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Original Research Article

Clinical profile of patients undergoing spinal Anaesthesia with intrathecal bupivacaine with clonidine and intrathecal bupivacaine with fentanyl

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Abstract: ***Introduction:*** Local anaesthetic like bupivacaine is commonly used in spinal anaesthesia, but the duration of spinal anaesthesia may be short and limited, and higher doses of rescue analgesics may be required in the postoperative period. This can be avoided by using higher doses of bupivacaine which again can produce cardiac toxicity. Studies have shown that duration of analgesia due to bupivacaine in spinal anaesthesia can be prolonged by using adjuvants such as midazolam, opioids, neostigmine, dexmedetomidine, and clonidine. Almost all opioids have been used as adjuvants intrathecally. ***Material and methods:*** This randomized controlled study was carried out over a period of 6 months, after obtaining approval from the Hospital Ethics Committee and written informed consent from the patients. Ninety-nine patients of Anaesthesiologists Classes I or II of either sex and of age 25-60 years, posted for lower abdominal surgery were randomly divided into 3 groups (n = 33) using computer-generated program. Assigned random group was enclosed in a sealed envelope to ensure concealment of allocation sequence. The anaesthesiologist, who was not involved in the study, opened the envelope in operation theatre and prepared the drug accordingly. The observation was done by the anaesthesiologist who was blinded to the drug. Patients having severe systemic disorders such as diabetes mellitus, hypertension, heart disease, allergy to bupivacaine, spine deformity, increased intracranial pressure, neurological disorders, haemorrhagic diathesis, and infection at the puncture site were excluded from the study. ***Result:*** A total of 106 patients initially enrolled in this study, 7 patients had to be excluded because of logistical reasons or other violations of the study protocol. Ninety patients were included and randomly assigned to their treatment groups. ***Conclusion:*** Intrathecal clonidine (75 μg) when added to bupivacaine in spinal anaesthesia provides prolonged duration of postoperative analgesia than 25 μg of fentanyl but with higher degree of sedation. Fentanyl (25 μg) may be recommended as a better option when sedation is not desirable. We concluded that intrathecal clonidine 75 μg with bupivacaine prolonged intraoperative anaesthesia and the time to first analgesic request compared to fentanyl, however, the total analgesic consumption in the first 24 h postoperative was similar in fentanyl and clonidine groups following elective lower abdominal surgeries**.**

Keywords: Intrathecal, postoperative analgesia, spinal anaesthesia, bupivacaine, clonidine.

INTRODUCTION

Local anaesthetic like bupivacaine is commonly used in spinal anaesthesia, but the duration of spinal anaesthesia may be short and limited, and higher doses of rescue analgesics may be required in the postoperative period. [1] This can be avoided by using higher doses of bupivacaine which again can produce cardiac toxicity. Studies have shown that duration of analgesia due to bupivacaine in spinal anaesthesia can be prolonged by using adjuvants such as midazolam, opioids, neostigmine, dexmedetomidine, and clonidine. Almost all opioids have been used as adjuvants intrathecally. [2]

Literature is divided regarding efficacy of both intrathecal clonidine and fentanyl in providing prolonged postoperative analgesia. Studies opined that intrathecal clonidine was more potent in providing prolonged analgesia compared to intrathecal fentanyl & concluded that intrathecal fentanyl and clonidine were comparable regarding requirement of first analgesia request. Another study has been concluded that intrathecal fentanyl was superior to intrathecal clonidine in knee arthroscopy. [3] Hence, all the above studies differ in their postoperative sensory and motor block characteristics. Hence, the present study is being undertaken to evaluate and compare the effects of clonidine and fentanyl as intrathecal adjuvants to hyperbaric bupivacaine in patients undergoing lower limb orthopaedic surgery. The primary objectives of this study were to evaluate and compare the effects of clonidine and fentanyl on time of request of first dose of rescue analgesic. Secondary objectives were to compare the effects of clonidine and fentanyl on time of onset

and duration of sensory and motor block, hemodynamic status, and side effects.

Potentiation of the effect of subarachnoid block and prolongation of postoperative analgesia can be achieved by using adjuvants to local anaesthetic agents such as midazolam, neostigmine, clonidine, and opioids. Wang et al. were the first to demonstrate the successful intrathecal administration of morphine and since then almost all opioids were used as adjuvant to local anaesthetic agent. [4,5] Among all the opioids, fentanyl became the adjuvant of choice because of its potency, rapid onset and short duration of action with lower incidence of respiratory depression. Nevertheless, addition of opioids as adjuvant to local anaesthetic agent is associated with side effects such as nausea, vomiting, pruritus, urinary retention, herpes labialis activation, and respiratory depression directed the research in favour of nonopioid adjuvant which resulted in the introduction of clonidine as adjuvant to local anaesthetic agent. Intrathecal clonidine is demonstrated to potentiate the effect of subarachnoid block as well as reduces the local anaesthetic agent requirement. Intrathecal clonidine also offers prolonged postoperative analgesia reduced shivering associated with subarachnoid block, and is devoid of side effects associated with intrathecal opioids. In this study, we have compared the intrathecal clonidine with intrathecal fentanyl as adjuvant to bupivacaine in terms of safety, efficacy, and postoperative analgesia in patients undergoing lower abdominal surgeries. [6,7]

MATERIAL AND METHODS

This randomized controlled study was carried out over a period of 6 months, after obtaining approval from the Hospital Ethics Committee and written informed consent from the patients. Ninety-nine patients of Anaesthesiologists Classes I or II of either sex and of age 25-60 years, posted for lower abdominal surgery were randomly divided into 3 groups (n = 33) using computer-generated program. Assigned random group was enclosed in a sealed envelope to ensure concealment of allocation sequence. The anaesthesiologist, who was not involved in the study, opened the envelope in operation theatre and prepared the drug accordingly. The observation was done by the anaesthesiologist who was blinded to the drug. Patients having severe systemic disorders such as diabetes mellitus, hypertension, heart disease, allergy to bupivacaine, spine deformity, increased intracranial pressure, neurological disorders, haemorrhagic diathesis, and infection at the puncture site were excluded from the study. Group C – Received hyperbaric bupivacaine (2.5 ml) +75 μg clonidine (diluted to 0.5 ml) administered intrathecally. Group F – Received hyperbaric bupivacaine (2.5 ml) + fentanyl 25 μg (diluted to 0.5 ml) administered intrathecally. Total volume of study drug was 3 ml. Preanesthetic check-up was done, and visual analog scale (VAS) was explained to all patients. All the patients were kept nil orally for 6 h before surgery. After shifting the patients to operation theatre, intravenous (IV) cannula was inserted, and preloading was done with Ringer solution (10 ml/kg). Preoperative parameters such as pulse rate, oxygen saturation, and blood pressure were recorded. Under all aseptic precaution, spinal anaesthesia was administered at the level of L3–L4 intervertebral space in sitting position using midline approach by 25-gauge Quincke spinal needle. The anaesthesiologist who administered anaesthesia was blinded to the group allocation. Pulse rate, respiratory rate, electrocardiogram, SpO2, and blood pressure were monitored. Pulse rate and blood pressure variations more than 20% of baseline were noted in both groups. Bradycardia and hypotension were treated with IV atropine and ephedrine, respectively. Sensory and motor block was monitored at 2, 4, 6, 8, 10, 15 min, and after that at 15 min interval. Sensory block was tested by pinprick method. The motor block was assessed according to the modified Bromage scale: Bromage 0: Patients able to move hip, knee, and ankle, Bromage 1: Patients unable to move hip but able to move the knee and ankle, Bromage 2: Patient unable to move hip and knee but able to move the ankle, Bromage 3: Patient unable to move hip, knee, and ankle. The onset of sensory block was taken from the time of intrathecal injection till loss of pin prick sensation at T10. Duration of sensory block was taken as time from maximum height of block till regression to Level 1. The onset of motor block was defined as time from intrathecal injection to motor blockade Level 2 in Bromage scale. Duration of motor blockade was taken as time from intrathecal injection till no motor weakness (Bromage 0). Duration of analgesia was defined as time from intrathecal injection till administration of first rescue analgesic. Any side effects such as nausea, vomiting, pain, shivering, pruritus, sedation, hypotension, bradycardia, and respiratory discomfort were noted. Patients were assessed for degree of sedation, and scoring was done with Campbell sedation score as: 1: Wide awake, 2: Awake and comfortable, 3: Drowsy and difficult to arouse, and 4: Not arousable. Postoperatively, the pain score was recorded by using VAS between 0 and 10 (0 = no pain, 10 = severe pain). Injection paracetamol (1 gm) was given intravenously as rescue analgesic when VAS was >5. Time of administering the first dose of rescue analgesia was noted.

Power analysis suggested that a sample size of forty patients per group was required to achieve a power of 80% and a level significance of 0.05 to be able to detect a difference in the mean duration of analgesia by 60 min between the groups. Interpretation of the data was carried out and analyzed using statistical package for social sciences (SPSS version 19, IBM Corp, NY, USA). Data was represented as mean ± standard deviation for continuous data and frequency (percentage) or median (range) for nonparametric (categorical) data. The two groups were compared using analysis of variance. The proportion of adverse effects

was compared using Chi-square test. P < 0.05 was considered statistically significant. P < 0.001 was considered highly statistically significant.

RESULT

A total of 106 patients initially enrolled in this study, 7 patients had to be excluded because of logistical reasons or other violations of the study protocol. Ninety patients were included and randomly assigned to their treatment groups (Figure 1).

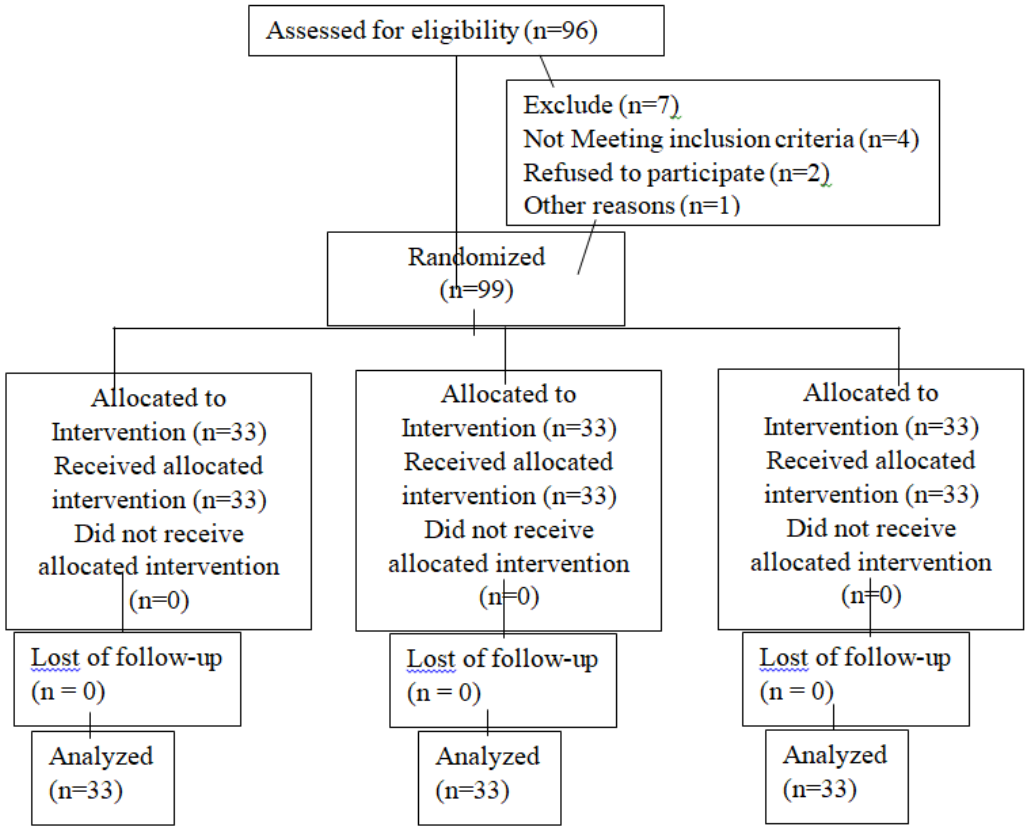

Figure 1: Consort Flow diagram

There were no significant differences in age, height, and weight among the three groups. The duration of surgery was also similar (Table 1).

The mean onset of sensory block was 91 ± 23 sec in group C 96.33 ± 39.17 sec in group F and 79.5 ± 26.00 sec in group P. The difference between group C versus group F (P = 0.523) and P (0.075) was insignificant. Similarly, this difference in groups F and P was also insignificant (P = 0.055). The mean duration of sensory block in group C (168.66 ± 25.68 min) was longer than group F (123.23 ± 32.76 min) and group P (134.53 ± 32.67 min). The difference between group C versus group F (P < 0.001) and P (P < 0.001) was significant, but the difference between groups F and P (P = 0.186) was found to be insignificant. The mean onset of motor block was 82.33 ± 26.72 in group C, 81.00 ± 30.63 in group F, and 82.83 ± 27.22 sec in group P. The difference between group C versus group F (P = 0.858) and P (P = 0.943) was insignificant. Similarly, the difference in groups F and P was insignificant (P = 0.807). The median value found for the maximum height of block was T6 for all three groups. The mean duration of motor blockade time was significantly longer in group C (183.66 ± 33.13 min) than F (135.76 ± 28.84 min) and P groups (144.16 ± 33.96). The difference in mean duration of motor blockade time between group C versus F (P < 0.001) and P groups (P < 0.001) was significant whereas no significant difference in duration of motor block between F and P groups was found (P = 0.435). The duration of anaesthesia in clonidine group (276.10 ± 96.08) was longer compared to the place (212.73 ± 74.81) and fentanyl (193.33 ± 30.32) groups. As shown in Table 2, the patients who were given clonidine had a significantly prolonged duration of anaesthesia compared with control (P < 0.001) and F groups (P = 0.006). As to the duration of anaesthesia, the mean time to first analgesic request was also significantly longer in group C (518.44 ± 86.26) than in groups F (278.88 ± 94.26) and P (236.43 ± 22.36 min). This difference between group C versus F (P < 0.001) and P groups (P < 0.001) was significant. Likewise, the difference between groups F and P was also significant (P =

0.022). The total number of analgesic requests by patients during 24 hours after surgery in clonidine group was significantly smaller than in control group (P = 0.002). Total analgesic consumption during 24 hours after surgery failed to demonstrate a significant difference between F and C groups (P = 0.318)

Table 1: Demographic data for three study groups

Groups	Group C (n = 33)	Group F (n = 33)	Group P (n = 33)
Age (years)	31.43 ± 3.74	31.20 ± 5.43	30.16 ± 5.16
Weight (kg)	87.5 ± 15.5	87.5 ± 13.7	88.7 ± 11.8
Height (cm)	167 ± 4.6	162 ± 8.4	164 ± 6.1
Duration of surgery (min)	86.63 ± 15.71	78.16 ± 20.12	82.70 ± 18.77

Values are presented as mean ± SD. C: clonidine, F: fentanyl, and P: placebo. There are no significant differences among

Table 2: Characteristics of spinal anaesthesia

Groups	Group C (n = 33)	Group F (n = 33)	Group P (n = 33)	P
Onset time of sensory block (second)	91 ± 23	96.33 ± 39.17	79.5 ± 26.00	NS
Duration of sensory block (min)	168.66 ± 25.68	123.23 ± 32.76	134.53 ± 32.67	<0.001
Onset time of motor block (second)	82.33 ± 26.72	81.00 ± 30.63	82.83 ± 27.22	NS
Duration of motor block (min)	183.66 ± 33.13	135.76 ± 28.84	144.16 ± 33.96	<0.001
Time to first request of analgesic (min)	518.44 ± 86.26	278.88 ± 94.26	236.43 ± 22.36	<0.001
Duration of spinal anaesthesia	276.10 ± 96.08	212.73 ± 74.81	193.33 ± 30.32	<0.001
Total ephedrine requirement	11.83 ± 5.27	5.16 ± 5.85	2.16 ± 5.53	<0.001
Total analgesic consumption in 24 h (Number of analgesic request)	2 (2-2)	2 (1–3)	3 (2-3)	0.011

Values are presented as mean ± SD or median IQR C: clonidine, F: fentanyl, and NS: nonsignificant (P > 0.05).

The difference between group C versus P (P = 0.761) and F (P = 0.571) groups was also insignificant as it was for the difference between groups F and P (P = 0.851). As shown in Figure 1, the three groups were found to have no significant difference in terms of other intraoperative and postoperative side effects including pruritus, nausea, vomiting, headache, shivering, and respiratory depression. No patient in either group showed any sensory or motor complications within the next six months follow up after surgery. All new-borns in our study were free of any adverse effect.

DISCUSSION

Based on the data found in our study, it was concluded that administration of intrathecal clonidine 75 μg with bupivacaine prolonged intraoperative anaesthesia and the time to first analgesic request after caesarean delivery compared to fentanyl and control groups. These findings are consistent with previous studies. [8] Analgesic properties of clonidine have been shown to depend on the activation of α2 receptors located in the dorsal horn. Presynaptic stimulation of α2 receptors inhibits neurotransmitter release and postsynaptic stimulation prevents neuronal transmission through hyperpolarisation.

The second observation which should be emphasized is that although intrathecal clonidine 75 μg with bupivacaine prolonged intraoperative anaesthesia and the time to first analgesic request compared to fentanyl yet the total analgesic consumption in the first 24 h postoperative was similar in fentanyl and clonidine groups after elective caesarean delivery. [9,10] The possible explanation for this finding is that the analgesic effect of clonidine follows a dose-dependent manner. Eisenach et al. reported that a dose of 150 μg clonidine is required to observe anti hyperalgesia effect, while a lower dose (50 μg) is ineffective. The selected dose of intrathecal clonidine in current study was based on several reasons. Firstly, intrathecal clonidine displays the risk of adverse intraoperative hemodynamic effects. Rochette et al. showed that clonidine at a dose of 1 μg/kg was not associated with hemodynamic disturbance. [11] Also, Bajwa et al. found that the optimal dose for clonidine to produce effective analgesia without inducing hypotension in emergency caesarean section is 37.5 μg. However, most studies have reported that although clonidine at a lower intrathecal dose less than 0.5 μg/kg body weight was devoid of its diverse side effects, at the same time the antinociceptive effect of this drug was also reduced significantly. Secondly, it is reported that intrathecal clonidine possesses an analgesic plateau effect at 75 μg and higher doses could only increase the duration but not the intensity of analgesia. [12]

The third finding which should be considered is that intrathecal clonidine clearly increases the duration of both sensory block and motor block as well as postoperative pain relief. This finding is also consistent with the previous studies. The mechanism of clonidine-induced potentiation of sensory block in spinal anaesthesia is reported to be dependent on presynaptic (decrease in transmitter release) and

postsynaptic (increase in hyperpolarization) action. [13] The fourth finding which should be taken into account is that transient hypotension episodes and vasopressor requirement in clonidine group were significantly greater than F and P groups, a finding in agreement with previous studies. Except for sympatholytic action of clonidine and profound analgesia which also reduces sympathetic activity, no other clear explanation is available. In contrast, some studies have reported that clonidine at doses between 37.5 and 150 μg failed to cause a significant decrease in blood pressure when added to a high dose of bupivacaine (18 mg). However, these apparently controversial findings may be due to either the difference in bupivacaine and clonidine doses or dissimilarity in population and the type of surgeries. [14] The fifth observation which should be noted is that clonidine lacks the ability to prevent post spinal shivering; by contrast, it is confirmed that clonidine, when administered intravenously, is an effective drug to prevent shivering in patients undergoing spinal anaesthesia, a finding compatible with that found in a study by Jeon et al. The possible reason for this finding could be attributed to the inability of clonidine to inhibit afferent thermal conduction at the level of spinal cord. [15]

CONCLUSION

Intrathecal clonidine (75 μg) when added to bupivacaine in spinal anaesthesia provides prolonged duration of postoperative analgesia than 25 μg of fentanyl but with higher degree of sedation. Fentanyl (25 μg) may be recommended as a better option when sedation is not desirable. We concluded that intrathecal clonidine 75 μg with bupivacaine prolonged intraoperative anaesthesia and the time to first analgesic request compared to fentanyl, however, the total analgesic consumption in the first 24 h postoperative was similar in fentanyl and clonidine groups following elective lower abdominal surgeries. Further studies are needed to evaluate the analgesic efficacy of clonidine with other neuraxial drug combinations such as epinephrine, ketamine, and magnesium to provide better analgesia and reduce the incidence and severity of side effects.

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