EFFECT OF SCALP NERVE BLOCK ON FENTANYL CONSUMPTION AND LEVELS OF TNF-α, CORTISOL, AND BLOOD GLUCOSE IN ELECTIVE CRANIOTOMY

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Background: Craniotomy is commonly performed worldwide. As a response to surgery, the body develops surgical stress response mediated by pain and inflammatory mediators as an adaptive and protective mechanism against tissue injury. Craniotomy is a major surgery that may cause intense surgical stress response. Intense and persistent surgical stress response will become pathological process that increase perioperative complications. Surgical stress response can be in the form of metabolic or immune stress response. Metabolic stress response increases cortisol and blood glucose concentration, while immune stress response elevates proinflammatory cytokines, including TNF-α. Ropivacaine used in scalp nerve block is expected to reduce pain and inflammatory mediator production.

Method: A prospective analytical experimental study was conducted on elective craniotomy patients at Dr. Soetomo Surabaya Hospital from October to November 2023. A total of 40 subjects were enrolled, divided into two groups, scalp nerve block (SNB) and non-scalp nerve block (non-SNB) group. The SNB group received scalp nerve block with 0.5% ropivacaine after induction of general anesthesia. Evaluation of pain relief was measured by fentanyl consumption during and 24 hours after surgery. TNF-α, cortisol, and blood glucose concentration were analyzed after induction, 6 hours after incision, and 24 hours after surgery as assessment of inflammatory response.

Results: Total fentanyl consumption during surgery in SNB group was significantly lower compared to non-SNB group (1.72±0.23 vs 5.98±0.79 mcg/kg; p<0.001). 24 hours after surgery, total fentanyl consumption in SNB group was also significantly lower [0,00 (0,00-0,93) vs 0,785 (0,00-1,47) mcg/kg; p=0.002]. Average time from scalp nerve block to incision was 30-60 minutes. TNF-α concentration in SNB group was significantly lower at 6 hours after incision compared to non-SNB group (40,27±3,69 vs 93,59±4,23 pg/mL; p=0.000), and was not significantly different at 24 hours after surgery (94.00±4.35 vs 95.74±3.91; p=0.191). The increase of cortisol 6 hours after incision was significantly lower in SNB group (0.88±2.39 vs 4.99±2.47; p<0.001). At 24 hours after surgery, cortisol concentration was also significantly lower in SNB group (9.60 ± 4.22 vs 12.18 ± 3.41; p=0.04). There was no significant difference in blood glucose concentration between both groups at 6 hours after incision and 24 hours after surgery (p=0.440 and p=0.498, respectively).

Conclusion: Scalp nerve block with ropivacaine effectively suppress elevation of TNF-α concentration for 6.5 to 7 hours after administration, but is not effective until 24 hours after surgery. Fentanyl consumption and elevation of cortisol concentration can be suppressed until 24 hours after surgery.

Keywords: scalp nerve block, ropivacaine, craniotomy, TNF-α, cortisol, blood glucose

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INTRODUCTION

Craniotomy is a common surgical procedure performed for various indications, including biopsy or resection of intracranial masses, treatment of intracranial vascular pathologies, epilepsy, and trauma. Reports from the United States in 2007 estimated 70,848 craniotomies for tumor cases, 2,237 for vascular surgeries, and 56,406 for other purposes (Vacas & Van De Wiele, 2017). In 2013, Dr. Soetomo General Academic Hospital Surabaya recorded 18.87%-25.27% of craniotomy cases out of a total of 1,411 brain injury cases (Wahyuhadi et al., 2014). Surgery triggers surgical stress response manifested as metabolic or immune stress responses. Surgical stress response is primarily caused by pain stimulation and release of inflammatory mediators (Zhan et al., 2017). It primarily acts as an adaptive and protective mechanism against tissue injury, but if it persists intensively, this response will become a pathological phenomenon that increases perioperative complications. Metabolic stress response begins with activation of Hypothalamic-Pituitary-Adrenal (HPA) axis. Corticotrophin Releasing Hormone (CRH) is secreted by the Paraventricular Nucleus (PVN) in the hypothalamus. CRH stimulates the anterior pituitary gland to release Adrenocorticotropic Hormone (ACTH). ACTH acts on adrenal cortex cells, stimulating cortisol secretion. Subsequently, cortisol stimulates proteolysis and gluconeogenesis in the liver, inhibiting glucose utilization by cells, leading to increased blood glucose concentration (Cusack & Buggy, 2020). Immune response involves production of proinflammatory cytokines as an early response to tissue injury, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) (Ivanovs et al., 2012).

Post craniotomy pain has been previously reported as a low–grade pain (Haldar et al., 2015); while in reality patients experience significant pain with varying degrees of intensity (Chowdhury et al., 2017). There are numerous modalities for post craniotomy pain therapy. Opioids are widely used, but come with potential side effects such as sedation, miosis, respiratory depression, nausea, vomiting, and intracranial hypertension. Nonsteroidal Anti-inflammatory Drugs (NSAIDs) can reduce the need for opioids, but their side effect of impairment of platelet function increases the risk of post craniotomy brain hemorrhage. Additionally, NSAIDs alone may not provide sufficient analgesia (Jia et al., 2019). COX-2 inhibitors can be used without platelet function disruption, but carry a thrombotic risk that may trigger cardiovascular disease. Multimodal analgesia with combination of systemic and local analgesia offers optimal analgesic effects, faster surgical recovery, and better outcomes (Ananda et al., 2021). Ropivacaine is frequently used as local anesthetic drug of choice. It provides analgesia effect by inhibiting nociceptive transmission from site of tissue injury, thereby inhibiting TNF-α release (Grosu & Lavand'homme, 2015). Scalp nerve block with ropivacaine administered before surgical incision provides preemptive analgesia, reducing post-surgery pain and minimizing excessive surgical stress response (Canakci, 2017).

This study aims to analyze impact of scalp nerve block with ropivacaine on surgical stress response, represented by TNF-α, cortisol, and blood glucose concentration, among elective craniotomy patients.

METHODOLOGY

Study Design and Sample Collection

A prospective analytical experimental study was conducted among patients undergoing elective craniotomy under general anesthesia at Dr. Soetomo General Academic Hospital Surabaya during October-November 2023. Subjects were selected based on the inclusion criteria of patients aged 18-64 years, Physical Status with American Society of Anesthesiologists (ASA) classification I-III, Glasgow Coma Scale (GCS) score ≥ 13, and elective craniotomy performed in morning shift. Patients with cardiovascular abnormality, impaired renal and hepatic function, diabetes mellitus, systemic and/or scalp local infection, and history of current dexamethasone administration were excluded from the study. 40 subjects were randomly divided into two groups, scalp nerve block (SNB) and non-scalp nerve block (non-SNB) group.

Study Variables and Procedures

The data collected in this study were TNF-α, cortisol, and blood glucose concentration, measured at 3 consecutive times, after induction of anesthesia, 6 hours after incision, and 24 hours after surgery. Total fentanyl consumption during surgery and 24 hours after surgery were also recorded and analyzed. TNF-α and cortisol concentration were measured with enzyme-linked immunosorbent assay (ELISA) using Human TNF-α ELISA kit (BT Lab Bioassay Technology Laboratory, Zhejiang, China). Blood glucose concentration was measured with Abbott automated chemistry analyzer.

Induction of general anesthesia is achieved by administrating fentanyl 1-2 mcg/kg, propofol 1-2 mg/kg, and rocuronium 0.6 mg/kg. After induction, all subjects received 1 gram of intravenous paracetamol. First blood sample was collected after induction. Afterwards, scalp nerve block was performed with 0.5% ropivacaine in the SNB group. Anesthesia was maintained with propofol target-controlled infusion (TCI) and continuous 0.15 mg/kg/hour of rocuronium pump. Non-SNB group received continuous 1 mcg/kg/hour of fentanyl as analgesia maintenance. During surgery, sudden rise of heart rate and blood pressure higher than 20% from baseline was considered as pain, and bolus of 1 mcg/kg fentanyl as rescue analgesia was administered afterward. 6 hours after incision, the second blood sample was collected. After surgery, all subjects received intravenous 30 mg ketorolac every 8 hours as analgesia. Pain scale was assessed using the Critical-care Pain Observational Tool (CPOT) every 4 hours. If the CPOT pain scale > 2, a bolus of 1 mcg/kg fentanyl as rescue analgesia was administered. 24 hours after surgery, the third blood sample was collected. Total fentanyl consumption during surgery and 24 hours after surgery were analyzed.

Statistical Analysis

All data obtained were statistically analyzed using SPSS 26 (SPSS Inc., Chicago, USA). Demographic homogeneity of subjects was tested with Levene's test for equality of variances. Data normality test was performed using Shapiro-Wilk test. TNF-α, cortisol, and blood glucose levels were compared between the two groups at the first, second, and third sampling with 2 independent t-test if the data is normally distributed or Mann-Whitney test if the data is not normally distributed. Within the same therapy group, changes in TNF-α, cortisol, and blood glucose concentration over time were also analyzed using ANOVA repeated measures if the data is normally distributed, or Friedman test if the data is not normally distributed. Total fentanyl consumption during surgery and 24 hours after surgery were compared between the two groups with 2 independent t-test if the data is normally distributed or the Mann-Whitney test if the data is not normally distributed.

RESULTS

A total of 40 patients were enrolled in the study. Based on Levene's homogeneity test, both groups were homogenous in terms of equality of variances, the characteristics of gender, age, weight, height, and BMI. The demographic characteristics of subjects are summarized in table 1.

Table 1. Demographic characteristics of subjects

Characteristics	Group		Total (n=40)	p value of homogeneity test
	SNB (n=20)	Non-SNB (n=20)		
Gender				
Male	9 (45,0%)	10 (50,0%)	19 (47,5%)	1,000[a]
Female	11 (55,0%)	10 (50,0%)	21 (52,5%)	
Age				
Range	38 - 61	41 - 60	38 - 61	0,302[b]
Mean ± SD	48,80 ± 5,83	50,80 ± 6,26	49,80 ± 6,06	
Body Weight				
Range	47 - 72	44 - 72	44 - 72	0,665[b]
Mean ± SD	57,35 ± 7,18	58,45 ± 8,71	57,90 ± 7,90	
Height				
Range	154 - 171	153 - 172	153 - 172	0,333[b]
Mean ± SD	161,0 ± 5,34	162,65 ± 5,29	161,82 ± 5,31	
BMI				
Range	19,14 - 24,91	18,43 - 25,82	18,43 - 25,82	0,884[b]
Mean ± SD	22,07 ± 1,93	21,97 ± 2,09	22,02 ± 1,98	

SNB : Scalp Nerve Block
Non SNB : Non Scalp Nerve Block
a : Chi-Square homogeneity test
b : Levene's test for equality of variances

The initial TNF-α concentration after induction, considered as baseline concentration, were insignificantly different between the two groups (34.60±4.82 pg/mL in SNB group, and 33.73±3.70 pg/mL in non-SNB group; *p*=0.524). At 6 hours after incision, TNF-α concentration in SNB group was significantly lower compared to non-SNB group (40.27±3.69 vs 93.59±4.23 pg/mL; *p*<0.000). At 24 hours after completion of surgery, there were no significant differences in TNF-α concentration between both groups (94.00±4.35 vs 95.74±3.91 pg/mL; *p*=0.191). Between both groups, the baseline cortisol concentration and 6 hours after incision were not significantly different (14.17±5.82 µg/dL in SNB group and 12.59±2.65 µg/dL in non-SNB group; *p*=0.279 and *p*=0.089, respectively). Increase in cortisol levels from baseline to 6 hours after incision was significantly lower in SNB group (0.876±2.391 µg/dL in SNB group and 4.986±2.473 µg/dL in non-SNB group; *p*<0.001). At 24 hours after surgery, cortisol concentration in SNB group was significantly lower compared to non-SNB group (9.60±4,22 vs 12.18±3.41 µg/dL; *p*=0.04). Blood glucose concentration in both groups at all sampling times did not show any significant difference (*p*=0.458, 0.440, and 0.498, respectively).

Table 2. TNF-α, cortisol, and blood glucose concentration

Variable	Sampling time		
	S_0 mean ± SD[a] or median (min - max)[b]	S_1 mean ± SD[a] or median (min - max)[b]	S_2 mean ± SD[a] or median (min - max)[b]
TNF-α (pg/mL)			
SNB	34,60 ± 4,82	40,27 ± 3,69	94,00 ± 4,35
Non-SNB	33,73 ± 3,70	93,59 ± 4,23	95,74 ± 3,91
Cortisol (μg/dL)			
SNB	14,17 ± 5,82	15,04 ± 5,78	9,60 ± 4,22
Non-SNB	12,59 ± 2,65	17,58 ± 2,30	12,18 ± 3,41
GDA (mg/dL)			
SNB	108,75 ± 16,70	108,45 ± 16,04	105,5 (98 - 141)
Non-SNB	104,85 ± 16,19	101,5 (89 - 141)	104,5 (97 - 129)

S_0 : After induction of anesthesia
S_1 : 6 hours after incision
S_2 : 24 hours after surgery
a : data is normally distributed
b : data is not normally distributed

Total fentanyl consumption (Table 3) during surgery and 24 hours after surgery in SNB group was significantly lower compared to non-SNB group ($p < 0.001$ and 0.002).

Table 3. Total fentanyl consumption

Type of Fentanyl Consumption	Group (mcg/kg) SNB	Non-SNB	p value
During surgery			
Mean ± SD	1,72 ± 0,23	5,98 ± 0,79	< 0,001[a]
24 hours after surgery			
Median (min – max)	0,00 (0,00 - 0,93)	0,785 (0,00 - 1,47)	0,002[b]

a : 2 independent t test
b : Mann-Whitney Test

DISCUSSION

At 6 hours after incision, TNF-α concentration in both groups were increased compared to baseline concentration. However, the magnitude of the elevation in SNB group was not as pronounced as in non-SNB group. This benefit of TNF-α reduction is sustained up to 24 hours after surgery, where TNF-α concentration was not significantly different between the two groups. This suggests the inhibitory effect of ropivacaine used in scalp nerve block on the elevation of TNF-α due to surgical process. A similar result was observed in prior research concerning ropivacaine; among patients with severe trauma, ropivacaine injection for stellate ganglion block significantly reduced the concentrations of IL-1, IL-6, and TNF-α (Liu et al., 2013). In another in-vitro study, ropivacaine was reported to decrease the expression of TNF-α by macrophages stimulated with lipopolysaccharide (Wu et al., 2019). Ropivacaine for femoral nerve block in elderly patients with hip fractures was reported to reduce the mean level of TNF-α (Jang et al., 2018). The use of ropivacaine for infraclavicular block in arteriovenous fistula repair surgery was also associated with a decrease in TNF-α concentration, one hour after administered (Behnaz et al., 2019).

In this study, TNF-α concentration elevated over time in different pattern between the two groups. SNB group exhibited an increase of TNF-α concentration from baseline to 6 hours after incision in a gentle curve, and then followed by another elevation in a sharp curve at 24 hours after surgery. Conversely, in non-SNB group, the pattern showed sharp-curved increase at 6 hours after incision, followed by a more gentle-curved rise at 24 hours after surgery. This pattern indicates that scalp nerve block with ropivacaine suppresses the excessive elevation of TNF-α production after surgical procedures. However, this effect appears effective only up to 6 hours after incision, with no significant impact observed at 24 hours after surgery. With an average time from scalp nerve block to incision ranging from 30 to 60 minutes, it can be concluded that the inhibitory effect of ropivacaine on TNF-α production remains effective for 6.5 to 7 hours after administration.

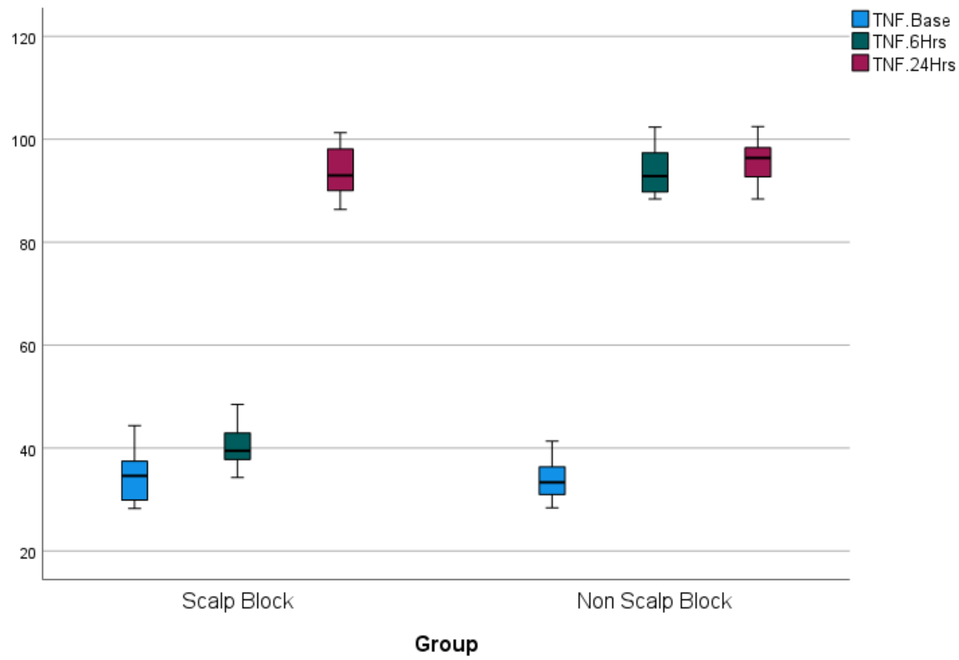

Figure 1. Trend of change on TNF-α concentrations

At 6 hours after incision, while there was an increase of cortisol concentration in both groups, the difference was insignificant. It is worth noting the elevation within SNB group was significantly lower. These results indicate that scalp nerve block with ropivacaine can attenuate the magnitude of cortisol elevation due to surgery. This is consistent with previous studies on ropivacaine infiltration. Sun et al reported a significant decrease in open hepatectomy wounds at 24 and 48 hours after local infiltration of ropivacaine post-surgery (Sun et al., 2017). Another study demonstrated that ropivacaine infiltration before incision or before skin closure in herniorrhaphy surgery in children prevented a significant increase in cortisol concentration 5 minutes after surgery completion (Sakellaris et al., 2004). In our study, both groups exhibited a decline in cortisol concentration returned to baseline level at 24 hours after surgery, with significantly lower level in SNB group. This cortisol decline might be influenced by the third sampling time that was between 16.30 and 17.30 pm. In normal condition, cortisol secretion is regulated by circadian rhythm; highest systemic concentration is in the morning around 08.00 a.m. and progressively decreases until it reaches the lowest concentration at midnight (Pagana & Pagana, 2015). Theoretically, cortisol elevation will trigger negative feedback, inhibiting ACTH and cortisol secretion. However, this negative feedback mechanism becomes ineffective after surgery, leading to persistent high levels of ACTH and cortisol (Desborough, 2000). Several study results suggest conflicting trends in cortisol concentration changes. A meta-analysis study concluded that cortisol concentration remains elevated for up to 7 days after surgery, contradicting earlier research reports of cortisol concentration returned to basal level within 24-48 hours after surgery (Prete et al., 2018). A study comparing cortisol levels in morning and afternoon surgeries showed that cortisol concentration increased in both groups up to 6 hours after surgery, but then decreased afterward (Kwon et al., 2019), which is similar with this study.

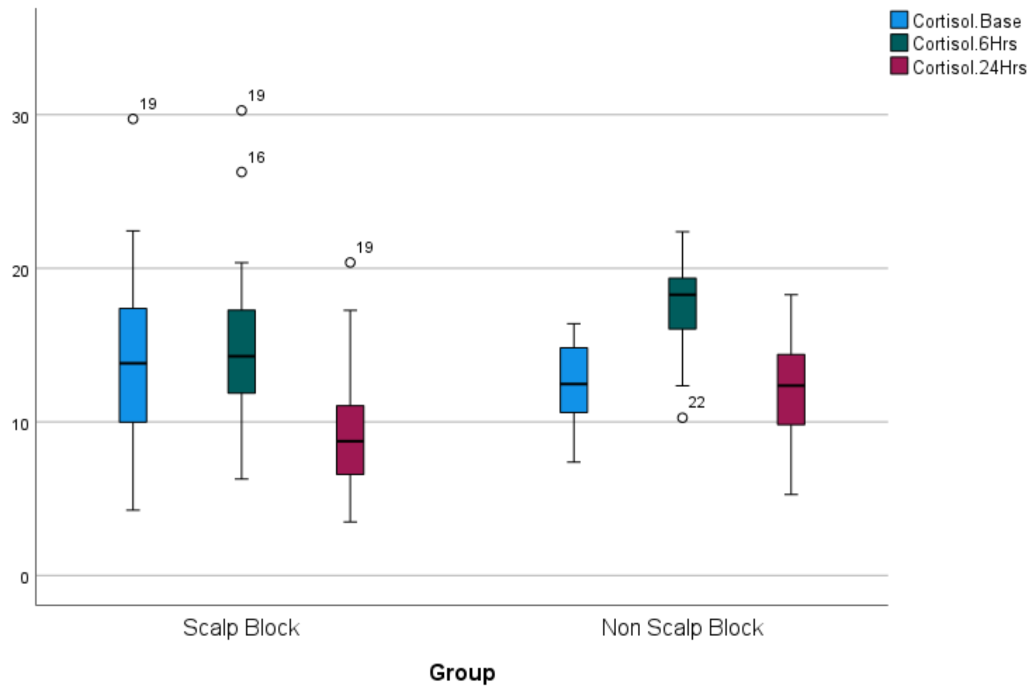

Figure 2. Trend of change on cortisol concentrations

The variability in cortisol level fluctuation among different studies may be attributed to multiple factors that affect cortisol secretion, such as patient-specific conditions, complexity of the surgical procedure, anesthesia techniques (Prete et al., 2018), and patient psychological factors or anxiety (Cusack & Buggy, 2020). Given the multitude of non pain-related factors influencing cortisol level, cortisol alone is not ideal to be used as a specific biomarker of metabolic surgical stress responses.

Blood glucose concentration in both groups did not exhibit significant differences at all sampling times. Furthermore, the blood glucose concentration within the same group were also statistically insignificant across all sampling times. This finding contradicts theoretical considerations; in theory, blood glucose concentration is expected to increase in response to surgery. Increased cortisol due to surgery inhibits glucose utilization by cells, leading to elevated blood glucose levels. Growth hormone, which is also elevated in response to surgical stress, can stimulate glycogenolysis in the liver and insulin resistance in tissues, resulting in increased hepatic glucose production and decreased glucose utilization by cells, thus causing a further increase in blood glucose concentration (Cusack & Buggy, 2020). The absence of elevation in blood glucose concentration may be attributed to the inhibition of pain stimulation during and after surgery, facilitated either by ropivacaine in the SNB group or by fentanyl in the non-SNB group. As pain, one of the primary causes of the stress response, is attenuated by ropivacaine (in the SNB group) or fentanyl (in the non-SNB group), the elicited stress response is consequently diminished. Stimulation of inflammatory mediators alone, without the presence of pain sensation, may not be potent enough to induce a cascade reaction that increase blood glucose concentration.

Total consumption of fentanyl during surgery and 24 hours after surgery in non-SNB group was significantly higher. This result is consistent with prior research indicating that scalp nerve block with ropivacaine during craniotomy reduces fentanyl consumption during surgery (Suryadani et al., 2020) and during the 24 hours postoperative period (Muhammad Aviv Pasa et al., 2020). The use of ropivacaine for sphenopalatine ganglion block in functional endoscopic sinus surgery can also reduce the amount of fentanyl consumption during surgery (Sumitro et al., 2022). In SNB group, two subjects received rescue analgesia during surgery, while in non-SNB group, rescue analgesia was administered to six subjects. After surgery, in SNB group, only three subjects required rescue analgesia, compared to 13 subjects in the non-SNB group. The higher number of non-SNB group patients requiring rescue analgesia indicates that postoperative pain in the non-SNB group is more severe than in the SNB group. This finding aligns with previous research indicating that in patients undergoing craniotomy with opioid use during surgery, 96% of patients still experienced moderate to severe pain within the 24-hour postoperative period (Gottschalk et al., 2007).

CONCLUSION

Administration of scalp nerve block with ropivacaine prior to craniotomy is effective in attenuating surgical stress response, encompassing both metabolic and immunological components. The elevation of TNF-α concentration as an indicator of immune stress response can be inhibited by ropivacaine for a duration extending up to 6.5-7 hours after administered, but this effect is not sustained until 24 hours after surgery. In contrast, the inhibitory effect on cortisol elevation by ropivacaine appears to persist up to 24 hours after surgery. Blood glucose concentration seemed to be influenced by numerous other factors, rendering it insufficient as a sole parameter for assessing surgical stress response. Scalp nerve block with ropivacaine prior to craniotomy also effectively reduces the overall consumption of fentanyl during surgery and within 24 hours postoperative period.

AUTHORS' CONTRIBUTION

NSK & PSA: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. *CSW, HZ, PK & DAS*: Data acquisition, interpretation, drafting, final approval and agree to be accountable forall aspects of the work.

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