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RESEARCH ARTICLE

The Effectivity of Clonidine Addition to Levobupivacaine 0.25% for Scalp Block in Patients Underwent Craniotomy Surgery

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Abstract

Background: The scalp nerve block technique is a relatively simple and safe technique. Clonidine is well-known as an agent that extends the analgesia effect of local anesthetic drugs. The goal of this study was to evaluate the effectiveness of clonidine addition as adjuvants in levobupivacaine 0.25% in scalp nerve block in craniotomy procedures. Patients and Methods: This was a clinical trial with a double-blind, randomized study using consecutive sampling technique. Inclusion criteria include patients underwent craniotomy surgery due to brain tumor using general anesthesia with endotracheal tube in 18-60 years of age. As an addition to general anesthesia, group a received levobupivacaine 0.25% and clonidine 2 µg/kg as a regiment for scalp block. Group B received levobupivacaine only for the same purpose. All other treatments were similar for both groups. Results: The intraoperative fentanyl requirement (100 (50-150) vs. 150 (75-200) mcg, p <0.001), the period to the postoperative first PCA dose (822.5±129.7 vs. 387.8±69.6 minutes, p <0.001), and the total need of postoperative morphine by PCA (2.0 (1.0-3.0) vs. 3.0 (2.0-7.0) mg, p <0.001) were lower in the clonidine-added levobupivacaine groups compared to levobupivacaine alone. 3 Conclusions: The addition of clonidine to levobupivacaine 0.25% on scalp block is effective in reducing the need for intraoperative and postoperative opioids, reducing postoperative pain, extending the duration of scalp nerve block, and delaying the first PCA dose.

Keywords: *Clonidine, Levobupivacaine, Fentanyl, Morphine, Pain, Requirements.*

Introduction

Brain tumors are abnormal growths of cells in or around the brain. Brain tumors can affect anyone with different symptoms. Brain tumor treatment is based on the type, size, and location of the tumor. Surgery is a procedure that provides effective results against brain tumors. According to the Central Brain Tumor Registry of the United States (CBTRUS), in 2010-2014 the incidence of tumors in the central nervous system is 22.64/100,000 per year. The incidence in adults (> 20 years) is 29.41/100,000 [1].

In 2018 there are estimated to be 79,870 new cases with a mortality rate of 4.33/100,000 [2].The most common were meningiomas (36.3%), pituitary tumors (16.2%) and glioblastoma (14.9%) [1].The goal of anesthesia in brain tumor surgery is to prevent secondary brain injury that can be caused by increased intracranial pressure, hypotension or hypertension [3].To get excellent hemodynamic stability can be done by giving opioids, deepening the anesthesia, or giving local anesthesia by infiltration or scalp nerve block. Excessive use of opioids is associated with longer conscious recovery time and excessive decrease in blood pressure when manipulation is minimal [3, 7]. Many studies showed that scalp block provides better hemodynamic stability in the intraoperative period and fewer intraoperative opioid requirements compared with the control group [4, 8].

They found that scalp nerve block was better in the management of postoperative pain with less consumption of opioids. Wajekar *et al* [9]. And Dash *et al* [10].Examined the administration of clonidine as an adjuvant in scalp nerve block, finding the addition of clonidine as an adjuvant provided better hemodynamic stability and prolongation of the effect of scalp nerve block.

The scalp nerve block technique is a relatively simple and safe technique. The goal of this study was to evaluate the effectiveness of clonidine addition as an adjuvant to levobupivacaine 0.25% in scalp nerve block in craniotomy procedures.

Patients and Methods

This was a clinical trial with a double-blind, randomized study using consecutive sampling technique. Inclusion criteria include patients underwent craniotomy surgery due to brain tumor using general anesthesia with endotracheal tube in 18-60 years of age. Exclusion criteria include ASA physical status IV-V, preoperative Glasgow Coma Scale (GCS) <15, history of hypertension, diabetes mellitus, or allergy to bupivacaine, coagulopathies, history or presence of psychiatric disorders that can affect the perception of pain perception, chronic pain, and body mass index (BMI) of ≤18.5 kg/m^2 or ≥30 kg/m^2.

Patients who eventually experience class 3-4 bleeding, developed LAST, required mechanical ventilation postoperatively, and surgery duration of >6 hours were dropped from this study. The randomization technique for subject allocation in each group was carried out by permuted block randomization technique. The subjects in this study were divided into two groups, where both the researchers and the patients were aware of the type of treatment given. As an addition to general anesthesia, group A received levobupivacaine 0.25% and clonidine 2 μg/kg as a regiment for scalp block. Group B received levobupivacaine only for the same purpose. All other treatments were similar for both groups. In the postoperative period, we installed a 50 mL PCA containing morphine 1 mg/ml (demand dose 1 mg, lockout interval 6 minutes, with a maximum dose of 10 mg in 4 hours). We prescribed intravenous paracetamol at 15 mg/kg as adjuvant of analgesia. Data analysis was carried out with SPSS 24.0 for Windows. We used the Shapiro-Wilk test for normality test and Levene's test for variance homogeneity test. The independent t-test was used if the data distribution is normally distributed. Otherwise, the Mann-Whitney test was carried out. A p-value of <0.05 was considered statistically significant.

Results

Descriptive statistical analyses were performed on the characteristics of the study subjects, including age, sex, BMI, ASA physical status, surgery duration. A description of the characteristics of the study subjects by the treatment group is shown in Table 1.

Table 1: Characteristics of the subjects

Variables	Groups	
	A (n=23)	B (n=23)
Age (years), mean±SD	36.74±14.004	40.04±13.258
Sex, n(%)		
Male	10 (43.5)	12 (52.2)
Female	13 (56.5)	11 (47.8)
BMI (kg/m^2), mean±SD	22.74±2.9	23.35±2.62
ASA physical status		
II	5 (21.7)	7 (30.4)
III	18 (78.3)	16 (69.6)
Surgery duration (minutes), median (min-max)	150 (120-300)	170 (120-300)

SD: standard deviation; BMI: body mass index; ASA: American Society of Anesthesiologists

We used fentanyl in the intraoperative period as a part of anesthesia maintenance. For the postoperative pain management plan, we installed each patient with morphine-containing PCA. The total use of both fentanyl and morphine were calculated and presented in Table 2.

Table 2: Intraoperative and postoperative opioids requirements

Variables	Groups		p
	A	B	
Intraoperative fentanyl requirements (mcg), median (min-max)	100 (50-150)	150 (75-200)	<0.001a
First PCA demand (minutes after the end of the surgery), mean±SD	822.5±129.7	387.8±69.6	<0.001a
Total postop morphine consumption (mg), median (min-max)	2.0 (1.0-3.0)	3.0 (2.0-7.0)	<0.001a

PCA: patient-controlled analgesia; SD: standard deviation; [a]Mann-Whitney test

In this study, we also assessed the postoperative pain level in our subjects. Table 3 shows us that the median NRS of the subjects in group a compared with Group B were statistically different at 12 and 24 hours after the surgery.

Table 3: Numerical rating scale (NRS) at 4-24 hours after the scalp blok

NRS at X hours after scalp block	Groups		p
	A	B	
4 hours, median (IQR)	1 (0-2)	1 (0-3)	0.110[a]
6 hours, median (IQR)	1 (0-2)	1 (0-3)	0.175[a]
12 hours, median (IQR)	1 (0-2)	1 (0-3)	0.020[a]
24 hours, median (IQR)	0 (0-1)	1 (0-3)	0.002[a]

IQR: interquartile range; [a]Mann-Whitney test

Discussion

In this study, the scalp block was carried out using 0.25% levobupivacaine solution with or without the addition of clonidine. Levobupivacaine works by the mechanism of nerve-wrap penetration followed by nerve conduction blocks by preventing action potentials in axons. Direct interaction with specific receptors on the Na^+ channel thus inhibiting the entry of Na^+ ions. The anesthetic drug molecule must pass through the cell membrane via passive non-ionic diffusion of the molecule and then bound to the Na^+ channel. Repeated stimulation causes additional bonding to the Na^+ channel [11]. Increased concentration causes the transmission of autonomic, somatosensory, and somatomotor impulses to stop, resulting in the blockage of the autonomic, sensory, and motor nervous systems in the area innervated by the nerves affected by the blockade [12, 13].

Clonidine as an adjunctive on peripheral nerve block has a local anesthetic effect and can inhibit the potential component of action of C fiber that is greater than A-α fiber [14].Clonidine also is having a pharmacokinetic impact on the redistribution of local anesthetics mediated by the vasoconstrictor effect on α2 receptors. Clonidine predominantly facilitates peripheral nerve block through hyperpolarization of cationic current activation [15, 16].We found that clonidine addition to 0.25% levobupivacaine for scalp block can reduce the need for intraoperative opioids ($p < 0.001$). The concept of peripheral nerve block of the scalp was first introduced by Harvey Cushing and George Crile in the 1900s. In 1910, Heinrick Braun added epinephrine to local anesthesia before the incision of craniotomy. The term scalp block itself was first used by Girvin in 1986. Levobupivacaine is a local anesthetic with a long duration.

The duration of action of local anesthesia in peripheral nerve blocks depends on the type of nerve that is blocked. The duration of action of levobupivacaine on nerve blocks is 180-360 minutes. Clonidine is an adjunct to peripheral nerve blocks that can extend the duration of local anesthetic drugs. Our results were consistent with other previous reports. One study reported that the intraoperative opioid need of the local anesthetic and clonidine group was 107.50±18.32 mcg compared to scalp blocks alone (165.00±20.52 mcg, $p < 0.05$) [10]. Another research reported significantly lower total intraoperative fentanyl use in the scalp block with clonidine group compared scalp block alone. This may be due to the synergistic inhibitory action of opioids and adrenoreceptor α2 agonists at the center of sympathetic flow [9]. The first PCA dose was defined as the time between the end of scalp block applications to the first time a patient push the button at his/her PCA to deliver an analgesic dose.

In this study, we found that the first PCA dose in the scalp block and clonidine group was significantly longer compared to scalp block group ($p < 0.001$). This prolonged effect is consistent with the study conducted by Wajekar *et al* [9].Who reported that the scalp block using bupivacaine+clonidine took 887.97±398.21 minutes compared to bupivacaine alone (408±209.81 minutes, $p < 0.05$). Jyothi *et al* [17].Also found a prolongation of the analgesic effect with the addition of α2 agonist adjuvants to levobupivacaine in patients who underwent abdominal surgery ($p=0.001$). Bernard *et al* [18].Conducted a study of the effects of intravenous clonidine analgesia in the postoperative period. They found intravenous administration of clonidine to be effective in reducing the need for intravenous opioids given through PCA. With the reduced use of morphine, it is expected that the side effects of morphine will also be reduced.

In this study, we assessed the NRS at 4, 6, 12 and 24 hours postoperatively. We did not find any significant differences in 4- and 6-hours mark, but we found statistically significant differences at 12- and 24-hours mark. Although the distinction was present, both groups demonstrated low NRS that can be classified as mild pain.

Can and Bilgin[8] reported that the visual analog scale (VAS) measurements that were carried out at 0, 2, 6, 8, 16, and 24 postoperatively after getting a scalp block with levobupivacaine showed that the VAS values obtained were in the range of 0.5-2.9 mm. Ayoub *et al* [19].Found that scalp nerve block appeared to be equivalent to morphine as analgesia in patients undergoing craniotomy surgery on a remifentanil basis. There are some limitations to this study. We did not measure the depth of anesthesia quantitatively because of technical difficulties in placing the bispectral index electrodes. We also used NRS instead of VAS, where we know that VAS is a more reliable measurement for pain due to its accuracy and subjectivity.

Conclusions

The addition of clonidine to levobupivacaine 0.25% on scalp block is effective in reducing the need for intraoperative and postoperative opioids, reducing postoperative pain, extending the duration of scalp nerve block, and delaying the first PCA dose. This combination is an effective choice of multimodal analgesia in patients underwent craniotomy surgery.

Acknowledgment

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