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Research Article

PERIOPERATIVE EFFECTS OF INTRATHECAL CLONIDINE AND FENTANYL WITH HYPERBARIC BUPIVACAINE IN SPINAL ANESTHESIA FOR VAGINAL HYSTERECTOMY

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ABSTRACT

Objectives: Intrathecal fentanyl and clonidine are effective analgesics with different mechanisms of action. This study compares 25 µg of both these drugs given intrathecally regarding onset, quality, and duration of hyperbaric bupivacaine-induced spinal block and side effects.

Methods: A total of 90 patients of ASA I and II were randomly allocated into three equal groups. Group A received 0.5 ml of 0.9% normal saline (placebo), Group B and Group C received 25 µg fentanyl and clonidine intrathecally added to 2.5 ml of 0.5% hyperbaric bupivacaine, respectively. The onset and regression time of sensory and motor blocks were recorded along with hemodynamic change, side effects, pain intensity (in terms of visual analog score (VAS), and time to first rescue analgesic.

Results: Intrathecal clonidine (25 µg) significantly prolongs sensory and motor blocks, with prolonged duration of analgesia in comparison with intrathecal fentanyl (25 µg) (325±15 minutes vs. 240±7.6 minutes). VAS score was similar, but sedation was more in clonidine group.

Conclusion: We conclude that low-dose intrathecal clonidine is an effective adjuvant to bupivacaine for spinal anesthesia and provides better postoperative analgesia in comparison with intrathecal fentanyl.

Keywords: Clonidine, Fentanyl, Bupivacaine, Regional, Spinal, Postoperative pain.

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INTRODUCTION

The administration of opioids by central neuraxial route provides adequate pain relief for longer duration [1,2]. However, intrathecal opioids are associated with worrisome side effects such as pruritus, nausea, vomiting, and delayed respiratory depression [3,4]. Fentanyl is a lipophilic opioid with a rapid onset of action, following intrathecal administration. In combination with bupivacaine, subarachnoid administration of fentanyl does not have any further depression of efferent, sympathetic activity [5], and it is possible to enhance the sensory blockade without altering the degree of sympathetic blockade. Clonidine is a potent analgesic, free of at least some of opioid-related side effects [6] and prolongs the duration of local anesthetics when administered intrathecally [7]. Intrathecal clonidine at the usual dose (1-2 µg/kg) is associated with side effects such as hypotension, bradycardia, and sedation [8]. A few studies have focused on small doses of intrathecal clonidine (15 µg to 37.5 µg) in surgical patients to avoid these complications [8,9].

In the review of the literature, we did not find any comparative study of clonidine and fentanyl intrathecally in this low-dose range. Hence, we have designed a randomized, double-blinded clinical study to evaluate the postoperative analgesic efficacy and side effects of 25 µg clonidine and 25 µg fentanyl administered intrathecally, with 0.5% hyperbaric bupivacaine as compared to hyperbaric bupivacaine alone in patients undergoing vaginal hysterectomy.

METHODS

After approval of the hospital ethics committee, 90 patients of ASA I and ASA II, aged between 50 and 70 years, scheduled for vaginal hysterectomy under spinal anesthesia were included in this prospective randomized, double-blinded study. Patients who had contraindication of spinal block, any psychiatric disorder, any chronic pain, allergy to study drugs, or on anti-hypertensive medications were excluded from this study. Written informed consent was taken on the day before surgery from patients included in this study. All patients received premedication with tablet alprazolam 0.5 mg on the night before surgery and tablet ranitidine 150 mg orally in the morning on the day of surgery. In the operating room, each patient was preloaded with 20 ml/kg Ringer's lactate solution. Monitoring of electrocardiography (ECG), non-invasive blood pressure, and pulse oximetry (SpO_2) were established. Pulse rate, blood pressure, SpO_2, ECG, and respiratory rate of each patient were recorded before spinal anesthesia. Patients were randomly allocated to one of three treatment groups, each comprising 30 patients, using computer-generated random numbers inserted into sealed envelopes marked 1-90, to receive either 2.5 ml of 0.5% hyperbaric bupivacaine plus 0.5 ml of 0.9% normal saline (as placebo, Group A); Group B (fentanyl group) received 2.5 ml 0.5% hyperbaric bupivacaine plus 25 µg preservative free fentanyl, and Group C (clonidine group) received 2.5 ml 0.5% hyperbaric bupivacaine plus 25 µg preservative free clonidine intrathecally. Total volume administered intrathecally was 3 ml in all the three groups.

Spinal anesthesia was performed using 25-gauge pencil point needle (Whitacre type, BD) with the patient in sitting position, the targeted inter-space being L_{3-4}. After noting the time of spinal injection, patients were placed in lithotomy position after they were unable to flex both knees, and O_2 (3 l/minutes) was given through a face mask. Vital signs, sensory level, motor block, pain score, and side effects were observed every 2 minutes for first 20 minutes, then 15 minutes thereafter until the end of surgery, and then every 30 minutes till rescue analgesic was given. Study solutions were prepared in a separate area by an anesthesiologist not involved in the patients' care, and the patients and anesthesiologist were blinded to the study solutions. The onset and duration of the sensory block were assessed by both losses of sensation to cold and pinprick method. Time from intrathecal injection to the highest level of sensory block was recorded as onset time, and sensory regression to the L_1 dermatome was recorded as the duration of sensory

block. The onset and duration of the motor block were noted. Grading of motor block was done as per modified Bromage scale [10]. Following confirmation of spinal block by losses of sensation to cold and pinprick up to T_{10} level, surgery was started. Hypotension was defined as a decrease in systolic BP >20% from baseline value and was treated with additional fluids or mephentermine 3 mg intravenous (IV) Bradycardia was defined as a fall in heart rate >20% from baseline or heart rate <50 beats/minutes and was treated with injection atropine 0.6 mg IV Patients were observed for any discomfort, nausea, vomiting, pruritus, and respiratory depression (respiratory rate <8 breaths/minutes). After surgery, pain intensity at rest and on movement (on head raising and with attempt to sit up) was assessed with a 10 cm (visual analog score [VAS]; 0=no pain and 10=worst imaginable pain), which was explained to all patients prior to surgery. Request for rescue analgesia for pain relief in postoperative period was provided with injection pethidine 75 mg I.V. and time was recorded. Duration of analgesia was taken from onset of the subarachnoid block to time of administration of rescue analgesic. Level of sedation (no sedation =0, drowsiness =1, asleep but arousable =2, severe sedation, i.e. loss of verbal contact =3) and pain score (0-10 cm VAS) were recorded before the onset of block and every 2 minutes for first 20 minutes of block, then every 15 minutes till end of surgery, and thereafter every 30 minutes until rescue analgesic was given. Patients were discharged from post-anesthesia care unit after sensory block regressed to L_1 dermatome.

To calculate the sample size, a power analysis (α=0.05 and β=0.80) showed that 28 patients per study group were needed to detect an increase of 30% in the time interval from spinal anesthesia to the first request for supplemental analgesia between the groups based on previously published studies. We chose 30 patients in each group to rule out any possible dropout. The groups were compared for single parametric, ordinal, and nominal variables by Student's unpaired *t*-test, Mann-Whitney *U*-test, and Fisher's exact test or Chi-squared analysis, respectively. The hemodynamic data were compared using analysis of variance for repeated measures, followed by Student's unpaired *t*-test. A p<0.05 was taken as statistically significant. Data are presented as mean values + standard deviation and numbers (percentage).

RESULT

The three treatment groups receiving three separate drugs (saline, fentanyl, or clonidine) intrathecally along with a specified amount of bupivacaine heavy (0.5%, 2.5 ml) were comparable with respect to demographical characteristics of age, height, ASA status, and duration of surgery (Table 1).

The characteristics of sensory and motor blockade of the study drugs (25 μg fentanyl and 25 μg clonidine, in Groups B and C, respectively) was compared to a control drug (saline, Group A). The highest sensory level achieved were T_7 (T_6-T_{10}), T_6 (T_6-T_7), and T_5 (T_4-T_7) in the three groups, respectively, which were comparable. The time of onset of peak sensory block was significantly faster (2.7±1.2 minutes, p<0.01) in clonidine group as compared to control (7±2.1 minutes) and fentanyl group (6.4±3.2 minutes). Similarly, time of onset of Grade III motor block (just able to move knees) was significantly quicker (3.3±0.25 minutes, p<0.01) in clonidine group as compared to either saline (8.34±0.3 minutes) or fentanyl (7.5±1.1 minutes). The mean time from injection to regression of level of sensory analgesia up to L_1 (i.e. duration of sensory block) was 190±14.14 minutes in clonidine group, which was significantly longer than the duration of 125±11.31 minutes in control group (p<0.01) and 155±8.01 minutes in fentanyl group (p<0.05). In this respect, the group receiving intrathecal fentanyl has significantly longer duration of sensory regression than the placebo group (p<0.05). Duration of motor block was 176±35.5 minutes in clonidine group was significantly more as compared to 115±12.5 minutes in the control group (p<0.05) and 127±7.1 minutes in fentanyl group (p<0.05). Duration of analgesia in the clonidine group (325±15 minutes) was significantly more in comparison to 160±12.5 minutes in control group (p<0.01) and 240±11.76 minutes in fentanyl group (p<0.05). Significantly, intrathecal addition of fentanyl in comparison to saline improves the duration of analgesia (p<0.05). Table 2 depicts the characteristics of sensory and motor blockade in detail.

Table 1: Demographic characteristics of patients undergoing vaginal hysterectomy

	Control group (Group A; n=30)	Fentanyl group (Group B; n=30)	Clonidine group (Group C; n=30)
Age	55±11.2	54±8.5	56±9
Height (cm)	153±4	152±4	151±5
Weight (kg)	56±12	55±12	55±9
ASA status (I/II)	25/5	26/4	22/8
Duration of surgery	99±27	98±30	101±32

Expressed in mean ± standard deviation, p>0.05

Table 3 demonstrates the hemodynamic changes and incidence of side effects of the control group and the two study drugs. Hypotension and bradycardia were more in clonidine group in comparison to control and fentanyl groups, but this difference was not statistically significant. Three patients in the clonidine group were treated with injection mephentermine 3 mg I.V. for hypotension while five patients of clonidine group (16.6%) had bradycardia and required injection atropine 0.6 mg I.V. The incidence of sedation as assessed by sedation score was significantly higher in clonidine group (p<0.01). However, all these patients had Grade I sedation (drowsy, but arousable) which was not clinically significant. Intraoperative and post-operative pain relief as assessed VAS score was lower with both intrathecal clonidine and fentanyl than control group. The incidences of nausea, vomiting, and pruritus in the three groups were similar, and no patient had respiratory depression.

DISCUSSION

Intrathecal clonidine (25 μg) significantly prolongs sensory and motor blocks, with prolonged duration of analgesia in comparison with intrathecal (25 μg) fentanyl. Fentanyl has proved to be a safer alternative than morphine for intrathecal administration and is an established method for postoperative analgesia [11,12]. Clonidine is a selective partial agonist of α_2 adrenoreceptors, and intrathecal clonidine increases both sensory and motors blockade of local anesthesia [13]. Several studies have shown that clonidine administered intrathecally has a substantial anti-nociceptive effect by its action on α_2 receptors in the dorsal horn of spinal cord [14,15]. A few studies [8,9,16] have used small doses of intrathecal clonidine in surgical patients. Clonidine 15 or 30 μg significantly prolonged sensory blockade of spinal anesthesia for surgery below the level of umbilicus [9], inguinal herniorrhaphy [8], and gynecological surgery [16]. We used a dose of clonidine 25 μg in our study which was in between the small doses range of intrathecal clonidine 15 μg [8] and 30 μg [8,16] used in surgical patients. We have chosen the dose of 25 μg of fentanyl as most studies have shown that this dose provides the maximum duration of postoperative analgesia, with minimum side effects such as pruritus and respiratory depression [17-20].

Results of this study show that 25 μg clonidine added to hyperbaric bupivacaine (0.5%, 2.5 ml) intrathecally significantly prolongs sensory (190±14.14 minutes) and motor block (176±35.5 minutes) in comparison with intrathecal bupivacaine alone and intrathecal bupivacaine with fentanyl 25 μg combination, which corroborate the observations of previous studies [9,16].

Patients in fentanyl group and clonidine group had improved postoperative analgesia as assessed by VAS score. The duration of analgesia (325±15 minutes) in clonidine group in the postoperative period was significantly prolonged in comparison to placebo and fentanyl groups, which was comparable to other studies [8,9]. The duration of pain-free period of intrathecal fentanyl in our study

Table 2: Characteristics of sensory and motor block after giving spinal anesthesia

	Control group (Group A; n=30)	Fentanyl group (Group B; n=30)	Clonidine group (Group C; n=30)
Highest level of sensory block	T7 (T6-T10)	T6 (T6-T7)	T5 (T4-T7)
Time to achieve peak sensory block (minute)	7±2.1	6.4±3.2	2.7±1.2**
Duration of sensory block (minute)	125±11.31	155±8.01*	190±14.14**
Onset of Grade III motor block (minute)	8.34±0.30	7.5±1.1	3.3±0.25**
Duration of Grade I motor block (minute)	115±12.5	127±7.1	176±35.5*
Time of rescue analgesic (minute)	160±12.5	240±11.76*	325±15**

Expressed in either range ( ) or mean±standard deviation *p<0.05, **p<0.01

Table 3: Characteristics of hemodynamic changes and occurrences of other side effects during study period

	Control group (Group A; n=30) (%)	Fentanyl group (Group B; n=30) (%)	Clonidine group (Group C; n=30) (%)
Bradycardia	2 (6.6)	2 (6.6)	5 (16.6)
Hypotension	6 (20)	6 (20)	8 (26.6)
Itching	Nil	3 (10)	Nil
Nausea/vomiting	3 (10)	0	1
Sedation	0	0	6** (20)
Respiratory depression	Nil	Nil	Nil

Expressed in percentages **p<0.01

(240±11.76 minutes) was similar to other studies done in the Indian context [20].

The three groups had similar levels of mean highest sensory blockade (T_5 to T_7), which corroborated with other studies [9,21]. In our study, we observed that intrathecal addition of fentanyl 25 μg prolongs the duration of bupivacaine-induced sensory block. This suggests a potential synergism between fentanyl and bupivacaine as reported in other studies [18,22]. The present study also shows that addition of 25 μg fentanyl to hyperbaric 0.5% bupivacaine (12.5 mg) intrathecally does not influence motor block significantly when compared to bupivacaine alone, which was similar to a previous study [23]. In our study, emetic episodes were less with fentanyl than other groups which corroborate with previous observations [24]. Three patients belonging to the intrathecal fentanyl group complained of pruritus but did not require any treatment. None of our patients experienced respiratory depression or desaturation. In intrathecal clonidine group, 20% of the patients were drowsy but arousable (Grade I sedation) compared to no sedation in both the placebo and fentanyl groups; this result was statistically significant. Similar incidence of sedation (15%) was observed with 15 μg intrathecal clonidine in a previous study [9]. In our study, the low dose of intrathecal clonidine with bupivacaine had similar hypotensive episodes as with intrathecal bupivacaine combinations with fentanyl or saline. The low incidence of hypotensive episodes with intrathecal clonidine was similar to other studies using low-dose clonidine [8,16]. The incidence of bradycardia with intrathecal clonidine (16.6%) was higher compared to the fentanyl and control group (6.6% in each group) though not of statistical significance. This was similar to other studies with low-dose clonidine [25].

A limitation of our study is that exact equianalgesic doses of clonidine and fentanyl are not known and also that these study drugs differ in their respective mode of action. Moreover, only a single dose of clonidine (25 μg) was chosen. We did not perform a dose–response study because previous studies have already shown that clonidine dose-dependently increases the local anesthetic effect [26]. Another possible limitation is that proper spinal interspace cannot be properly identified by a significant number of anesthesiologists, leading to injection in a higher interspace in up to 51% of administered spinal anesthetics [27].

In conclusion, intrathecal clonidine (25 μg) in comparison to fentanyl (25 μg) when administered with hyperbaric bupivacaine 0.5% provides improved postoperative analgesia, with faster onset and prolonged duration of sensory blockade.

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