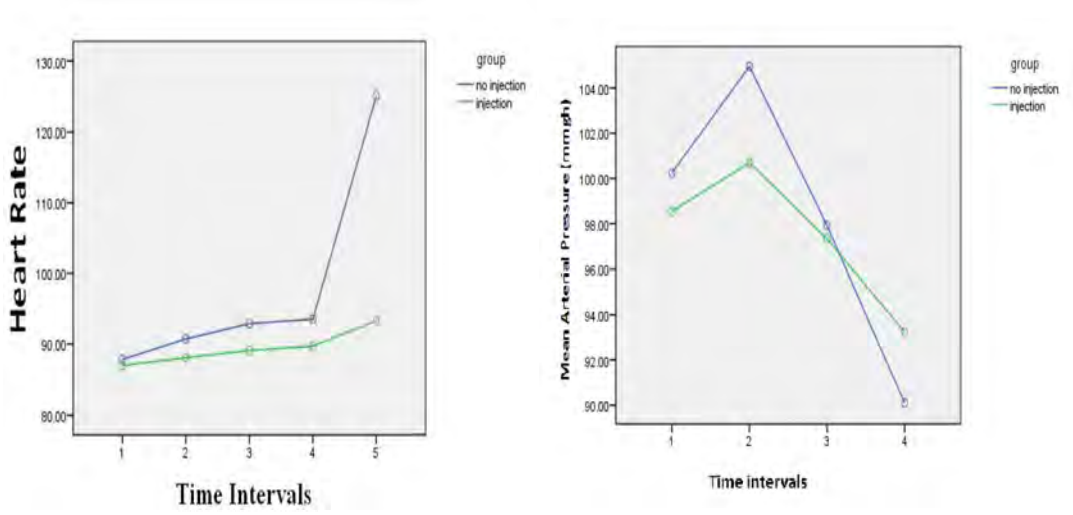

Fig. 1. Comparison of heart rate and mean arterial pressure between the group

that neuraxial blockade may attenuate the metabolic-endocrine response, but not the local and systemic inflammatory response (12). Besides, they suggested that one might propose that the dense block caused by the spinal local anesthetic would have an effect on the inflammatory markers; it is unlikely because the spinal block is lasting for a short duration, and it may have an insufficient effect to attenuate the establishment of hyperalgesia.

Previous animal experiments have shown that the neurogenic inflammatory response can be attenuated by experimental nerve section and nerve block (13). Neurogenic mediators liberated at tissue level may contribute to the development of peripheral and systemic inflammation (14). Therefore, local tissue inflammation caused by injury or inflammatory processes may be reduced by section or local anesthetic block of the nerve innervating the inflamed area.

In humans, continuous lumbar plexus and sciatic nerve blocks with ropivacaine contributed to the attenuation of the postoperative inflammatory response in knee arthroplasty (15). Those investigators concluded that blocking of all afferent and efferent fibers innervating the surgical area during intra and post- operative period could prevent primary and secondary hyperalgesia and consequently may attenuate postoperative inflammatory responses.

This study may be subject to a number of limitations. One limitation is use of CRP serum titer for following inflammation in the patients because of financial reasons. It might be better to use more specific biomarkers such as IL-1, IL-6 and NGAL for this purpose. The other limitation is that the extent of inflammation is under influence of size of tissue damage through surgical manipulation, but we didn't consider this as one of contributors of the extent of inflammation. However, both groups of patients were under such confounding factor with the same chance because of meticulous randomization. Also, only surgeries of supra-tentorial tumors included in this study to minimize heterogeneity in surgical site and the extent of surgical manipulation between groups. Only elective surgical patients were included in this study; it limits our results to this group of patients.

Conclusion

The results of this study suggest that local anesthetic scalp infiltration before skull-pin holder fixation and skin incision could not decrease C-reactive protein level significantly, and the role of local anesthetics used for the subcutaneous infiltration and the possible clinical implications of this intervention need to be clarified through future investigations.

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