

Comparative study of intrathecal hyperbaric Bupivacaine with Clonidine, Fentanyl and Midazolam for quality of anaesthesia and duration of post operative pain relief in patients undergoing elective caesarean section

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Abstract:

Pain free postoperative period and early ambulation are the need of the day for mothers caring for their neonates. The use of adjuvants in spinal analgesia has gained popularity in recent times. This prospective randomized study was carried out among 120 patients scheduled for elective caesarian section. They were divided into 4 groups. Group A (Control) received Injection Bupivacaine (Hyperbaric) along with 0.9% Normal saline, Group B, C and D received Clonidine 75 µg, Fentanyl 25 µg and Midazolam 2.5 mg along with injection Bupivacaine (H) respectively.

The results of the present study showed that intrathecal Clonidine, Fentanyl and Midazolam can be used safely in parturient, provided strict protocol for preloading is followed by vigilant operative and post-operative monitoring by a trained person. Requirement of postoperative analgesics was found to be significantly reduced in all the study groups when compared with the control group. The highest duration of pain relief was found with Clonidine. Adverse effects were minimal and could be easily managed; no adverse foetal effect was noted with the use of any drug in this study.

Key Words: Clonidine, Fentanyl, Midazolam, Hypotension & Preloading.

Introduction:

Considering the special group of patients (Mothers) undergoing caesarean section, it is moral responsibility of Anaesthesiologist to provide a safe and pain free postoperative period with various drug combinations and techniques.

The α_2 -adrenergic agonist Clonidine has a variety of different actions including the ability to potentiate the effects of local anesthetics (Eisenach et al, 1996). Intrathecal Clonidine is being extensively evaluated as an alternative to neuraxial opioids for control of pain and has proven to be a potent analgesic, free of some of the opioid-related side effects (Neves et al, 2006).

Fentanyl, a phenylpiperidine derivative, is a synthetic μ opioid receptor agonist. It is preferred as an adjuvant in spinal anaesthesia because of its rapid onset and short duration of action with lesser incidence of respiratory depression. Intrathecal Fentanyl improves the quality of spinal anaesthesia without having any deleterious effects on the neonate or mother (Hunt et al, 1989).

Discovery of benzodiazepine receptors in spinal cord triggered the use of intrathecal Midazolam for analgesia (Mohler & Okada, 1977). Several investigators have shown that intrathecal or epidural administration of Midazolam produces a dose dependent modulation of spinal nociceptive processing in animals and humans and is not associated with neurotoxicity, respiratory depression or sedation (Naguib et al, 1995). This study was designed to evaluate the characteristics of the spinal block achieved with the use of adjuvants with Bupivacaine and whether the use of intrathecal Clonidine had any advantage over the others.

Materials & Methods:

This was a prospective, randomized comparative study; randomization was done by computer generated data. The study was initiated after obtaining permission from the Institutional Ethical Committee. Pre-operative evaluation included thorough clinical history and examination as well as requisite investigations. Patients with height less than 150 cm, any contraindication to regional anaesthesia and any known drug allergy were excluded from the study. All patients were explained about Ten Point visual analogue scale (VAS). One hundred twenty women of ASA (American Society of Anesthesiologist) status I or II scheduled for lower segment elective caesarean section (LSCS) were included in the study.

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Written informed consent was obtained from all patients. Patients were randomly allocated to 4 groups of 30 each to receive either 2.2ml injection Bupivacaine (H) + 0.5ml Normal Saline (Group A) or 2.2ml injection Bupivacaine (H) + 0.5 ml injection Clonidine 75 µg (Group B) or 2.2ml injection Bupivacaine (H) + 0.5 ml injection Fentanyl 25µg (Group C) or 2.2ml Injection Bupivacaine (H) + 0.5ml injection Midazolam 2.5mg (Group D). All the study drugs were introduced intrathecally, and the total volume of agents administered was 2.7 ml.

In the operation theatre, monitors were attached to the patient and parameters like heart rate, systemic arterial pressure and peripheral arterial oxygen saturation were noted. All patients were pre-loaded with 10ml/kg of Ringer lactate and premedication of injection Ranitidine 50 mg and injection Ondansetron 4 mg.

In a sitting position, under all aseptic precautions and using midline approach, subarachnoid block was achieved in L3-L4 space with 23G Quincke’s spinal needle. Drug was injected as per the assigned group.

Patient was immediately placed in the supine position & wedge was placed under the right hip. All patients received oxygen supplementation via Hudson’s mask at a rate of 4 L/min. The onset of sensory analgesia and motor blockade were tested. The level of sensory anaesthesia, defined as the loss of sharp sensation by using a pinprick test (20 gauge hypodermic needle), was recorded bilaterally at the mid-clavicular line. Motor blockade was assessed with modified Bromage score. Time taken for complete motor blockade was recorded every minute till first 20 minutes.

Time taken to achieve highest sensory level was noted. Patient’s heart rate, blood pressure, respiratory rate, oxygen saturation were monitored every minute initially for 5 minutes, then at 5 minute interval for next 30 minutes and then every 10 minutes till the end of surgery. Oxytocin infusion of 15U in 500ml of Ringer lactate was administered. Foetal assessment was done by using Apgar score at 1min, 5min and 10min.

Regression of motor blockade and duration of postoperative analgesia was noted. Visual Analogue Scale was used for assessment of postoperative pain relief. At a score of 5, Injection Diclofenac 75mg was given intramuscularly as a rescue therapy.

In the present study, hypotension was defined as a decrease of systolic blood pressure more than 20% of baseline. It was treated with intravenous (IV) fluids and Injection Ephedrine Hydrochloride.

Bradycardia was defined as a decrease in pulse rate to less than 60 per min and was treated with IV injection of Atropine Sulphate 0.6mg. All patients were observed for next 24 hours. Any period during operative and postoperative period till 24hrs was recorded and treated accordingly.

Results were statistically analysed. The comparison of normally distributed continuous variables between the groups was performed by one-way analysis of variance (ANOVA) and followed by Dunnett’s multiple comparison test.

Results:

The study & control groups did not differ significantly with respect to any demographic variables (Table I).

Table I: Demographic parameters in all 4 groups.

Demographic Variables	Group A	Group B	Group C	Group D
Age (yrs)	23.00±1.92	23.63±4.17	22.50±2.31	22.12±2.12
Weight (Kg)	54.60±3.29	54.43±3.44	54.66±2.80	54.82±2.12
Height (cm)	153.70±2.43	152.83±2.06	153.00±2.05	153.12±2.10
*ASA I/II	26/4	28/2	27/3	26/4

* American society of anesthesiologists (ASA)

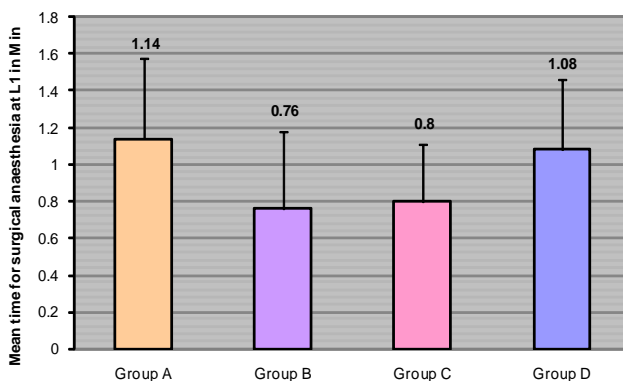


Fig.I: Mean time for surgical anaesthesia at L1 in Min.

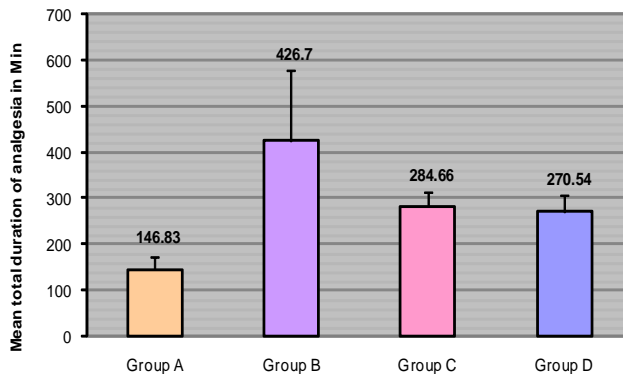


Fig.II: Mean total duration of analgesia.

The mean time required for surgical anaesthesia at L1 in groups A,B,C and D were 1.14 ± 0.44, 0.76 ± 0.42, 0.80 ± 0.31 and 1.08 ± 0.38 minute

respectively (Fig. I). Total duration of analgesia was significantly higher in Clonidine, Fentanyl and Midazolam groups as compared to the control group ($p < 0.001$) & was also statistically significant when compared with each other. When group B was compared with C & D, the difference was significant for group C ($p = 0.03$) and for group D ($p = 0.004$). Duration of analgesia, for group B was 426.70 ± 151.83 , group C was 284.67 ± 30.19 , for group D was 270.54 ± 36.22 and group A was 146.83 ± 26.60 minutes (Fig. II). Mean Apgar scores at 1, 5 and 10 minutes were comparable among all the 4 groups.

Though, the mechanism of side effects were different among the study drugs, their incidence was comparable, and data was not significant statistically (Table II).

Table II: Comparison of side-effects in all the 4 groups.

Side effects	Group A	Group B	Group C	Group D	p-value
Hypotension	12(40%)	10(33.3%)	12(40%)	11(36.6%)	0.94
Bradycardia	1(3.3%)	--	1(13.3%)	--	0.56
Nausea/ Vomiting	3(10%)	--	2(6.7%)	--	0.13
Shivering	4(13.3%)	--	3(10%)	--	0.05
Itching	--	--	2(6.7%)	--	0.10
Sedation	--	4(13.3%)	--	6(20%)	0.05

The hemodynamic parameters are as depicted graphically (Fig. III, IV & V).

Discussion:

In the present study, the effects of addition of different adjuvants to Bupivacaine were observed to find out the best additive among them by weighing effects versus side effects. Various studies have demonstrated that addition of Clonidine to bupivacaine, even in very small doses, significantly improves the onset and duration of sensory block. This action of clonidine is because of spinal cord anti-nociception via post-junctional α_2 -adrenoreceptor mediated noradrenaline release in the dorsal horn (Eisenach et al, 1996). In the present study, immediate postoperative analgesia was better with Clonidine (Group B) as observed by a significant delay in the first request for analgesia, less need for rescue analgesic diclofenac and lower VAS score in this group. Duration of analgesia was noted to be upto 120 minutes in a study by van Tuijl et al (2006) in contrast to the present study where analgesia remained for 426.6 minutes, which is much longer than above study.

In the present study the onset of surgical anaesthesia at L1 was early in Clonidine group as

compared to Fentanyl, Midazolam and Control groups ($p < 0.001$). The duration of analgesia with Fentanyl was 284.66 minutes as is line with earlier studies by Biswas et al (2002) and Belzarena (1992); $12.5 \mu\text{g}$ Fentanyl produced analgesia that lasted for 248 ± 11 minutes (Biswas et al, 2002) and duration of analgesia with $25 \mu\text{g}$ Fentanyl was noted to last for 305 ± 89 minutes (Belzarena, 1992). In the present study, muscle relaxation was found to be good in patients who received Clonidine as judged by surgeons; this is in accordance with the study by Kothari et al (2011) and Ogun et al (2007).

The duration of analgesia with Midazolam was 270.54 ± 36.22 minutes in the present study. However, in a study with intrathecal lignocaine and 2 mg Midazolam in LSCS patients, analgesia lasted for 196.5 ± 3.3 minutes (Sen et al, 2001). A preclinical study has demonstrated the potential role of spinal benzodiazepine receptors in segmental anti-nociceptive action of intrathecal midazolam. Administration of benzodiazepine antagonist flumazenil and GABA-A antagonist (Bicuculline) has been reported to reverse the analgesic effect of intrathecal Midazolam, suggesting that antinociceptive action is mediated via benzodiazepine/ GABA-A receptor complex which are abundantly present in lamina II of dorsal horn ganglia of spinal cord (Edwards et al, 1990).

Comparable Apgar score in all the groups at 1, 5 and 10 minutes signifies that Clonidine, Fentanyl and Midazolam have no deleterious effect on the neonates and mothers. Further, there is very little information, and no evidence that any anaesthetic agent given in a single dose, is secreted in clinically significant amounts in breast milk (Rolbin & Morgan, 2002).

Hypotension and bradycardia are the most commonly reported adverse events in women undergoing LSCS with the use of intrathecal Clonidine. It is of utmost importance to prevent and treat hypotension promptly in this special group of patients, so as to maintain the uteroplacental circulation for a better foetal outcome. In the present study, hypotension occurred but was not statistically significant. ($p = 0.94$). This could be because all patients in the present study were preloaded with 10ml/kg of Ringer lactate and wedge was provided immediately after spinal block. This observation was at par with the findings of van Tuijl et al (2006) who in their study with $75 \mu\text{g}$ intrathecal Clonidine noted that although mean arterial pressure (MAP) decreased but was not

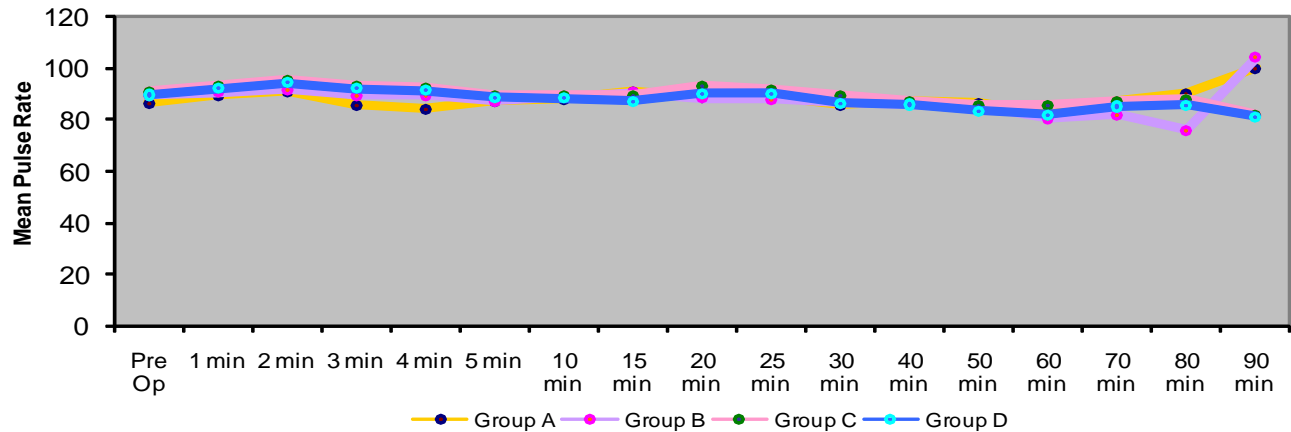


Fig.III: Mean pulse rate in control and study groups.

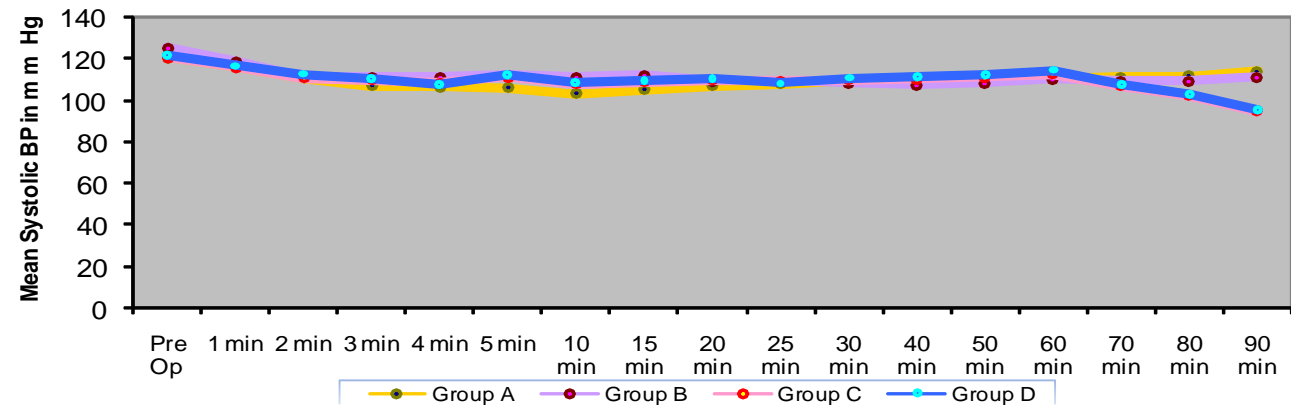


Fig.IV: Mean systolic blood pressure in control and study groups.

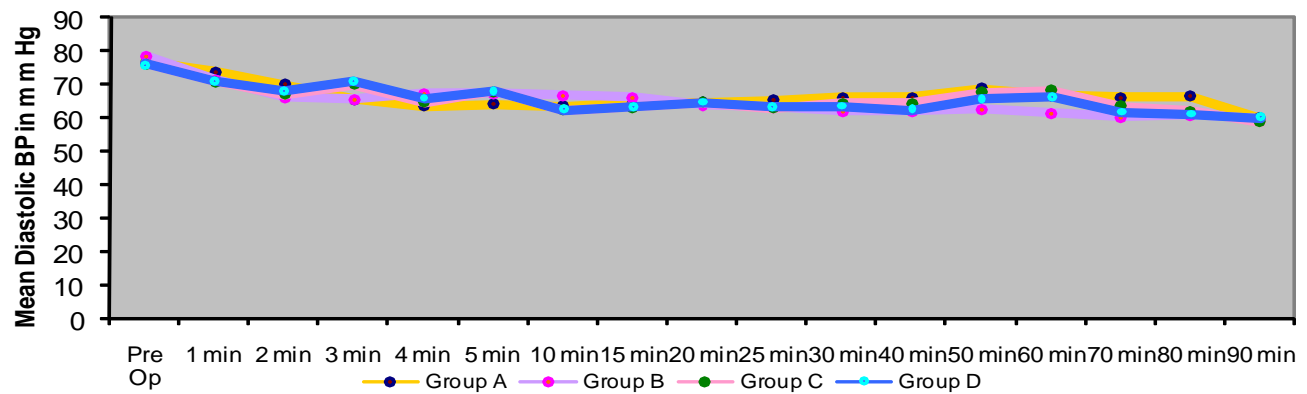


Fig.V: Mean diastolic blood pressure in control and study groups.

clinically important.

Visceral pain is a common problem in the casarean section under spinal anesthesia. It is a poorly localized type of pain that appears to come from deep structures of the body. It is often associated with autonomic activity causing nausea, vomiting, sweating with change in blood pressure and heart rate. Visceral pain in the casarean section is experienced, when the uterus is exteriorized and peritoneum is closed. In the present study, patients of the control group, Midazolam and Fentanyl groups experienced pain, nausea and

vomiting during operation, but none of the patient from Clonidine group had above effects. Dobrydnjov et al (2002) states that the incidence of visceral pain could be reduced with a lower dose of Bupivacaine (8 mg) by adding 50µg of Clonidine. They further observed that by the addition of Clonidine, adequate depth of spinal anesthesia can be achieved at much lower doses of Bupivacaine.

Sedation was observed in 4 patients in Clonidine group and 6 patients in Midazolam group, but there was no respiratory depression or fall in saturation.

None of the patient from any group needed active oxygen supplementation.

Pruritus was reported in 3 patients and nausea and vomiting in 2 patients in Fentanyl group. Urinary retention is more common after neuraxial opioid administration, and is most likely due to opioid receptors located in sacral part of the spinal cord promoting inhibition of sacral parasympathetic outflow. All the patients of the present study, routinely had a foley's catheter for 24 hours, therefore, urinary retention could not be evaluated. Patients were also evaluated for any neurological deficit during their stay in the hospital as well as in their follow up visit. None of the patient in the study groups demonstrated any signs of neurological deficit which was at par with the findings of Prakash et al (2006).

Conclusion:

The present study demonstrated that addition of Clonidine, Fentanyl and Midazolam to Bupivacaine significantly improves the onset and duration of sensory and motor block with relative haemodynamic stability, prolongs the duration of analgesia and reduce the consumption of systemic analgesics in comparison to Bupivacaine alone.

Hence, we suggest that addition of preservative free Clonidine is excellent additive to Bupivacaine for quality of anaesthesia and prolonged duration of analgesia without any deleterious effects on the mother and baby.

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