ORIGINAL ARTICLE

Comparison of the effect of scalp block analgesia bupivacaine 0.25% and clonidine 2 µg/kg with bupivacaine 0.25% and dexamethasone 8 mg on cortisol levels and Numeric Rating Scale in craniotomy tumour

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ABSTRACT

Introduction: Craniotomy tumour is brain surgery that can induce a stress response. The stress response can be measured using haemodynamic parameters and plasma cortisol concentration. The stress response that occurs can affect an increase in sympathetic response, such as blood pressure and heart rate, which can lead to an increase in intracranial pressure. Scalp block can reduce the stress response to surgery and post-operative craniotomy tumour pain. The local anaesthetic drug bupivacaine 0.25% is effective in reducing post-operative pain and stress in the form of reducing plasma cortisol levels. The adjuvant addition of clonidine 2 µg/kg or dexamethasone may be beneficial.

Materials and Methods: A randomised control clinical trial was conducted at the Central Surgery Installation and Hasan Sadikin General Hospital Bandung and Dr. Mohammad Husein Hospital Palembang from December 2022 to June 2023. A total of 40 participants were divided into two groups using block randomisation. Group I receives bupivacaine 0.25% and clonidine 2 µg/kg, and group II receives bupivacaine 0.25% and dexamethasone 8 mg. The plasma cortisol levels of the patient will be assessed at (T0, T1 and T2). All the patient were intubated under general anesthaesia and received the drug for scalp block based on the group being randomised. Haemodynamic monitoring was carried out.

Results: There was a significant difference in administering bupivacaine 0.25% and clonidine 2µg/kg compared to administering bupivacaine 0.25% and dexamethasone 8 mg/kg as analgesia for scalp block in tumour craniotomy patients on cortisol levels at 12 hours post-operatively (T1) (p=0.048) and 24 hours post-surgery (T2) (p=0.027), while post-intubation cortisol levels (T0) found no significant difference (p=0.756). There is a significant difference in Numeric Rating Scale (NRS) at post-intubation (T0) (p=0.003), 12 hours post-operatively (T1) (p=0.002) and 24 hours post-surgery (T2) (p=0.004), There were no post-procedure scalp block side effects in both groups.

Conclusion: The study found that scalp block with 0.25% bupivacaine and 2µg/kg clonidine is more effective in reducing NRS scores and cortisol levels compared bupivacaine 0.25% and dexamethasone 8mg in tumour craniotomy patients.

KEYWORDS:
Bupivacaine, clonidine, cortisol, dexamethasone, scalp block

INTRODUCTION

Craniotomy surgery for tumour is a brain surgery that can induce stress response, especially during laryngoscopy, cranial pin placement and skin incisions. During these procedures, it is important to adhere to the principles of neuroanesthesia to prevent increased intracranial pressure and ensure optimal cerebral perfusion and oxygenation. Tissue trauma that occurs during surgery not only has an impact on peripheral sensitisation but also has an impact on the endocrine system.[1,2]

Anaesthesia management in neuroanaesthesia patients is based on the effects of drugs on the physiology of the central nervous system, including cerebral blood flow, cerebral blood volume, intracranial pressure, autoregulation, response to carbon dioxide, and the production and absorption of cerebrospinal fluid. Anaesthesia drugs can affect cerebral haemodynamics, cerebral metabolism and intracranial pressure to improve outcomes in patient with brain tumour. The qualifications of anaesthetic drugs includes must be easy to control, the drug must have a stable intracranial haemodynamic and homeostatic effect, must not affect neurophysiological monitoring, have an antinociceptive effect and must protect the brain against pain due to tissue trauma during surgery.[3,4]

The pain of craniotomy surgery for brain tumour can activate the hypothalamic–pituitary–adrenal (HPA) axis and trigger the release of releasing factor. The releasing factor then triggers the anterior pituitary to secrete adrenocorticotropic hormone and release cortisol. The increase in cortisol levels due to surgery varies depending on the degree of surgery. The stress response functions to secrete hormones are needed by the body for pain regulatory functions, including tissue protection and regeneration, immunological activity and metabolic regulation. Studies

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show that high cortisol levels correlate with severe post-operative pain intensity. Excessively elevated cortisol levels can contribute to post-operative changes in the immune system, and the patient's outcome may be worse. Increased cortisol levels have an immunosuppressive effect, reducing the ability of natural killer (NK) cells and T cell responses and can cause cognitive impairment in patients.[5,6]

Peripheral nerve block is effective in reducing stress and pain response and can be used as an analgesic in craniotomy surgery. Scalp block combined with general anaesthesia can reduce the response to pinning and incision, as well as maintain haemodynamic stability and perioperative analgesia. A study showed that scalp block using 0.5% bupivacaine succeeded in reducing the neuroendocrinal stress response which was characterised by decreased plasma cortisol levels. This peripheral nerve block can be given as an adjuvant and combined with general anaesthesia to provide good pain control during and post-operative period. Several studies have investigated the potentiation and prolongation of the sensory effects of peripheral nerve blocks with the use of clonidine or dexamethasone. The addition of an adjuvant to the scalp block resulted in an earlier onset of the block with better perioperative hemodynamic stability.[3,7,8] Aim of this study is for alternative analgesia to reduce intracranial pressure.

MATERIALS AND METHODS

This study is a randomised control clinical trial. Patients were predetermined by a double-blind (patients and researcher) randomised process for group selection by block randomisation. Participants were recruited with inclusion and exclusion criteria. Inclusion criteria include patients aged 18–65 years, and brain tumour sufferers diagnosed with supratentorial tumour who will undergo craniotomy surgery, tumour size <10 cm and Glasgow Coma Scale 15. Exclusion criteria with patients suffering from pituitary and pheochromocytoma tumours, a patient has an extracranial tumour.

Researchers determined that each block consisted of two subjects, and each block consisted of group I, namely bupivacaine 0.25% and clonidine 2µg/kg. and group II, namely bupivacaine 0.25% and dexamethasone 8 mg. For example, blocks are given odd number codes for blocks I-II and even numbers for blocks II-I. Next, randomisation of the numbers is carried out and then replaced with related blocks. Participants were patients at the Central Surgery Installation who is planned for elective craniotomy surgery for tumour from December 2022 until sample size is reached. The patients were treated post-operatively in the ICU Hasan Sadikin Hospital (RSHS) Bandung and Dr. Mohammad Husein Hospital (RSMH) Palembang. The sample size was 40 patients divided into two treatment groups of 20 patients in each group. The data collected includes primary data derived from the patients' medical records.

Group 1 received scalp block bupivacaine 0.25% and clonidine 2 µg/kg. Group 2 received bupivacaine 0.25% and dexamethasone 8 mg. Group 1 will be administered clonidine 2µg/kg, (according to the patient's ideal body weight). In 3cc syringe which was mixed into the bupivacaine 25cc (70mg) syringe that had been prepared earlier. Group 2, dexamethasone 8mg was given, put into a 3cc syringe and then mixed into the bupivacaine 25cc (70mg) syringe that had been prepared earlier.

Blood samples from the participants were taken T0-before surgery, T1-12 hours after T0, and T2-24 hours after T0 check plasma cortisol levels and hemodynamics. A 5 ml of blood sample was taken and stored is put into the EDTA tube. The cortisol levels were examined using the ELISA technique.

After taking the blood at T0, the patients were intubated under general anaesthesia with neuroanesthesia principles. The patients were given the following induction drug doses of propofol 2mg/kg, fentanyl 2µg/kg and rocuronium 1.2mg/kg. Patients were given sevoflurane maintenance not more than 1 MAC, intravenous propofol 1-2 mg/kg/hour and intermittent rocuronium 10 mg every hour. Each drug for scalp block was prepared according to randomisation.

The scalp block was given on seven nerves, the supraorbital nerve, supratrochelear nerve, auriculotemporal and zygomaticotemporal nerve, Greater occipital nerve (GON) and occipital nerve (TON). On each nerve, 2cc is needed at each point. Haemodynamic monitoring was conducted for each patient, if there is an intraoperative pain response characterised by an increase in heart rate (HR) and blood pressure (BP) of more than 20%, fentanyl rescue may be given mg/kg body weight with an interval of 30 minutes which can be repeated up to three times. Blood pressure, heart rate, respiratory rate and peripheral oxygen saturation were measured and recorded. The scalp suturing operation on the craniotomy was completed; the patient was extubated and monitored in the intensive care unit and was given post-operative analgesic paracetamol 1 gram per 8 hours for 5 days.

Univariate analysis was performed to determine the frequency distribution of the variables studied. Univariate analysis presents the frequency of events in the form of numbers and percentages. Bivariate analysis was conducted to determine the average difference between the dependent and independent variables.

Analysis using the unpaired T-test statistic to compare mean cortisol at T0, T1, T2, between Group 1 and Group 2 participants. Analysis of data categories with Chi-square test. If the chi-square test requirements are not met, then the Fisher Exact test will be carried out. All analysis has a degree of confidence of 95% and an α value of 0.05. Primary data is entered into SPSS 24.0.

RESULTS

In the calculation of the difference in cortisol levels 12 hours post-operation (T1) compared to the initial cortisol levels (T0), there is a slight increase in the mean cortisol levels, namely 1.66+15.74 in the group receiving 0.25% bupivacaine and 2 µg/kg (Group 1) clonidine, while in the group receiving 0.25% bupivacaine and 8 mg dexamethasone (Group 2) , there is an increase in the mean

Tabel I: Sociodemographics characteristics of respondent

Variables	Bupivakain 0.5% + Klonidin 0.2 µg/ kg		Bupivakain 0.5% + Dexametason 8mg/kg	
	n	%	n	%
Age				
17-40 years	3	15.0	5	21.6
41-64 years	17	85.0	12	78.4
Gender				
Male	4	20.0	7	35.0
Female	16	80.0	13	65.0
Body mass index (kg/m2)				
Low (<18.5)	0	0	0	0
Normal (18.5-24.9)	20	100.0	19	95.0
Overweight (>25)	0	0	1	5.0
Duration (O'clock)				
<4 O'clock	19	95.0	17	85.0
>4 O'clock	1	5.0	3	15.0

Group 1: Bupivacain 0.5% + Clodine 0.2 µg/ kg
Group 2 : 0,5% +Dexamethasone 8mg/kg

Table II: Differences in plasma cortisol levels between test groups

Variables	Bupivacain 0.5% + Dexamethasone 0.2 µg/ kg (Group 1) Mean + SD	Bupivacain 0.5% + Dexamethasone 8 mg/kg (Group 1) Mean + SD	p*
Cortisol T0	9.87 + 8.06	8.02 + 5.05	0.756*
Cortisol T1	11.53 + 17.59	17.13 + 12.35	0.048*
Cortisol T2	12.22 + 24.13	25.85 + 27.71	0.027*
Cortisol ΔT0-T1	1.66 + 15.74	9.10 + 11.50	0.030*
Cortisol ΔT0-T2	2.34 + 22.60	17.83 + 27.84	0.009*

*Uji Mann–Whitney.

Table III: Differences in Numeric Rating Scale (NRS) between test groups

Variable	Bupivacain 0.5% + Clonidine 0.2 µg/ kg Mean + SD	Bupivacaine 0.5% + Dexamethasone 8 mg/kg Mean + SD	p*
NRS T0	3.6+1.84	2.10+0.71	0.003*
NRS T1	2.15+1.13	3.30+1.08	0.002*
NRS T2	2.10+1.02	3.45+1.57	0.004*

*Uji Mann-Whitney ($p < 0.05$).

cortisol levels of 9.10±11.50. According to Mann–Whitney test, a significant difference was found in the difference in cortisol levels 12 hours post-operation compared to the initial cortisol levels (ΔT0–T1) between these two groups ($p<0.001$).

In the calculation of the difference in cortisol levels 24 hours post-operation (T2) compared to the initial cortisol levels (T0), there is a slight increase in the mean cortisol levels, namely 2.34±22.60 in the group receiving 70 mg bupivacaine and 2 µg/kg clonidine, while in the group receiving 0.25% bupivacaine and 8 mg dexamethasone, there is an increase in the mean cortisol levels of 17.83±27.84. According to Mann–Whitney test, a significant difference was found in the difference in cortisol levels 24 hours post-operation compared to the initial cortisol levels (ΔT0-T2) between these two groups ($p<0.05$). The complete result is shown in Table II.

In 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) at baseline (T0) was 3.6+1.84, which was higher compared 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 2.10+0.71. Based on the Mann-Whitney test, there was a significant difference in the initial Numeric Rating Scale (NRS) between these two groups ($p<0.01$).

In the 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) 12 hours post-operation (T1) was 2.15+1.13, which was lower compared to the 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 3.30+1.08. Based on Mann–Whitney test, there was a significant difference in the Numeric Rating Scale (NRS) 12 hours post-operation (T1) between these two groups ($p<0.05$).

In the 0.25% bupivacaine and 2 µg/kg clonidine group, the mean Numeric Rating Scale (NRS) 24 hours post-operation (T2) was 2.10+1.02, which was lower compared to the 0.25% bupivacaine and 8 mg dexamethasone group, with a mean NRS of 3.45+1.57. Based on the Mann-Whitney test, there was a significant difference in the Numeric Rating Scale (NRS) 24 hours post-operation (T2) between these two groups. More details are presented in Table II.

All research subjects in both the group receiving 0.25% bupivacaine and 2 µg/kg clonidine, as well as the group receiving 0.25% bupivacaine and 8 mg dexamethasone, did

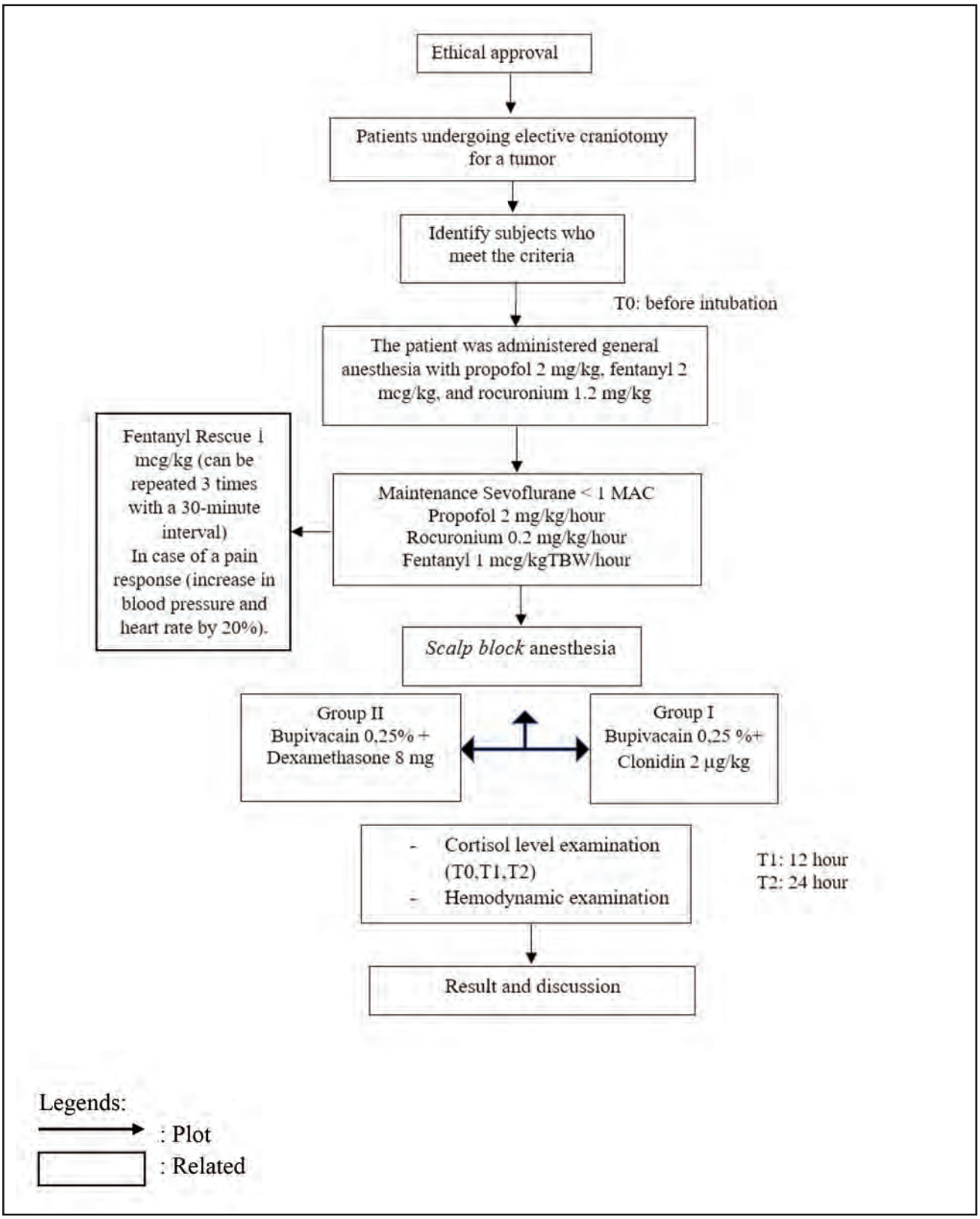

Fig. 1: Study procedural

not experience any side effects such as bradycardia, hypotension or post-procedure allergies following scalp block.

All research subjects, in the group given bupivacaine 0.25% and clonidine 2 µg/kg, or in the group given bupivacaine 0.25% and dexamethasone 8 mg, had no side effects after the scalp block procedure. These results are supported by scalp block studies with 0.25% bupivacaine in the addition of clonidine 2µg/kg (group III), in the group addition clonidine 1 µg/kg (group II), compared with group I (control) at each time of hemodynamic calculation, both during pin placement, skin incision and dura incision. In the group with the addition of clonidine 1µg/kg (group II), there was a significant difference compared to the control group at the time of pin placement, while in the skin incision and dura incision, there was no significant difference compared to the control group. It appears that there is an effect of accelerating onset. Treatment side effects were also observed during the study. Observed side effects such as bradycardia, hypotension and desaturation were not found in any study subjects. Giving a scalp block with clonidine up to 2µg/kg is safe for craniotomy patients.

In the assessment of pain using the Numeric Rating Scale (NRS), patients are asked to evaluate the pain they are experiencing using a scale of 0-10. The higher the number chosen, the more intense the pain experienced. A score of 0 means no pain, 1-3 means mild pain, 4-6 means moderate pain and 7-10 means severe pain. Post-operative pain management for craniotomy is typically performed routinely, especially 24 hours post-operation, due to the risk of post-operative edoema and bleeding.

In the assessment of the first 24 hours post-craniotomy using the NRS, 87% of patients experienced pain (NRS 1-3: 32%, NRS 4-7: 44%, NRS 8-10: 11%). During the first 24 hours after craniotomy, 87% of patients experienced pain. Despite post-operative pain management with strong analgesics, more than 44% of patients suffered from moderate pain, and 10% of patients experienced severe pain during the first 24 hours after craniotomy. The high incidence of moderate to severe pain after craniotomy makes standard pain evaluation using the NRS important for routine assessment.

The findings of this study are supported by research that compared groups receiving 0.25% levobupivacaine with the addition of 2 µg/kgBB clonidine and those receiving single 0.25% levobupivacaine in craniotomy patients. Their findings indicated a decrease in NRS and a significant difference in NRS ($p<0.05$) in the group receiving 0.25% levobupivacaine with the addition of 2µg/kg BB clonidine, especially at 12 and 24 hours post-craniotomy. The use of clonidine as an adjunct to peripheral nerve blocks has a local anaesthetic effect and can inhibit the potential working component of C fibres, which is greater than that of A-α fibres. In scalp blocks, the addition of clonidine primarily facilitates peripheral nerve block through the hyperpolarization of cationic current activation. In sodium currents in dorsal root ganglia, clonidine reduces the amplitude of sodium currents that are sensitive to tetrodotoxin and resistant to tetrodotoxin.

Dexamethasone has been used as an adjuvant to local anesthaesia in peripheral and neuraxial nerve blocks. Dexamethasone acts on K+ channels in nociceptive C fibres via glucocorticoid receptors thereby influencing fibre activity. Reduces local anaesthetic absorption by inducing vasoconstriction levels and decreasing C fibre activity by inhibiting potassium channels. The combination of regional and general anaesthesia for surgery has proven to be beneficial for patients with the aim of reducing the perioperative stress response in the form of pain, thereby reducing the activation of the HPA axis stress response.

DISCUSSION

In craniotomy surgery, tissue damage occurs and the release of inflammatory mediators, resulting in peripheral sensitisation and causing a stress response. The stress response is thought to be due to stimulation during scalp incision, periosteal release, dural opening and brain retraction, which activates the HPA system which functions to secrete hormones needed by the body for pain-regulating functions, including tissue protection and regeneration. immunological activity and metabolic regulator. Studies show that high cortisol levels correlate with severe pain intensity after surgery. Elevated cortisol levels have an immunosuppressive effect, namely reducing the ability of NK and T cells responses and can cause cognitive impairment in patients. Therefore, it is important to reduce cortisol levels.[9-12]

Scalp block technique used in craniotomy surgery with 0.25% bupivacaine as an adjuvant to general anaesthesia can provide an option to improve intraoperative analgesia with more stable haemodynamics, as well as the need for less intravenous anaesthesia or volatile anaesthetics. However, this scalp block technique can only last for a few hours. This situation demands prolongation of analgesia which can be achieved by improving the quality of local anaesthesia. To overcome this problem, several drugs have been clinically tested and proven useful as additional agents for local anaesthesia which are called adjuvants.[13-15]

The scalp consists of five layers, which are called SCALP, namely skin, connective tissue or subcutaneous tissue, aponeurosis galea, loose areolar tissue or loose connective tissue, and pericranium (pericranium). The five layers are shortened to scalp. Scalp block is a regional anaesthetic for the peripheral nerves that innervate the scalp and provides an analgesic effect over a long period of time and relieves post-operative pain.[8,16,17]

Preemptive analgesia by scalp block prevents the initiation of physiological and neurological responses to stimulation, thus reducing patient morbidity, leading to faster recovery, better surgical outcomes, decreased endocrine stress response to surgery, reduced hyperglycaemic response, improved respiratory function, early mobilisation, early discharge and reduced healthcare costs. This peripheral nerve block can be supplemented with adjuvants and combined with general anaesthesia to provide effective pain control during and after surgery.[5]

The results of this study are in line with other studies of patients undergoing elective supratentorial craniotomy. A study of 80 patients, 43 male and 37 female who underwent elective supratentorial craniotomy. These were randomly divided into two equal groups. Group A patients received under general anaesthesia with fentanyl. Group B patients received scalp blocks using bupivacaine (0.5%) and epinephrine (1:400.000) and patients received fentanyl 2µg/kg (during maintenance of general anaesthesia). The fentanyl group had higher plasma cortisol levels than Group B. Group B had a faster recovery period.

Cortisol was considered to have significantly decreased in the group that underwent scalp block with bupivacaine. This occurred because during the craniotomy surgery there was damage to the tissue and the release of inflammatory mediators, resulting in peripheral sensitisation and causing a stress response[12,18,19]

The decrease in cortisol levels when using a scalp block occurs because clonidine potentiates the action of the local anaesthetic bupivacaine, improving the quality of anaesthesia and extending the duration of sensory block. Sensory block reduces activation of the HPA axis, then reducing cortisol production. A meta analysis study compared the cortisol levels of patients undergoing minimally invasive surgery (grade 1) against patients undergoing moderate and highly invasive surgery (degrees 2 and 3), it was found that cortisol levels increased 2 times in grade I, 4 times in grade II and 3.5 times in grade III when compared with healthy control individuals at 24 hours post-operatively. Plasma cortisol levels then decreased after 24 hours after surgery and reached stable levels at 36-72 hours after surgery. Other studies showed that cortisol levels decreased in patients who underwent scalp block with bupivacaine 0.5%, baseline 12.5±2.24 and after skin incision 9.9±2.63, after skin incision 8.6±2.74, after dura mater closure 9.2±1.72 compared to the group receiving fentanyl 2 µg/kg (during maintenance of general anaesthesia).[1] In the scalp block study with bupivacaine 0.25% with the addition of clonidine 2 µg/kg (group III), the group adding clonidine 1 µg/kg (group II), was compared with group I (control) at each time of hemodynamic calculation, both times pin placement, skin incision and duramater incision show that scalp block administration with up to clonidine 2µg/kg is safe for craniotomy patients.39 Sensory block scalp block study on bupivacaine 0.25% supplemented with clonidine 2µg/kg 887.97±398.21 minutes, longer than the group that only received bupivacaine 0.25% (408.17 ± 209.81 minutes). Through a prospective cohort study showed that the addition of clonidine 2 µg/kg to bupivacaine 0.25% in scalp block resulted in rapid onset time, improved quality of anaesthesia and prolonged duration of sensory block.[14,20,21]

Clonidine, an α2 agonist, is an option for administering adjuvants to scalp blocks. Clonidine acts on centrally acting presynaptic α2 adrenoreceptors, α2 mediating a decrease in systemic vascular resistance and an increase in vagal tone resulting in a decrease in mean arterial pressure and heart rate. This also causes a decrease in norepinephrine secretion from peripheral nerve endings thereby reducing the stress response. Clonidine inhibits the larger C-fibere action potential component of the A-α fibres through hyperpolarising the activation of cationic currents. The effect of clonidine on Na+ currents in the dorsal root ganglia decreases the amplitude of sodium currents. Hyperpolarization of nucleotide-gated ion channels results in prolonged nerve block by local anaesthetic.[13-15]

In this study, cortisol levels in the test Group 2 of bupivacaine 0.25% and dexamethasone 8 mg showed an increase 12 hours after scalp block (T1) ΔT0-T1= 9.10 (±11.50), and 24 hours after scalp block (T2) ΔT0-T2 = 17.83 (±27.84). The addition of dexamethasone 4 mg to bupivacaine 0.5% can cause an increase in the quality of anaesthesia and a prolonged duration of sensory block.1 Scalp block patients at craniotomy with ropivacaine 0.2% added to dexamethasone 8 mg experienced sensory block for 760 minutes. The addition of 4 mg perineural dexamethasone to an interscalene brachial plexus block with ropivacaine 0.75% prolonged the duration of motor and sensory block compared to the group receiving ropivacaine 0.75% + 1 ml isotonic saline and ropivacaine 0.75% + 1 ml isotonic saline + dexamethasone 4 mg intravenously.[22]

CONCLUSION

The administration of scalp block with 0.25% bupivacaine and 2 mcg/kg clonidine is more effective in reducing NRS scores and suppressing the increase in cortisol levels compared to using 0.25% bupivacaine and 8 mg dexamethasone in patients undergoing craniotomy for tumour resection.

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