

A comparative study of the effect of clonidine, fentanyl, and the combination of both as adjuvant to intrathecal bupivacaine for postoperative analgesia in total abdominal hysterectomy

Fareed Ahmed, Mamta Khandelwal, Anil Sharma

Department of Anaesthesiology, SMS Medical College, Jaipur, Rajasthan, India

Abstract

Background and Aims: The aim of this study was to evaluate the level of sensory block, onset and duration of motor block, postoperative analgesia, and adverse effects of combination of clonidine and fentanyl given intrathecally with hyperbaric bupivacaine (HB).

Material and Methods: Three hundred and twenty eight patients were randomized into four groups. Group bupivacaine (group B) received 15 mg of HB; group bupivacaine clonidine (group BC) received 15 mg of HB plus 25 µg clonidine; group bupivacaine fentanyl (group BF) received 15 mg of HB plus 25 µg fentanyl and group bupivacaine clonidine fentanyl (group BCF) received 15 mg of HB plus 25 µg clonidine and 25 µg fentanyl intrathecally. All groups were evaluated for level of sensory block, onset and duration of motor block, postoperative analgesia, VAS score, sedation score and adverse effects of study drugs. All the data were analyzed using unpaired *t*-test. *P* < 0.05 was considered significant.

Results: The level of sensory block, onset, and duration of motor block were comparable in all groups. Total duration of analgesia was 407.3 ± 20 min in group BCF compared to 242.1 ± 2 min and 209.2 ± 16 in groups BC and BF, respectively. Lesser doses of rescue analgesic were required in group BCF. The time interval from intrathecal injection to two-segment regression was statistically significant in study groups. Only 2.4% patients showed mild sedation in BCF group.

Conclusion: We found that combination of intrathecal clonidine and fentanyl along with bupivacaine increases the total duration of analgesia without significant side effects.

Key words: Abdominal hysterectomy, clonidine, fentanyl, intrathecal

Introduction

Management of postoperative pain increases patient satisfaction, leads to earlier mobilization, shortens hospital stay, and reduces hospital costs.^[1-3] A major goal in the management of postoperative pain is to minimize the dose of medications in view to reduce incidence of side effects while still providing adequate analgesia. This goal is best accomplished with a multimodal approach.^[4]

Regional and neuraxial technique can provide superior analgesia compared to systemic drugs. Spinal anesthesia using only local anesthetics is associated with relatively short duration of action and thus early analgesic intervention is needed in the postoperative period. A number of adjuvants such as midazolam, clonidine, dexmedetomidine etc. have been used to prolong the duration of spinal anesthesia. Fentanyl is a potent, short-acting, highly lipophilic, synthetic opioid. It has been commonly used as an adjuvant for postoperative analgesia in neuraxial block.^[5,6]

Address for correspondence: Dr. Mamta Khandelwal,
Flat No. 201, B-80, Sona Enclave, Rajendra Marg,
Bapu Nagar, Jaipur, Rajasthan, India.
E-mail: drmamtakhandelwal@gmail.com

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Clonidine is a α -1 and α -2 adrenoceptor agonist with a predominant α -2 action ($\alpha_2:\alpha_1$: 200:1).^[7] Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimulation. Substance P release inhibits the cGMP for its analgesic effect.^[8,9]

The primary aim of this study was to compare the effect of intrathecal clonidine, fentanyl, and the combination of both with bupivacaine for duration of postoperative analgesia.

Material and Methods

This prospective, randomized, double-blind study was conducted at a tertiary care center after approval from the hospital Ethics Committee. Three hundred twenty eight female patients of 30-50 years, weighing between 45-65 kg, belonging to American Society of Anesthesiologists (ASA) physical status I or II and scheduled for abdominal hysterectomy were included in the present study. Patients with a contraindication to spinal anesthesia or major neurological, cardiovascular, metabolic, respiratory, renal disease, or coagulation abnormalities were excluded from the study.

The procedure was explained to the patient, and written informed consent was taken. In the holding room, the concept of a visual analog scale (VAS),^[10] which consists of a 100 mm line with zero denoting no pain at all and 100 denoting the worst possible pain, was introduced to the patient. Randomization was done by chit in box method. Patients were divided into four groups each consisting of 82 patients. ($n = 82$).

Group bupivacaine (group B) received 15 mg of 0.5% hyperbaric bupivacaine (HB) intrathecally, group bupivacaine clonidine (group BC) received 15 mg of hyperbaric 0.5% bupivacaine plus 25 μ g clonidine hydrochloride intrathecally, group bupivacaine fentanyl (group BF) received 15 mg of 0.5% HB plus 25 μ g fentanyl citrate intrathecally, and group bupivacaine clonidine fentanyl (group BCF) received 15 mg of 0.5% HB plus 25 μ g clonidine hydrochloride and 25 μ g fentanyl citrate intrathecally. In all four groups, normal saline was added to make the total volume 4 ml.

In the operating room, fasting status, consent, PAC were checked, and intravenous access was secured. After the establishment of intravenous (IV) line and attachment of standard monitors [non-invasive blood pressure (NIBP), electrocardiography (ECG), and pulse oximetry (SpO_2)], all patients were premedicated with midazolam 1 mg intravenously. Hydration consisted of 10 ml/kg Ringer lactate solution preoperatively and 10 ml/kg/hr after spinal anesthesia.

Spinal anesthesia was performed in the operating room at the L_3 - L_4 interspace, with the patient in the left lateral position. A volume of 4 ml of the study drug was injected over 30s through a 25-gauge spinal needle. The patient was placed in the supine position with a 15° head down tilt immediately after spinal injection to achieve a block level of T5-T6. The drug combination was prepared by one anesthetist and administered by another anesthetist who was unaware of the nature of drug solution. All the observations were done by the second anesthetist.

Intraoperatively the level of sensory block, onset of motor block, patient's hemodynamic parameters, and sedation score were recorded. The level of sensory block was assessed using a 22-gauge needle and recorded as a loss of sensation to pin prick, checking in a caudal to cephalic direction. Motor block was recorded according to the Bromage scale.^[11] NIBP was recorded at 5 min interval throughout the surgery and HR and SPO_2 were recorded continuously. Fluid administration was continued intraoperatively, and a decrease in mean arterial pressure >15% below the preanesthetic baseline value was treated with incremental doses of injection mephentermine 5 mg intravenous (IV). A decrease in HR below 50 beats/min was treated with incremental doses of atropine 0.3 mg IV. Intraoperative nausea was treated with ondansetron 4 mg IV.

Postoperatively, time for two segment regression and total duration of motor block was recorded. VAS was assessed at 2 h interval and at the time of giving rescue analgesia. Adverse effects (hemodynamic changes, respiratory depression, shivering, nausea, vomiting, pruritus, and headache) were observed over 24 h. The duration of effective analgesia was defined as the time from intrathecal drug administration to the patient's first request for rescue analgesic. This constituted the primary end point of the study, though the patients were kept under observation for a total period of 24 h. Patients were allowed to receive rescue analgesics on demand. Gluteal intramuscular diclofenac (75 mg) was given as rescue analgesic. The duration of motor block was defined as the time of attainment of Bromage grade IV block (onset) until reversal to Bromage grade II.

Statistical analysis

The expected mean VAS among A, B, and C group were 23 (± 71), 17 (± 6), and 2 (± 1), respectively, and the expected mean duration of time for the request of first analgesic in (A), (B) and (C) were 137 (± 35), 183 (± 80), and 215 (± 79) min, respectively (as per seed article).^[10] The sample size required to determine these differences in three groups at 95% confidence interval and 80% power would be 82 in each group. This sample size would cover both observations.

Statistical analysis was performed with SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Categorical data, that is, ASA grade, type of surgery and the incidence of adverse events (hypotension, bradycardia, respiratory depression, shivering, nausea, pruritis, and headache) are presented as numbers (percent) and were compared among groups using the Chi-square test. $P < 0.05$ was considered statistically significant.

Results

Three hundred forty patients were assessed for eligibility. Twelve patients did not fulfill the study criteria and were excluded. 328 patients were enrolled. All the groups were comparable with respect to age, gender, weight, ASA status, type of surgery, and duration of surgery [Table 1].

The characteristics of sensory and motor blockade are given in Table 2. Visual analog scale scores at 2 h and at the time of giving rescue analgesia are shown in Table 3. The average VAS pain score at the time of giving rescue analgesic medication was similar among groups.

In groups B and BC, all the patients were awake and alert (grade I). In group BF; 97.6% patients were awake and alert (grade I), 2.4% patients showed mild sedation (grade II). In group BCF, 97.6% patients were awake and alert (grade I), 2.4% patients showed mild sedation (grade II).

In all four groups, patients were hemodynamically stable in intraoperative and postoperative period. There were no significant differences among groups regarding the incidence of perioperative adverse effects [Table 4].

Discussion

Neuraxial adjuvants have been used to improve or prolong analgesia, decrease the adverse effects associated with high doses of a single local anesthetic agent, to increase the speed of onset of neural blockade (reduce latency), improve the quality, and prolong the duration of neural blockade. Many drugs (fentanyl, morphine, vasoconstrictors such as epinephrine and phenylephrine, α_2 -agonists) have been used as an additive to local anesthetics.^[12]

Benhamou *et al.*^[12] in a study observed that adding a small dose of intrathecal clonidine (75 μg) and fentanyl (12.5 μg) to bupivacaine increased the quality of intraoperative analgesia and decreased pain during cesarean section. In our study, we have used 25 μg of clonidine instead of 75 μg intrathecally and observed significantly prolonged duration of postoperative analgesia with good hemodynamic stability.

Santos *et al.*^[13] showed that both 20 μg of fentanyl and 10 μg of clonidine promoted satisfactory anesthesia and good postoperative analgesia in patients undergoing anal surgery. Even a very low intrathecal dose of 15 μg of clonidine was able to

Table 1: Demographic profile of groups

Observations	Group B n = 82	Group BC n = 82	Group BF n = 82	Group BCF n = 82
ASA grade (I/II)	46/36	41/41	48/34	37/45
Age (year)	44.3 \pm 7.3	44.0 \pm 6.5	41.44 \pm 7.6	43.7 \pm 6.2
Weight (kg)	54.2 \pm 6.0	55.6 \pm 4.7	56.4 \pm 4.2	55.2 \pm 6.7
Surgical time (min)	56.8 \pm 7.7	59.2 \pm 11.0	57.8 \pm 9.1	59.0 \pm 11.3
Type of surgery				
TAH + BSO	42	38	39	41
TAH	40	44	43	41

Values are mean \pm SD. NS = Not significant, SD = Standard deviation, ASA = American Society of Anesthesiologists, BSO = Bilateral salpingo-oophorectomy, TAH = Total abdominal hysterectomy

Table 2: Characteristics of sensory and motor block

Parameters	Group B	Group BC	Group BF	Group BCF
Sensory level (pinprick)				
5 min	T ₉ (T ₇ -T ₉)	T ₉ (T ₇ -T ₁₀)	T ₉ (T ₇ -T ₉)	T ₉ (T ₇ -T ₉)
10 min	T ₆ (T ₅ -T ₇)	T ₆ (T ₅ -T ₇)	T ₆ (T ₅ -T ₇)	T ₆ (T ₅ -T ₇)
Time for 2 segment regression (min) [¶]	79.2 \pm 12.7	131.2 \pm 20.9	126.0 \pm 22.6	133.6 \pm 30.6
Total duration of analgesia (min.) [#]	118.0 \pm 14.0	242.1 \pm 23.3	209.2 \pm 16.1	407.3 \pm 20.2
Onset of motor block [@] (min)	9 \pm 1.4	8.5 \pm 1.1	8.7 \pm 1.1	8.5 \pm 1.4
Total duration of motor block [§] (min)	117.3 \pm 9.7	123.8 \pm 16.6	122.8 \pm 14.9	122.1 \pm 15.0

[@]Bromage Grade IV, [§]Return to Bromage Grade II, $P > 0.05$ (nonsignificant), $P < 0.05$ or 0.01 (significant), $P < 0.001$ (highly significant), [¶]Statistically significant difference between group B was compared with group BC ($P = 0.000$), group BF ($P = 0.0000$) and group BCF ($P = 0.000$), [#]Statistically significant difference between group B was compared with group BC ($P = 0.000$), group BF ($P = 0.000$) and group BCF ($P = 0.000$); when group BC was compared with group BF ($P = 0.000$) and group BCF ($P = 0.000$)

Table 3: Pain score

Variable	Group B	Group BC	Group BF	Group BCF
VAS score (2 h) #	29.5±6.7	0.7±2.5	0.7±2.6	0.0
VAS score at first rescue analgesic	28.9±6.8	21.2±5.2	21.2±5.1	23.8±7.0

0-100 mm VAS, VAS = Visual analog scale

Table 4: Characteristics of hemodynamic and incidence of side effects (intraoperative and early postoperative period)

Side effects	Group B (%)	Group BC (%)	Group BF (%)	Group BCF (%)
Hypotension [#]	2 (2.4)	3 (3.6)	3 (3.6)	2 (2.4)
Bradycardia [§]	3 (3.6)	1 (1.2)	0 (0)	2 (2.4)
Respiratory depression [¶]	0 (0)	0 (0)	0 (0)	0 (0)
Shivering	2 (2.4)	4 (4.9)	2 (2.4)	3 (3.6)
Nausea, vomiting	2 (2.4)	3 (3.6)	0(0)	2 (2.4)
Pruritus	0 (0)	0 (0)	2 (2.4)	2 (2.4)
Headache	0 (0)	2 (2.4)	1 (1.2)	0 (0)

[#]BP reduction > 20% from baseline, [§]HR < 60 beats per/min, [¶]Respiratory rate <9 breaths/min or oxygen saturation <90%. HR = Heart rate, BP = Blood pressure

increase motor block duration. In our study, we did not find any effect on the duration of motor block even with 25 µg of clonidine. Garg *et al.*^[14] have shown an increase in postoperative analgesia when fentanyl 25 µg is added to intrathecal bupivacaine in patients undergoing total abdominal hysterectomy.

Biswas *et al.*^[15] showed that the addition of 12.5 µg of fentanyl markedly improved intraoperative anesthesia, and significantly reduced the demand for postoperative analgesia with good satisfaction and well-being for patient. Khanna and Singh^[16] reported an increase in duration of sensory block, improvement in intraoperative analgesia, and good pain relief in the postoperative period along with high incidence of pruritus and desaturation with fentanyl added to intrathecal bupivacaine in geriatric patients.

Dobrydnjov *et al.*^[17] concluded that the addition of clonidine 15 µg and 30 mg to bupivacaine prolonged time to first analgesic request and decreased postoperative pain with minimal risk of hypotension. Khandelwal *et al.*^[18] found that time to first analgesic request is prolonged by addition of clonidine in a dose of 50 µg. In their study, total duration of analgesia was 302 ± 54 which was more than that observed in our study because they used a higher dose of clonidine.

Though we use 25 microgm of clonidine and fentanyl each, further research is desirable to validate the various dosage combinations of clonidine and fentanyl.

Conclusion

The combination of intrathecal clonidine and fentanyl with hyperbaric bupivacaine significantly prolonged the duration of postoperative analgesia with good hemodynamic stability and nonsignificant adverse effect.

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Conflicts of interest

There are no conflicts of interest.

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