Original Article

Analgesia nociception index and hemodynamic changes during skull pin application for supratentorial craniotomies in patients receiving scalp block versus pin-site infiltration: A randomized controlled trial

ABSTRACT

Background: Noxious stimulation such as skull pin insertion for craniotomy elicits a significant hemodynamic response. Both regional analgesic techniques (pin-site infiltration [PSI] and scalp block [SB]), and systemic strategies (opioids, alpha-2 agonists, anesthetics, and beta-blockers) have shown to attenuate this response. Analgesia Nociception Index (ANI) provides objective information about the magnitude of nociception and adequacy of analgesia. This study compared ANI and hemodynamic changes in patients receiving local anesthetic SB versus PSI during skull pin application for craniotomy.

Materials and Methods: Sixty adult patients scheduled for elective supratentorial tumor surgery were randomly allocated to receive local anesthetic SB or PSI for skull pin insertion after the induction of anesthesia. Data regarding heart rate (HR), blood pressure (BP), and ANI were collected every minute for 5 min after the skull pin insertion beginning from the baseline.

Results: A significant difference was observed in ANI values between the SB (higher ANI) and the PSI groups during skull pin insertion, $P < 0.001$ and $P = 0.003$ for ANIi and ANIm, respectively. Similarly, a significant difference was seen in HR and BP both within and between the two groups during skull pin insertion ($P < 0.001$ for both). The magnitude and duration of change were smaller in the SB group compared with the PSI group for the parameters studied. A strong negative linear correlation was noted between ANI and hemodynamic parameters.

Conclusions: The changes in HR, BP, and ANI were significantly less with local anesthetic SB compared with PSI during skull pin insertion in patients undergoing supratentorial craniotomy.

Key words: Analgesia nociception index; craniotomy; local anesthetic infiltration; pain; scalp block; skull pin

Introduction

Insertion of Mayfield skull pins for stabilizing the skull for craniotomy elicits a significant hemodynamic response despite the optimal depth of general anesthesia.[1-3] The changes in heart rate (HR) and blood pressure (BP) reflect an autonomic (sympathetic) response to noxious stimulation from skull pin application, as the scalp and the periosteum are

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richly innervated with nerve fibers.[4] The degree of noxious stimulation and clinical manifestation of pain are difficult to assess in the absence of objective intraoperative analgesia monitor. Regional analgesia techniques, such as pin-site infiltration (PSI) of local anesthetic[2,3,5] and scalp block (SB) with local anesthetic,[5] and systemic strategies, such as opioids,[6-8] alpha-2 agonists,[9,10] anesthetics,[11,12] antiepileptic drugs,[13] and beta-blockers,[14] have been employed to attenuate response to this noxious stimulation. Regional anesthesia techniques, while reducing the response to skull pin application, also minimize the need for administration of systemic agents and hence, the accompanying adverse effects. In addition, techniques such as SB provide good perioperative analgesia and reduce opioid consumption. Recently, Analgesia Nociception Index (ANI) has come into neuroanesthesia practice to quantify intraoperative nociception.[15] Impact of noxious stimulation such as skull pin insertion on ANI has not yet been evaluated.

The primary objective of this study was to compare ANI during skull pin insertion for craniotomy in patients who receive SB versus who receive PSI. The secondary objectives were to compare changes in HR and mean BP during skull pin insertion with SB and PSI and evaluate the correlation between the ANI and the hemodynamics.

Materials and Methods

Study design and population

After institutional ethics committee approval and written informed consent, adult patients (18–65 years) belonging to either sex were recruited into this randomized controlled study if they were scheduled for an elective supratentorial craniotomy for brain tumors. The exclusion criteria were: diabetes mellitus, systemic hypertension, significant arrhythmias, chronic pain, allergy to local anesthetic drugs, coagulopathy, scalp infection, prior craniotomy, pregnancy, and treatment with vasoactive drugs.

Study conduct

In the operating room, standard monitoring such as electrocardiogram (ECG), noninvasive BP, and pulse oximeter were applied. The ANI monitoring was performed with a commercially available ANI monitor (MetroDoloris Medical Systems, Lille, France) as per the manufacturer's instructions. Anesthesia was induced with fentanyl 2 μg/kg and thiopentone 5 mg/kg, and intubation was facilitated with vecuronium 1.2 mg/kg. Lignocaine 1.5 mg/kg was administered to suppress the cardiovascular response to intubation. Fentanyl infusion (0.5 μg/kg/h) was started after intubation. Anesthesia was maintained with 1 minimum alveolar concentration of sevoflurane with oxygen–nitrous oxide (50%). Following intubation, patients were randomized to receive either SB (n = 30) or PSI (n = 30) with local anesthetic solution 8 min before skull pin application using a computer-generated random number table. The local anesthetic solution consisted of a mixture of 10 mL of lignocaine 2% with adrenaline 1:200,000 concentration and 10 mL of bupivacaine 0.5%. In the SB group, this solution was used to block the following scalp nerves – supra-trochlear, supraorbital, zygomatico-temporal, auriculotemporal, greater auricular, lesser occipital and greater occipital – bilaterally and 0.9% saline was used to infiltrate the pin sites. In the PSI group, this solution was used to infiltrate the three sites of skull pin insertion (1.5 mL at each site) and 0.9% saline was used to perform the SB. Fentanyl 1 μg/kg was administered if the ANIm value decreased below 50 at any time point during the study. No other systemic drugs were administered in both the groups for skull pin application. The data regarding HR, mean BP, and ANI were collected once every minute for 5 min starting just before skull pin insertion.

Analgesia Nociception Index

The ANI is computed from the ECG and calculated from the analysis of HR variability (HRV) and is described in detail earlier.[16] The ANI values are represented from 0 to 100, with 0 = strong sympathetic tone and 100 = strong parasympathetic activity. The ANI monitor provides ANIi (instantaneous) and ANIm (mean: obtained from a 2-min averaging of ANIi signal). An ANI >50 predicts adequate analgesia, whereas a value of <30 predicts autonomic response to painful stimuli.[17]

Sample size estimation

As there was no previous study comparing ANI during skull pin insertion between two groups, we conducted a pilot study on twelve patients undergoing craniotomy to determine the sample size. The estimated marginal mean difference (between subjects effect) of ANIi in the SB and the PSI group during skull pin insertion was observed to be 6.571 with an effect size (partial η^2) of 0.074. Considering an alpha of 0.05 and a beta of 0.8 (80% power), the total sample size was estimated to be 60.

Statistical analysis

The demographic parameters (age, gender, and weight) were tested using the Mann–Whitney U test or χ^2 test. A within-group comparison of time course data was performed using repeated measures analysis of variance (ANOVA) with Greenhouse Geisser correction for sphericity assumption violation after testing normality of residuals using the Shapiro-Wilk test. Pair-wise comparisons were done using Bonferroni correction. Between group comparison and time*group interaction of time course

data were done using mixed models ANOVA. Because of repeated measures nature of data, testing of the association between the ANI variables and the HR and the BP was done using linear mixed-effect models with random intercept and slope using maximum likelihood estimation and assuming a scaled identity covariance matrix. A P value of < 0.05 was considered significant. The statistical tests were performed using a SPSS version 17.

Results

Of the 60 patients recruited, data of 3 patients was not analyzed as complete data were not available. Data of 57 patients, 28 in the PSI group and 29 in the SB group, were analyzed. There was no difference in age (38.8±13.5 vs. 38.9 ± 16.1 years; $P = 0.97$), male gender ($n = 15$ vs. 14; $P = 0.90$), and weight 60.1 ± 9.3 vs. 59.2 ± 9.1 kg; $P = 0.90$) between PSI versus SB group.

Changes in the ANI during skull pin fixation

ANIi decreased significantly during skull pin application and remained significantly lower compared with the baseline at 1, 2, and 3 min after skull pin application in the PSI group. ANIi recovered to the baseline values at fourth minute [Figure 1]. The decrease in ANIm trailed that of ANIi by a minute and was significantly lower at 1, 2, and 3 min after pin fixation. ANIm did not recover to baseline value at 5 min [Figure 2].

ANIi values decreased minimally during and at 1 and 2 min of pin fixation in the SB group after which it increased above the baseline values and this increase was significant at 4 and 5 min [Figure 1]. The changes in ANIm values from baseline were not significant at any time point after pin fixation [Figure 2].

The changes in the ANIi and ANIm values during skull pin fixation in the PSI were significant ($P < 0.001$ for both). Similarly, changes in the ANIi and ANIm in the SB group were also significant ($P < 0.001$ and 0.003, respectively). The difference in the ANIi and ANIm values between PSI and SB groups was also significant ($P < 0.001$ and 0.003, respectively).

Though the ANI values decreased immediately with pin fixation in both the groups, both ANIi and ANIm values remained above the threshold level of 50 in the SB group during skull pin insertion, whereas these values decreased below the threshold in the PSI group.

Changes in the heart rate during skull pin fixation

The HR increased immediately upon skull pin fixation in both the groups (more in PSI compared with SB). This increase was limited to two time points (0 and 1 min) in the SB group, whereas it remained elevated for four time points (0, 1, 2, and 3 min) in the PSI group before decreasing below the baseline values in both the groups. The changes in HR in both the groups were significant ($P < 0.001$ for both). No overall difference in HR was observed between the two groups ($P = 0.166$); however, the trend of change in HR over the time was significantly different between the groups ($P < 0.001$) [Table 1].

Changes in the mean blood pressure during skull pin fixation

The MBP increased from the time of pin application till 4 min after which it decreased below the baseline value in the PSI group. In the SB group, MBP increased only at pin application followed by a decrease below the baseline value at all subsequent time-points. The change in the MBP over time within the groups was significant ($P < 0.001$ for both groups). The difference in the MBP between the two groups and the trend of change in MBP over time were also significant ($P < 0.001$ for both) [Table 2].

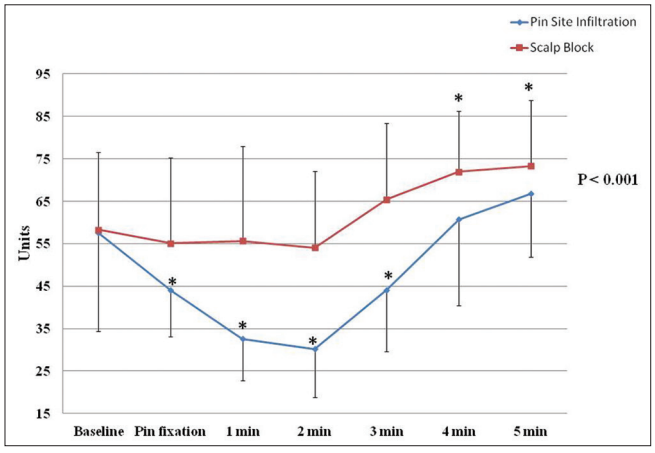

Figure 1: Changes in the ANI instantaneous (ANIi) during skull pin fixation in scalp block and pin-site infiltration groups

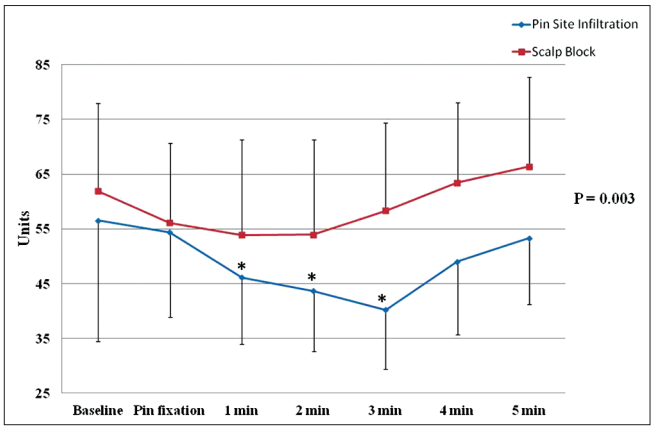

Figure 2: Changes in the ANI mean (ANIm) during skull pin fixation in scalp block and pin-site infiltration groups

Table 1: Changes in HR within and between scalp block and pin-site infiltration groups

Heart rate (bpm)	Pin-site infiltration	Within group *P*	Scalp block	Within group *P*	Between group *P*	Time*Group interaction *P*
Baseline	75.86±11.98	<0.001	79.31±8.35	<0.001	0.166	<0.001
At pin fixation	93.21±13.91		83.17±8.92			
1 min post pin fixation	90.39±13.74		80.38±10.07			
2 min post pin fixation	83.5±13.32		78.24±8.71			
3 min post pin fixation	78.89±17.13		74.93±9.71			
4 min post pin fixation	74.07±13.65		73.97±12			
5 min post pin fixation	71.36±13.91		71.21±11.11			

HR: Heart rate

Table 2: Changes in MBP within and between scalp block and pin site infiltration groups

MBP (mmHg)	Pin-site infiltration	Within group *P*	Scalp block	Within group *P*	Between group *P*	Time*Group interaction *P*
Baseline	81.21±14.95	<0.001	82.21±14.53	<0.001	0.001	<0.001
At Pin fixation	97.93±18.33		83.62±18.67			
1 min post pin fixation	96.86±17.75		79.03±18.66			
2 min post pin fixation	94.54±15.05		75.1±15.72			
3 min post pin fixation	86.93±13.14		72.79±12.22			
4 min post pin fixation	86.46±13.13		75.38±12.1			
5 min post pin fixation	78.79±11.65		70.93±10.72			

MBP: Mean blood pressure

Correlation of ANI with HR and MBP

There was a significant negative correlation between ANIi and HR (estimate –0.594, $P < 0.001$) and between ANIi and MBP (estimate –0.534, $P < 0.001$). Similarly, there was a significant negative correlation between ANIm and HR (estimate –0.161, $P = 0.007$) but the correlation was not significant between ANIm and MBP (estimate –0.091, $P = 0.085$) [Table 3].

Table 3: Correlation between ANI and HR and between ANI and MBP

ANI variable	Hemodynamic variable	Estimate	*P*	95% CI of estimate	
ANIm	HR	−0.161	0.007	–0.276	−0.045
	MBP	−0.091	0.085	–0.194	0.013
ANIi	HR	−0.594	< 0.001	–0.748	−0.440
	MBP	−0.534	< 0.001	–0.667	−0.400

ANIi: Analgesia nociception index instantaneous, ANIm: Analgesia nociception index mean, CI: Confidence interval, HR: Heart rate, MBP: Mean blood pressure

Discussion

Summary of findings

There were significant differences in ANIi and ANIm values between PSI and SB groups following skull pin fixation. The ANI changed significantly in both the groups, but the magnitude and duration of change was more in the PSI group compared with the SB group suggesting that the SB group was more effective in ablating the nociceptive response to skull pin insertion. The HR increased in both PSI and SB groups after skull pin insertion; however, the magnitude and the duration of the increase was more in the PSI group compared with the SB group. Similar findings were observed for MBP changes within and between PSI and SB groups. There was a strong negative correlation of ANIi with HR and MBP. While the negative correlation between ANIm and HR was significant, it was not so between ANIm and MBP. Five minutes after pin fixation, both HR and MBP were below the baseline values, whereas the ANIi was higher than the baseline value. This finding is likely because of the absence of noxious stimuli during this "silent" period – from skull pin insertion to surgical incision – and, continuous infusion of fentanyl and the deeper plane of anesthesia.

Comparison with the published literature

There is no previous literature objectively evaluating the autonomic response to noxious stimulation from skull pin application using ANI. Previous studies mainly evaluated hemodynamic changes such as HR and BP during skull pin insertion with regional techniques such as PSI[2,3,5] and SB,[5] and systemic strategies such as opioids,[6-8] alpha2 agonists,[9,10] anesthetics,[11,12] anti-epileptic drugs,[13] and beta-blockers.[14]

Effect of regional techniques on hemodynamics

Both SB and PSI techniques have been extensively studied with regard to hemodynamic response during skull pin

insertion. We observed a significant increase in the HR in the PSI group after skull pin fixation compared with the pre-pin fixation values. Conflicting findings were seen in earlier studies with one study observing changes similar to our findings[5] while others noting no significant changes in the HR during pin fixation with local anesthetic PSI.[12,18] Misra *et al*. however observed that a combination of oral gabapentin 2 h before anesthetic induction with lignocaine PSI was more effective in ablating hemodynamic response to skull pin insertion than oral gabapentin or lignocaine PSI alone.[13]

Two studies compared PSI with SB. In this study, though HR and MBP increased during pin insertion in both PSI and SB groups, the change was less in the SB group. Similar results were noted in earlier studies. Geze *et al*. observed a significant increase in HR and MBP during pin fixation in the bupivacaine PSI group and the control group when compared with the SB group after pin insertion.[5] Similarly, Akcil *et al*. observed an increase in HR but not BP in the bupivacaine PSI group, whereas no significant change was seen in HR and BP with SB during skull pin application for infratentorial surgeries.[19] In children, infiltration with lignocaine 0.5%, 1 min before pin application failed to blunt hemodynamic response during and up to 1 min after pin application.[20]

Effect of systemic techniques on hemodynamics

Intravenous alfentanil 10 μg/kg and PSI of 0.5% lignocaine did not elicit a significant hemodynamic response up to 3 min after Mayfield skull pin application, whereas intravenous esmolol 1 mg/kg and thiopentone sodium 1.5 mg/kg failed to prevent the increase in the HR and BP when administered 3 min before pin application.[14] Thongrong *et al*. observed that dexmedetomidine 1 μg/kg bolus administered 5 min before the pin application reduced HR and BP response during the 10-min study period better than 1 μg/kg fentanyl administered 3 min before pin application. There were more episodes of hypertension with fentanyl, whereas hypotension was more with dexmedetomidine in their study with 60 patients.[21] In another study comparing dexmedetomidine 1 μg/kg ($n = 20$) with saline ($n = 20$), HR and MBP were significantly higher in the saline group at 1 and 5 min of pin insertion. Glucose, prolaction, and cortisol values were also higher in the saline group as compared with the dexmedetomidine group.[9] Dexmedetomidine at both 0.5 and 1 μg/kg doses effectively blunted HR and MBP response to pin insertion during the 30-min study period.[22] Another recent study compared intravenous clonidine (2 μg/kg) with intravenous lignocaine (1.5 mg/kg) for ablating hemodynamic response to skull pin insertion in 60 patients. Both HR (76 vs 98 bpm) and MBP (76 vs 87 mmHg) were significantly lower ($P < 0.001$) in the clonidine group compared with the lignocaine group after pin insertion.[23]

Possible reason for the observed difference

Inappropriate application of skull pins outside the sites of local anesthetic infiltration was noted at 20/84 sites in the PSI group resulting in an accuracy of only 76% and this could have contributed to the observed difference in our study. Unlike in the PSI group, inappropriate or reapplication of skull pins would not alter ANI and hemodynamic responses in the SB group as the SB covers the entire scalp region.

Strengths and limitations

This is the first study to evaluate changes in the ANI, an index of intraoperative nociception, during skull pin insertion in patients receiving SB and PSI, and assess correlation between ANI and systemic hemodynamics. Second, unlike previous studies, in this study, we compared two active regional analgesic techniques (SB and PSI) for hemodynamic response (HR and MBP) and nociception (using ANii and ANIm) with skull pin insertion. The limitations include the absence of a passive control group (saline), which would have quantified the actual autonomic response to skull pin insertion.

Conclusions

The SB reduced the autonomic response to noxious stimulus of skull pin application better than the PSI as evaluated by ANI and hemodynamic parameters. A strong negative linear correlation is seen between ANI and HR, and ANI and MBP following skull pin application.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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