

ORIGINAL ARTICLE

A COMPARATIVE STUDY OF BUPIVACAINE AND BUPIVACAINE WITH CLONIDINE UNDER SPINAL ANESTHESIA IN PATIENT FOR TOTAL ABDOMINAL HYSTERECTOMY

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ABSTRACT: BACKGROUND: Bupivacaine is the most commonly used drug for spinal anesthesia. To improve upon the quality of analgesia and prolong the duration of its action, many adjuvants have been tried. Intrathecal clonidine an α_2 adrenoreceptor agonist with analgesic effect at spinal level mediated by postsynaptically situated adrenoreceptor in dorsal horn of spinal cord. Low doses of clonidine and buprenorphine have shown effectiveness in intensifying spinal anesthesia. **AIM:** This study is designed to evaluate the effectiveness of spinal blockade by adding 50 μ gm clonidine to bupivacaine. **SETTINGS AND DESIGN:** This a prospective, randomized, comparative clinical study involved 60 ASA grade I/II patients aged 18-55 years undergoing elective hysterectomy under spinal anesthesia after approval from hospital ethics committee with written and informed consent of patients. **MATERIALS AND METHODS:** 60 ASA grade I/II patients aged 18-55 years selected for the study are divided in two groups of 30 each. Group B (Bupivacaine group) patients will receive intrathecally 0.5% hyperbaric bupivacaine 4 ml (Total 4 ml) whereas Group C (Clonidine group) patient will receive intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50 μ g (Total 4 ml). The onset time to reach peak sensory and motor level, post-operative analgesia, hemodynamic changes, and side effects were recorded. **RESULTS:** The onset of sensory and motor blockade was faster in the group C compared to group B [137.60 seconds and 112.22 seconds] ($p < 0.001$), [231.80 seconds and 165.1 seconds] ($p < 0.001$). Duration of sensory block, motor block and postoperative analgesia [221.4 minutes in group B vs. 362.84 minutes in group C] ($P < 0.001$), was significantly prolonged in group C. There were no significant hemodynamic changes in both the groups. **CONCLUSION:** Clonidine potentiates bupivacaine spinal anesthesia by increasing the duration and improving the quality of analgesia without significant hemodynamic side effects.

KEYWORDS: Spinal anesthesia, Bupivacaine, Clonidine, Complete, effective and postoperative analgesia.

INTRODUCTION: Spinal anesthesia or sub-arachnoid block (SAB) is a form of regional anesthesia involving injection of a local anesthetic into the subarachnoid space. It is defined as 'the regional anesthesia obtained by blocking nerves in the subarachnoid space is a popular and common technique used worldwide.¹

Spinal anesthesia with Bupivacaine is well known procedure for gynecological surgery. If proper pain relief is provided, ambulation of patient in post op period is faster providing faster recovery of patient.

Clonidine (1-2 μ g/kg) intrathecal dose is shown to prolong action of Bupivacaine.

ORIGINAL ARTICLE

α_2 adrenergic agonist clonidine can cause:

1. Hypotension which can significantly lower BP in some patients requiring administration of mephenteramine and or
2. Bradycardia also may require to give Inj. atropine for treatment.
3. Duration of analgesia (as defined by the time from intrathecal administration to first request for supplemental analgesia by patient) is 6-8 hour of analgesia.

CLONIDINE: α_2 adrenergic agonist has central brain stem action and peripheral action.²

Hypothalamic α_2 adrenoceptors are inhibitory and causes decrease in outflow from the vasomotor centers and sympathetic centers.

This explains resultant decrease in peripheral vascular resistance heart rate, and blood pressure, cardiac output.

Action by transdermal application is better → gives consistent blood levels and less side effects.³

Mechanical treatment for sympathetically maintained pain.

Mainly used for hypotensive anesthesia by IV route.

Extra dural analgesic action is because of post synaptic activation of descending inhibitory pathway that synapses into dorsal horn of spinal cord.

On withdrawal of drug concentration of catecholamine's increases suddenly and can cause rebound Hypertension. Therefore it should not be withdrawn abruptly after surgery

Prolongs spinal anesthesia when combined with local anaesthetic.⁴

BUPIVACAINE: Bupivacaine is a local anaesthetic drug belonging to the amino amide group.⁵ Bupivacaine binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, no initiation or conduction of a pain signal can occur.

The rate of systemic absorption of bupivacaine and other local anaesthetics is dependent upon the dose and concentration of drug administered, the route of administration, the vascularity of the administration site, and the presence or absence of epinephrine in the preparation.^{6,7}

- Onset of action (route and dose-dependent): 1-17 min.
- Duration of action (route and dose-dependent): 2-9 hr.
- Half-life: neonates, 8.1hr, adults: 2.7 hr.
- Time to peak plasma concentration (for peripheral, epidural or caudal block): 30-45 min.
- Protein binding: about 95%.
- Metabolism: hepatic.
- Excretion: renal (6% unchanged).

Bupivacaine is indicated for local infiltration, peripheral nerve block, sympathetic nerve block, and epidural and caudal blocks.

Bupivacaine is contraindicated in patients with known hypersensitivity reactions to bupivacaine or amino-amide anaesthetics.

ORIGINAL ARTICLE

MATERIALS AND METHODS:

METHODOLOGY: This study was carried out in the department of Anesthesiology, Navodaya medical College, Raichur from November 2012 to December 2014. The study was conducted after approval of ethical committee of the institution. Written informed consent was obtained from all the patients.

60 patients A.S.A. grades I and II scheduled for gynecological surgery were selected. They were divided into 2 groups of 30 each. Group B (Bupivacaine group) patients received intrathecally 0.5% hyperbaric bupivacaine 4ml (Total 4ml) whereas Group C (Clonidine group) patient received intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50µg (Total 4 ml).

PROCEDURE: After PAC and required investigations obtained, demographic data of age, weight obtained for each case. Patients were trained for 10 cm VAS score for pain at PAC. After adequate fasting, vitals checked IV started with wide bore canula preloading with 4 ml /kg of RL solution given 15 minutes before SA. Fluids were administered according to need of patient as dictated by blood loss and hemodynamic instability.

Spinal anesthesia with standard protocol was administered, patient received total 4 ml of intrathecal volume, and baseline observations were recorded on each patient - Pulse, BP, Resp. rate, O₂ saturation.

All patients received IV Midazolam 0.1 mg/kg body wt. as premedication- level of block achieved was assessed in each patient. Patients were monitored continuously using noninvasive blood pressure, pulse oximeter and electrocardiogram. After spinal anesthesia, Oxygen (4L/min) by facemask was given. Fluid therapy was maintained with lactated Ringer's solution (10mL/kg/hr).

Clinically relevant bradycardia was defined as pulse rate < 50 per minute and was treated with 0.6 mg IV atropine.

Clinically relevant hypotension was decided by 20% decrease in systolic blood pressure from baseline values and was treated with mephenteramine 3 to 6 mg. IV.

Patients were monitored continuously Heart Rate, Blood Pressure, Respiratory Rate and SpO₂ monitoring at 1, 3, 5, 10, 15, 20, 30 minutes and half an hourly till the end of surgery.

The onset of sensory block was tested by pin-prick method using a hypodermic needle. The time of onset was taken from the time of injection of drug into subarachnoid space to loss of pin prick sensation.

The highest level of sensory block and time required to achieve it was noted.

Assessment of motor blockade was assessed by Bromage scale*.

The time interval between injections of drug into subarachnoid space, to the patient's inability to lift the straight extended leg was taken as onset time (Br. 3). The duration of motor block was taken from time of injection to complete regression of motor block. (Ability to lift the extended leg) (Br 0).

Modified Bromage Scale:

- Grade 0 - Full flexion of knees and feet.
- Grade 1 - Just able to flex knees, full flexion of feet.
- Grade 2 - Unable to flex knees, but some flexion of feet possible.
- Grade 3 - Unable to move legs or feet.

ORIGINAL ARTICLE

Postoperative analgesia were assessed by VAS. All the patients were instructed about the VAS and to point out of the intensity of pain on the scale 0- no pain, 10- worst pain.

Duration of complete analgesia was defined as the time from the intrathecal injection to VAS >0 - <2 and duration of effective analgesia as the time to VAS >1-<4. Analgesics were avoided until demanded by the patient and the time taken for the first pain medication was also noted (ie., when VAS >5).

VAS was also recorded 3, 6, 12 hours postoperatively.

Quality of Relaxation & field of surgery were recorded. Complete recovery from spinal anesthesia was demonstrated in all patients. Side effects such as nausea, vomiting, pruritis were recorded. The results are expressed as mean \pm SD.

INCLUSION CRITERIA:

1. ASA Grade 1 and 2 patients.
2. Age group of 18 – 55 Years.
3. Patient given valid informed consent.
4. Those patients scheduled to undergo elective total abdominal hysterectomy.

EXCLUSION CRITERIA:

1. Patient refusal.
2. Patients belonging to ASA grade 3 and 4.
3. Patients on opioids and α 2 agonist like clonidine.
4. Patient with gross spinal abnormalities, localized skin sepsis, hemorrhagic diathesis or neurological involvement and diseases.
5. Head injury cases.
6. Patient with cardiac, pulmonary, hepatic or renal disorders.
7. Patient with peripheral neuropathy.

STATISTICAL ANALYSIS: The demographic data were analysed using either Student's t-test or Chi square test. Quantitative data was analysed by student's 't' test and qualitative data was analysed by Chi-square test. All values were expressed as mean \pm standard deviation. P <0.05 was considered statistically significant.

RESULTS: Total 60 patients were divided into 2 groups with plain bupivacaine 4 ml and 50 μ g of clonidine with 3.5ml bupivacaine. Drugs were studied for Onset and duration of sensory block and motor block, highest level of sensory blockade, Duration of post-operative analgesia, vitals and side effects were assessed.

1. Demographic data like mean age, bodyweight, height, gender of surgeries of both the groups were comparable and there is no statistical significance. (p=0.637) table-1.

Parameter	Group B mean \pm S.D	Group C mean \pm S.D	P-Value, Result
Age (Years)	41.13 \pm 5.3	41 \pm 4.91	0.69,NS
Sex: Female	30	30	---
Height (Ft)	158.03 \pm 3.66	157.47 \pm 2.93	0.306,NS
Weight (Kgs)	54.87 \pm 3.16	53.83 \pm 3.02	0.887,NS

TABLE 1: DEMOGRAPHIC PROFILE

ORIGINAL ARTICLE

2. In our study, the mean time for onset of sensory block in group B was 137.60 seconds and 112.22 seconds in group C ($p < 0.001$). The mean time for onset of motor block in group B was 231.80 seconds and in group C was 165.1 seconds ($p < 0.001$) table-2.

	Group B	Group C	P-Value, Result
Sensory block (sec)	137.60	112.22	<0.001,HS
Motor block (sec)	231.80	165.1	<0.001,HS

TABLE 2: ONSET OF SENSORY AND MOTOR BLOCK

3. The mean time to achieve peak sensory level in group C compared to group B was 6.93 minutes vs 11.5 minutes ($p < 0.001$) table-3. This implied that group C achieved highest level of sensory block.

	Group B	Group C	P-Value, Result
Time to peak sensory block (in min)	11.5	6.93	<0.001,HS

TABLE 3: TIME TO PEAK SENSORY BLOCK

4. In patients of group C, 63.33% attained T4 level, 33.33% achieved T6 level and 3.33% achieved T8 level. Whereas in group B, 43.33% achieved T4 level followed by 46.67% T6 level and 10% T8 level. table-4.

	Group B n, (%)	Group C n, (%)
T4	13(43.33)	19(63.33)
T6	14(46.67)	10(33.33)
T8	3(10)	1(3.33)

TABLE 4: HIGHEST LEVEL OF SENSORY BLOCK

5. The duration of complete analgesia in group B was 165.1 min and in 240.2 min in group C ($p < 0.001$). Effective analgesia was 212.6 minutes in group B and 332.64 minutes in group C ($p < 0.001$). The time for first request of rescue analgesic postoperatively was 221.4 minutes in group B and group C it was 362.84 minutes ($P < 0.001$) table-5, thereby reducing the requirement of analgesics in the early postoperative period. The quality of analgesia was better in group C than in group B.

	Group B	Group C	P-Value, Result
Duration of complete analgesia	165.1	240.2	<0.001,HS
Duration of effective analgesia	212.6	332.64	<0.001,HS
Time to first pain medication(in min)	221.4	362.84	<0.001,HS

TABLE 5: DURATION OF ANALGESIA

ORIGINAL ARTICLE

6. In our study also there was significant reduction in the VAS scores of the patients receiving clonidine in comparison with higher VAS scores in patients receiving bupivacaine alone. It was 0.48 and 0.94 in the first three hours ($p < 0.003$), 1.66 and 3.68 in six hours ($p < 0.001$), 2.72 and 4.32 in twelve hours post operatively respectively ($p < 0.001$) table- 6. This implies better quality of analgesia postoperatively, and reduced the for analgesia with the use of intrathecal clonidine.

Time	Group B	Group C	P-Value, Result
3hrs	0.94	0.48	0.003,Sig
6hrs	3.68	1.66	<0.001,HS
12hrs	4.32	2.72	<0.001,HS

TABLE 6: VISUAL ANALOGUE SCALE (VAS) SCORE

7. The Occurrence of the side effects is statistically not significant. In our study, group C, 17% patients experienced mild sedation with no other side effects. 20% had hypotension in group C, 7% in group B. 13% bradycardia in group C. Since there was mild sedation during perioperative period, Respiratory rate was monitored to detect respiratory depression and there was no evidence of respiratory depression in either group (table-7).

Adverse effects	Group B n,%	Group C n,%
Nausea/vomiting	0(0)	0(0)
Sedation	0(0)	5(16.67)
Mouth dryness	0(0)	0(0)
Bradycardia	0(0)	4(13.2)
Hypotension	2(6.6)	6(19.8)
Urinary retention	0(0)	0(0)
Respiratory depression	0(0)	0(0)

TABLE 7: PERIOPERATIVE COMPLICATIONS

DISCUSSION: Spinal anesthesia with hyperbaric bupivacaine 0.5% is a popular method. The duration of spinal analgesia can be prolonged by the adjuvants like vasoconstrictors, opioids, neostigmine, ketamine, midazolam, etc. Clonidine is a selective partial agonist for α_2 adrenoreceptors. It is known to increase both sensory and motor block of local anesthetics.^{8,9,10} The analgesic effect following its intrathecal administration is mediated spinally through activation of postsynaptic α_2 receptors in substantia gelatinosa of the spinal cord and it works by blocking the conduction of C and A delta fibers, increases potassium conductance in isolated neurons invitro and intensifies conduction block of local anesthetic.

The present study was carried out to assess the efficacy of bupivacaine and clonidine with bupivacaine in spinal anesthesia in patient for total abdominal hysterectomy. Our study design consisted of 60 patients aged between 18 - 55 years, ASA physical status I / II underwent elective hysterectomy were randomly divided into two groups after taking informed consent.

ORIGINAL ARTICLE

Group B (Bupivacaine group) patients will receive intrathecally 0.5% hyperbaric bupivacaine 4ml (Total 4 ml) whereas Group C (Clonidine group) patient will receive intrathecally 0.5% hyperbaric bupivacaine 3.5 ml + 50µg (Total 4 ml).

The study has demonstrated that the combination of bupivacaine with clonidine in spinal anesthesia significantly decreases the onset time, prolongs the duration of sensory, motor blockade and postoperative analgesia than bupivacaine group.

In our study, majority of patients were middle aged in both the groups i.e. between 18-55 years. The group B mean age was 41.13 ± 5.3 years and in group C 41 ± 4.91 years. The mean weight in group B was 54.87 ± 3.16 kg and in group C 53.83 ± 3.02 kg. The mean heights of two groups were 158.03 ± 3.66 and 157.47 ± 2.93 respectively. These parameters were kept identical in both the groups to avoid variations in intraoperative and postoperative outcome of patients.

In our study, the mean time for onset of sensory block in group B was 137.60 seconds and 112.22 seconds in group C ($p < 0.001$). The mean time for onset of motor block in group B was 231.80 seconds and in group C was 165.1 seconds ($p < 0.001$). There was statistically significant difference with regard to onset of sensory and motor block between the groups with faster onset in group C compared to group B.

B. S. Sethi et al,¹¹ in his study with 60 patients evaluated the effect of low dose 1µ/kg, intrathecal clonidine as adjuvant to bupivacaine and found that the onset of action was clinically and statistically significant with faster onset in clonidine group compared to bupivacaine groups.

Our result correlates with the above-mentioned study. Hence we conclude that addition of clonidine has a faster onset and longer duration of sensory and motor blockade.

The mean time to achieve peak sensory level in group C compared to group B was 6.93 minutes vs 11.5 minutes ($p < 0.001$) by unpaired t- test. This implied that group C achieved highest level of sensory block. In patients of group C, 63.33% attained T4 level, 33.33% achieved T6 level and 3.33% achieved T8 level. Whereas in group B, 43.33% achieved T4 level followed by 46.67% T6 level and 10% T8 level.

Gurudatta et al¹² in his study clonidine group attained a cephalic block of T4 level in 18 patients, T6 level in 7 patients. In bupivacaine group, a block up to T4 level was obtained in 9 patients, T6 level in 16 patients. p value was 0.021. B. S. Seti et, in his study evaluated the effect of clonidine 1µg/kg added to hyperbaric bupivacaine and found that the highest level of sensory analgesia was clinically and statistically significant among the clonidine group.

Dobrydnjov et al,¹³ in his comparative study of different doses of clonidine of 15µ (BC15) and 30µ (BC30) combined with small dose of bupivacaine during spinal anesthesia concluded that the highest level of sensory analgesia was T10 in bupivacaine group, T6 in group BC 15 and T8 in group BC30. This was clinically and statistically significant among the clonidine group.

From the above study, we conclude that addition of clonidine intrathecal to hyperbaric bupivacaine results in higher level of sensory blockade and faster onset when compared to bupivacaine.

We found that the duration of complete analgesia in group B was 165.1 min and in 240.2 min in group C ($p < 0.001$). Effective analgesia was 212.6 minutes in group B and 332.64 minutes in group C ($p < 0.001$).

The time for first request of rescue analgesic postoperatively was considerably delayed in group C by 110-120 minutes compared to group B (221.4 vs 362.84 minutes), thereby reducing the

ORIGINAL ARTICLE

requirement of analgesics in the early postoperative period. The quality of analgesia was better as the VAS was lower in group C than in group B.

In our study also there was significant reduction in the VAS scores of the patients receiving clonidine in comparison with higher VAS scores in patients receiving bupivacaine alone. It was 0.48 and 0.94 in the first three hours ($p<0.003$), 1.66 and 3.68 in six hours ($p<0.001$), 2.72 and 4.32 in twelve hours post operatively respectively ($p<0.001$) (table: 6). This implies better quality of analgesia postoperatively, and reduced the for analgesia with the use of intrathecal clonidine.

B. S. Sethi et al in their study found out that the duration of effective analgesia defined as the time from intrathecal injection to the time of first analgesic requirement was significantly prolonged with addition of clonidine (614mins) and bupivacaine group (223mins) respectively. No patient in the clonidine group required additional intraoperative analgesics compared with 17.6% in the Bupivacaine group alone. There was improved patient comfort and reduced need for intra-muscular and intravenous analgesia in the immediate postoperative period.

Our results were similar to the above studies. Hence we infer that addition of clonidine to bupivacaine intrathecally results in significantly prolonged duration of complete analgesia, effective analgesia and the time to first pain medication is longer with improved quality of analgesia and reduced requirements of analgesics postoperatively.

VITAL PARAMETERS:

HAEMODYNAMICS – HEART RATE & BLOOD PRESSURE: In our study, the two groups did not differ significantly with respect to heart rate at any interval. There were few episodes of bradycardia in clonidine group. The changes in mean systolic blood pressure at any time interval was statistically and clinically insignificant. Whereas changes in mean diastolic blood pressure was statistically significant at 20 minutes, 30 minutes and one hour, but clinically insignificant.¹⁴

SIDE EFFECTS: In our study, group C, 17% patient's experienced mild sedation with no other side effects. Whereas group B, none have sedation. No nausea and vomiting in both groups. 20% had hypotension in group C, 7% in group B. 13% bradycardia in group C whereas none had bradycardia in group B. There was no mouth dryness and urinary retention in either group. Since there was mild sedation during perioperative period, Respiratory rate was monitored to detect respiratory depression and there was no evidence of respiratory depression in either group.^{15,16}

Dobrydnjov et al.¹³ in his study concluded that small dose of intrathecal clonidine is not usually associated with systemic side effects such as bradycardia, hypotension or sedation.

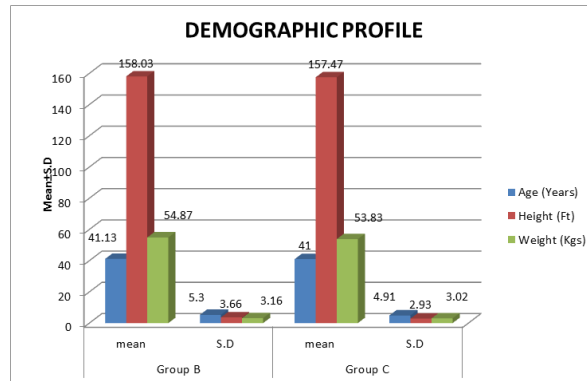
Many studies are being conducted with bupivacaine for prolonging the postoperative analgesia. The aim of these studies has been to optimize the dose of intrathecal clonidine for prolonging the duration of postoperative analgesia with least side effects.

CONCLUSION: On the basis of the present clinical comparative study, we can conclude that the addition of 50µg clonidine to 0.5% hyperbaric Bupivacaine 3.5ml in spinal anesthesia significantly decreases the onset time prolongs the duration of both sensory and motor blockade. It prolongs the duration and improves the quality of postoperative analgesia with better hemodynamic stability and good sedation as compared to bupivacaine alone.

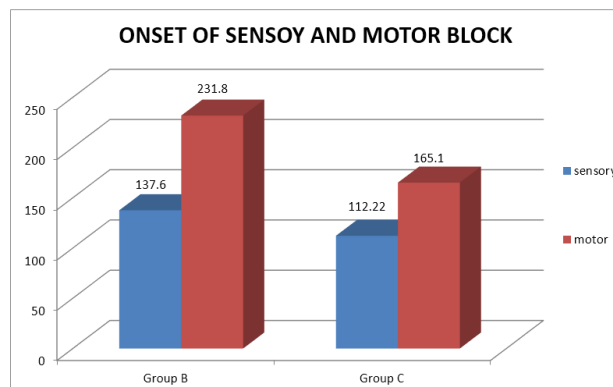
ORIGINAL ARTICLE

It is an attractive alternative to opioids for prolonging spinal anesthesia. Clonidine will expand the scope and improve the reliability and efficacy of regional anesthesia.

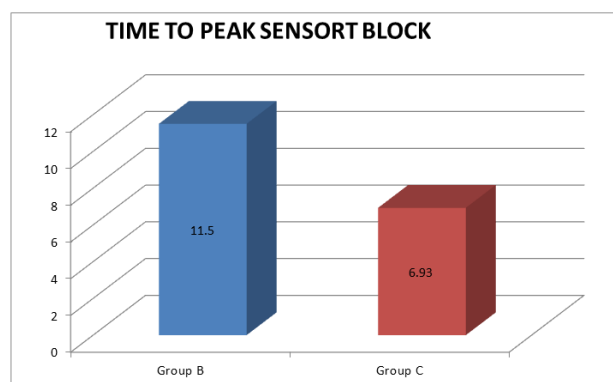
Thus, the study concluded that "Addition of clonidine potentiates bupivacaine spinal anesthesia.



GRAPH 1: DEMOGRAPHIC PROFILE

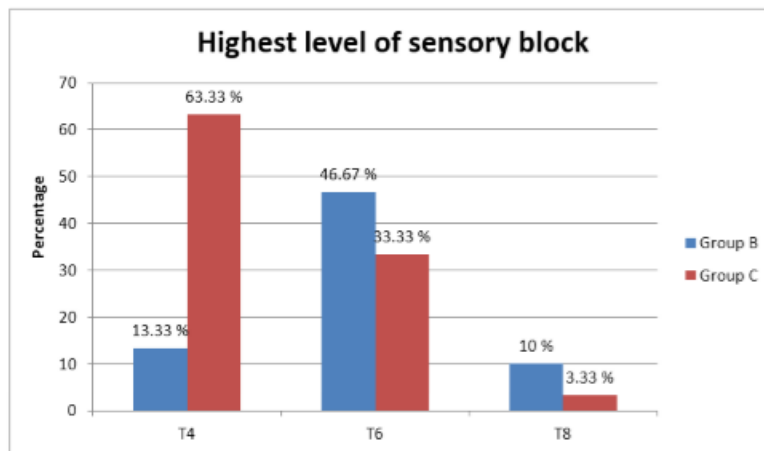


GRAPH 2: ONSET OF SENSORY AND MOTOR BLOCK

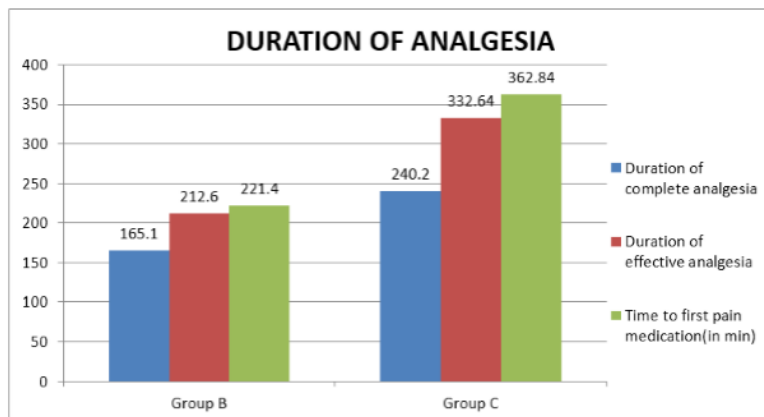


GRAPH 3: TIME TO PEAK SENSORY BLOCK

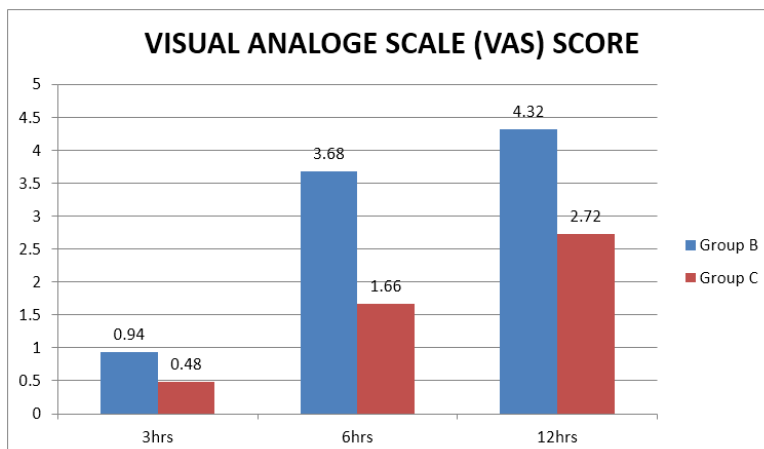
ORIGINAL ARTICLE



GRAPH 4: HIGHEST LEVEL OF SENSORY BLOCK



GRAPH 5: DURATION OF ANALGESIA



GRAPH 6: VISUAL ANALOGUE SCALE (VAS) SCORE

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ORIGINAL ARTICLE

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