Original Article

A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine

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Abstract

Background: Various adjuvants have been used with local anesthetics in spinal anesthesia to avoid intraoperative visceral and somatic pain and to provide prolonged postoperative analgesia. Dexmedetomidine, the new highly selective α2-agonist drug, is now being used as a neuraxial adjuvant. The aim of this study was to evaluate the onset and duration of sensory and motor block, hemodynamic effect, postoperative analgesia, and adverse effects of dexmedetomidine or fentanyl given intrathecally with hyperbaric 0.5% bupivacaine.

Materials and Methods: Sixty patients classified in American Society of Anesthesiologists classes I and II scheduled for lower abdominal surgeries were studied. Patients were randomly allocated to receive either 12.5 mg hyperbaric bupivacaine plus 5 μg dexmedetomidine (group D, $n=30$) or 12.5 mg hyperbaric bupivacaine plus 25 μg fentanyl (group F, $n=30$) intrathecal.

Results: Patients in dexmedetomidine group (D) had a significantly longer sensory and motor block time than patients in fentanyl group (F). The mean time of sensory regression to S1 was 476±23 min in group D and 187±12 min in group F ($P<0.001$). The regression time of motor block to reach modified Bromage 0 was 421±21 min in group D and 149±18 min in group F ($P<0.001$).

Conclusions: Intrathecal dexmedetomidine is associated with prolonged motor and sensory block, hemodynamic stability, and reduced demand for rescue analgesics in 24 h as compared to fentanyl.

Key words: Bupivacaine, dexmedetomidine, fentanyl, spinal anaesthesia

Introduction

Spinal anesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. However, postoperative pain control is a major problem because 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 clonidine and midazolam, and others have been studied to prolong the effect of spinal anesthesia.[1,2]

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A common problem during lower abdominal surgeries under spinal anesthesia is visceral pain, nausea, and vomiting.[3] The addition of fentanyl to hyperbaric bupivacaine improves the quality of intraoperative and early postoperative subarachnoid block.[4] The addition of opioids to local anesthetic solution have disadvantages, such as pruritus and respiratory depression. Dexmedetomidine, a new highly selective α2-agonist, is under evaluation as a neuraxial adjuvant as it provides stable hemodynamic conditions, good quality of intraoperative and prolonged postoperative analgesia with minimal side effects.[5-7] Dexmedetomidine has been approved by Food and Drug Administration (FDA) as a short-term sedative for mechanically ventilated intensive care unit (ICU) patients. Based on earlier human studies, it is hypothesized that intrathecal 5 μg dexmedetomidine would produce more postoperative analgesic effect with hyperbaric bupivacaine in spinal anaesthesia with minimal side effects.[5-7] Till date, there has been no study comparing the addition of dexmedetomidine to hyperbaric bupivacaine with hyperbaric fentanyl to bupivacaine, although various studies have compared dexmedetomidine and fentanyl with isobaric bupivacaine.[5,6]

Materials and Methods

The study was conducted after approval of ethical committee of the institution. Written informed consent was obtained from all patients. Inclusion criteria were American Society of Anesthesiologists (ASA) physical status I or II, either sex, age 18–50 years, presenting for lower abdominal surgeries. Exclusion criteria were patient allergic to drug, heart block/dysrrhythmia, or on therapy with adrenergic receptor antagonist, calcium channel blocker, and/or ACE inhibitor.

All patients received diazepam 0.2 mg/kg orally, the night before surgery. The patients were preloaded with Lactated Ringer's solution 15 mL/kg. They were monitored with automated noninvasive blood pressure, pulse oximetry, and electrocardiogram. 25G Pencil point spinal needles were introduced through L3–L4 interspaces in sitting position using aseptic precautions. Patients were randomly divided into the following groups: Group D—to receive 2.5 mL volume of 0.5% hyperbaric bupivacaine and 5 μg dexmedetomidine in 0.5 mL of normal saline intrathecal (dexmedetomidine (100 μg/mL) was diluted in preservative-free normal saline) and Group F—to receive 2.5 mL volume of 0.5% hyperbaric bupivacaine with 25 μg fentanyl intrathecal. Intrathecal injection was given over approximately 10–15 s. Immediately after completion of the injection patients were made to lie supine.

Oxygen (2 L/min) was administered via a mask if the pulse oximeter reading decreased below 90%. Hypotension, defined as a decrease of systolic blood pressure by more than 30% from baseline or a fall below 90 mmHg, was treated with incremental IV doses of ephedrine 5 mg and IV fluid as required. Bradycardia, defined as heart rate < 50 bpm, was treated with IV atropine 0.3–0.6 mg. The incidence of adverse effects, such as nausea, vomiting, shivering, pruritus, respiratory depression, sedation, and hypotension were recorded. Sensory testing was assessed by loss of pinprick sensation to 23G hypodermic needle and dermatomes levels were tested every 2 min until the highest level had stabilized by consecutive tests. On achieving T7 sensory blockade level, surgery was allowed. Testing was then conducted every 10 min until the point of two segment regression of the block was observed. Further testing was performed at 20-min intervals until the recovery of S2 dermatome. The surgeon, patient, and the observing anesthesiologist were blinded to the patient group. Data regarding the highest dermatome level of sensory blockade, the time to reach this level from the time of injection, time to S1 level sensory regression, time to urination, and incidence of side effects were recorded. Sedation was assessed by a modified Ramsay sedation scale.

Modified Ramsay sedation scale

- Anxious, agitated, restless.
- Cooperative, oriented, tranquil.
- Responds to commands only.
- Brisk response to light glabellar tap or loud noise.
- Sluggish response to light glabellar tap or loud noise.
- No response.

Postoperatively, the pain score was recorded by using visual analog pain scale (VAS) between 0 and 10 (0 = no pain, 10 = most severe pain), initially every 1 h for 2 h, then every 2 h for the next 8 h and then after every 4 h till 24 h. Diclofenac was given intramuscularly as rescue analgesia when VAS was >4. A follow-up was carried out 1 week postoperatively by the blinded anesthesiologist, who asked about postoperative headache as well as postoperative pain and dysesthesia in the buttock, thighs, or lower limbs.

Statistical analysis was done using the Statistical Package for Social Science (SPSS15.0 Evaluation version). To calculate the sample size, a power analysis of $\alpha=0.05$ and $\alpha=0.90$, showed that 30 patients per study group were needed. Data are expressed as either mean and standard deviation or numbers and percentages.[8] Continuous covariates were compared using analysis of variance (ANOVA). The comparison was studied using the Chi-square test or Fisher's exact test as appropriate, with the P value reported at the 95% confidence interval. $P<0.05$ was considered statistically significant.

Results

The groups were comparable with respect to age, height, and weight, and ASA physical status [Table 1]. There was no significant difference in the type and duration of surgery [Table 1]. The characteristics of sensory block are summarized in Table 2. There was no difference between groups D and F in the highest level of block achieved in the two groups (T5 and T6, respectively) or in the time to reach peak level. Block regression was significantly slower with the addition of intrathecal dexmedetomidine as compared with fentanyl, as both time to two segment regressions and time to S2 regression were significantly more with intrathecal dexmedetomidine. There was no difference in the onset time to Bromage 3 motor block (11.6±1.8 min in group D and 11.2±1.3 min in group F) but the regression of motor block to Bromage 0 was significantly slower with the addition of dexmedetomidine [Table 2]. The time to rescue analgesic was significantly longer in group D as compared to group F. The requirement of diclofenac in the first 24 h was significantly lower in group D as compared to group F [Table 2].

Although the patients in both groups remained hemodynamically stable intraoperatively [Figures 1 and 2], the sedation score was more in group D patients. The mean sedation score was 3.8±0.5 in group D as compared to 2.2±0.53 in group F, which was statistically significant ($P<0.05$).

There were no complications, such as nausea, vomiting, shivering, itching, pruritus, sedation, respiratory depression,

Table 1: Demography

	Group D (n=30)	Group F (n=30)	P value
Age (years)	42.21 ± 3.80	44.35 ± 4.08	>0.05
Sex (M:F)	18:7	20:5	>0.05
Height (cm)	158 ± 1.3	156 ± 1.8	>0.05
ASA I: II	21:9	22:8	>0.05
Weight (kg)	65.13 ± 13.4	64.42 ± 9.6	>0.05
Duration of surgery (min)	180 ± 45	170 ± 40	>0.05
Hysterectomy	15	14	>0.05
Inguinal hernia	5	6	>0.05
Urinary bladder and ureteric surgery	10	10	>0.05

ASA, American Society of Anesthesiologists.; Values given in mean ± SD.

Table 2: Characteristics of sensory block

	Group D (n=30)	Group F (n=30)	P value
Highest sensory level	T5(T4–T8)	T6(T4–T7)	>0.05
Time from injection to highest sensory level (min)	12.3 ± 1.8	12.1 ± 1.7	>0.05
Time of two segment regression from the highest sensory level (min)	120 ± 22.2	76 ± 20.3	<0.001
Time for sensory regression to S1 from highest sensory level (min)	476 ± 20	187 ± 12.3	<0.001
Total analgesic dose in first 24 h (mg)	80 ± 67	180 ± 70	<0.001
Time to rescue analgesia (min)	251.7 ± 30.69	168.96 ± 15.96	<0.001
Onset to Bromage 3 (min)	11.6 ± 1.8	11.2 ± 1.3	0.14
Regression to Bromage 0 (min)	421 ± 21	149.3 ± 18.2	<0.0001

Values given in mean±SD.

Table 3: Side effects

	Group D (n=30)	Group F (n=30)	P value
Nausea	1	2	>0.05
Vomiting	0	1	>0.05
Pruritus	0	1	>0.05
Respiratory depression	0	0	—
Hypotension	3	2	>0.05
Bradycardia	1	0	>0.05
Urinary retention	1	2	>0.05

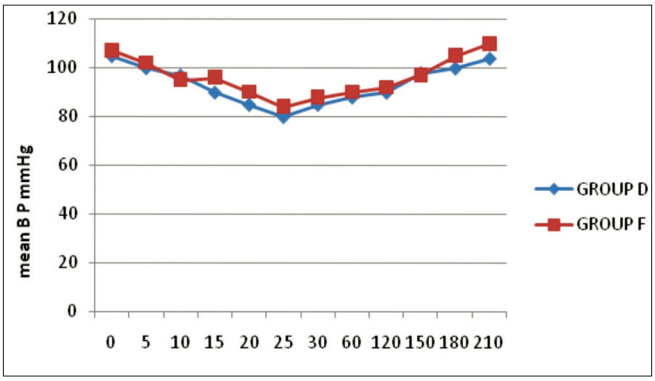

Figure 1: Intraoperative mean arterial blood pressure (mean±SD)

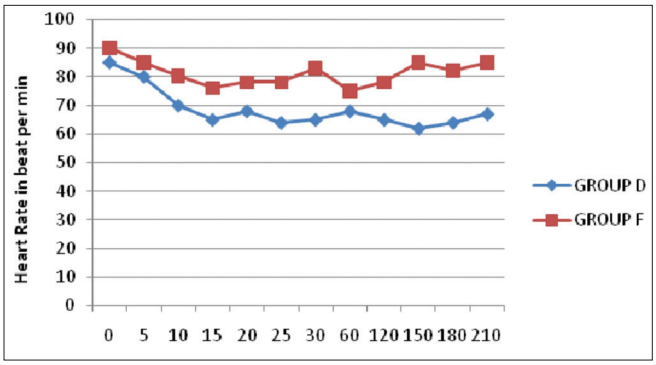

Figure 2: Intraoperative heart rate (mean±SD)

and hypotension, in patients of either group [Table 3]. Intraoperative ephedrine requirement was more in group D (10±4 mg) as compared to group F (6±3 mg). One patient in group D had bradycardia (HR<50/min) but it was successfully managed with atropine 0.4 mg IV. No patient had residual neurologic deficit, postdural puncture headache or transient neurologic symptoms.

Discussion

The mechanism by which intrathecal α_2-adrenoceptor agonists prolong the motor and sensory block of local anesthetics is not well known. They act by binding to presynaptic C-fibers and postsynaptic dorsal horn neurons. Their analgesic action is a result of depression of the release of C-fiber transmitters and hyperpolarisation of postsynaptic dorsal horn neurons.[9] Local anesthetic agents act by blocking sodium channels. The prolongation of effect may result from synergism between local anesthetic and α_2-adrenoceptor agonist, while the prolongation of the motor block of spinal anesthetics may result from the binding of α_2-adrenoceptor agonists to motor neurons in the dorsal horn.[10] Intrathecal α_2-receptor agonists have been found to have antinociceptive action for both somatic and visceral pain.[5] Fentanyl is a lipophilic μ-receptor agonist opioid. Intrathecally, fentanyl exerts its effect by combining with opioid receptors in the dorsal horn of spinal cord and may have a supraspinal spread and action.[11]

The use of intrathecal clonidine has been studied with local anesthetics.[1] Studies using a combination of intrathecal dexmedetomidine and local anesthetics are lacking. In our study, the intrathecal dose of dexmedetomidine selected was based on previous animal studies.[12] A number of animal studies conducted using intrathecal dexmedetomidine at a dose range of 2.5–100 μg did not report any neurologic deficits with its use.[13-17]

Fukushima *et al* administered 2 μg/kg epidural dexmedetomidine for postoperative analgesia in humans but did not report neurologic deficits.[18] Our study has shown that the addition of 5 μg dexmedetomidine with hyperbaric bupivacaine significantly prolongs both sensory and motor block. Both fentanyl and dexmedetomidine provided good quality intraoperative analgesia and hemodynamic stability. The analgesia was clinically better in group D as compared to group F but it was not statistically significant. Small doses of intrathecal dexmedetomidine (3μg) used in combination with bupivacaine in humans have been shown to shorten the onset of motor block and prolong the duration of motor and sensory block with hemodynamic stability and lack of sedation.[7] Al-Ghanem *et al* had studied the effect of addition of 5 μg dexmedetomidine or 25 μg fentanyl intrathecal to 10 mg isobaric bupivacaine in vaginal hysterectomy and concluded that 5 μg dexmedetomidine produces more prolonged motor and sensory block as compared with 25 μg fentanyl.[5] In our study, in the dexmedetomidine group we found longer duration of both sensory and motor blockade, stable hemodynamic condition, and good patient satisfaction. Al-Mustafa *et al* studied effect of dexmedetomidine 5 and 10 μg with bupivacaine in urological procedures and found that dexmedetomidine prolongs the duration of spinal anesthesia in a dose-dependent manner.[6]

Visceral pain usually occurs during abdominal surgery under spinal anesthesia. Intrathecal fentanyl when added to local anesthetics reduces visceral and somatic pain.[19] In our study as no patient perceived visceral pain in both D and F groups.

In our study hypotension was more in the dexmedetomidine group than in the fentanyl group, but it was not statistically significant. A 4-week follow-up showed that intrathecal dexmedetomidine, at a dose of 5 μg, was not associated with any new onset of back, buttock, or leg pain, weakness or neurologic deficit. Pruritus after intrathecal fentanyl is known but it was not significant in the present study. The α-2 adrenergic agents also have antishivering property as observed by Talke *et al*.[20] We too did not find any incidence of shivering in the two groups.

In conclusion, 5 μg dexmedetomidine seems to be an attractive alternative to 25 μg fentanyl as an adjuvant to spinal bupivacaine in surgical procedures. It provides good quality of intraoperative analgesia, hemodynamically stable conditions, minimal side effects, and excellent quality of postoperative analgesia.

References

1. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: Systematic review of randomized trials. Reg Anesth Pain Med 2008;33:159-67.
2. Boussofara M, Carlès M, Raucoules-Aimé M, Sellam MR, Horn JL. Effects of intrathecal midazolam on postoperative analgesia when added to a bupivacaine-clonidine mixture. Reg Anesth Pain Med 2006;31:501-5.
3. Alahuhta S, Kangas-Saarela T, Hollmén AI, Edström HH. Visceral pain during caesarean section under spinal and epidural anaesthesia with bupivacaine. Acta Anaesthesiol Scand 1990;34:95-8.
4. Hunt CO, Naulty JS, Bader AM, Hauch MA, Vartikar JV, Datta S, *et al*. Perioperative analgesia with subarachnoid fentanyl–bupivacaine for Cesarean delivery. Anesthesiology 1989;71:535-40.
5. Al-Ghanem SM, Massad IM, Al-Mustafa MM, Al-Zaben KR, Qudaisat IY, Qatawneh AM and Abu-Ali HM. Effect of Adding

Dexmedetomidine versus Fentanyl to Intrathecal Bupivacaine on Spinal Block Characteristics in Gynecological Procedures: A Double Blind Controlled Study. Am J Appl Sci 2009;6:882-7.
6. Al-Mustafa MM, Abu-Halaweh SA, Aloweidi AS, Murshidi MM, Ammari BA, Awwad ZM, *et al*. Effect of dexmedetomidine added to spinal bupivacaine for urological procedure. Saudi Med J 2009;30:365-70.
7. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, *et al*. Effect of low-dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta Anesthesiol Scand 2006;50:222-7.
8. Murphy KR, Myors B. Statistical power analysis: A simple and general model for traditional and modern hypothesis tests. 2nd ed. Mahwah, NJ: Lawrence Erlbaum Associates; 2004.
9. Eisenach JC, De Kock M, Klimscha W. α2-Adrenergic Agonists for Regional Anesthesia: A Clinical Review of Clonidine (1984 - 1995). Anesthesiology 1996;85:655-74.
10. Harada Y, Nishioka K, Kitahata LM, Kishikawa K, Collins JG. Visceral antinociceptive effects of spinal clonidine combined with morphine, enkephalin, or U50, 488H. Anesthesiology 1995;83:344-52.
11. Kalso E, Poyhia R, Rosenberg P. Spinal antinociception by dexmedetomidine, a highly selective α_2-adrenergic agonist. Pharmacol Toxicol 1991;68:140-3.
12. Lo WC, Harris J, Clarke RW. Endogenous opioids support the spinal inhibitory action of an alpha 2-adrenoceptor agonist in the decerebrated spinalised rabbit. Neurosci Lett 2003;340:95-8.
13. Talke P, Xu M, Paloheimo M, Kalso E. Effects of intrathecally administered dexmedetomidine, MPV-2426 and tizanidine on EMG in rats. Acta Anaesthesiol Scand 2003;47:347-54.
14. Xu M, Kontinen VK, Kalso E. Effects of radolmidine, a novel alpha2-adrenergic agonist compared with dexmedetomidine in different pain models in the rat. Anesthesiology 2000;93:473-81.
15. Horvath G, Joo G, Dobos I, Klimscha W, Toth G, Benedek G. The synergistic antinociceptive interactions of endomorphin-1 with dexmedetomidine and/or S(+)-ketamine in rats. Anesth Analg 2001;93:1018-24.
16. Shimode N, Fukuoka T, Tanimoto M, Tashiro C, Tokunaga A, Noguchi K. The effects of dexmedetomidine and halothane on the Fos expression in the spinal dorsal horn using a rat postoperative pain model. Neurosci Lett 2003;343:45-8.
17. Onttonen T, Pertovaara A. The mechanical antihyperalgesic effect of intrathecally administered MPV-2426, a novel alpha2-adrenoceptor agonist, in a rat model of postoperative pain. Anesthesiology 2000;92:1740-5.
18. Fukushima K, Nishimi Y, Mori K, Takeda J. Effect of epidurally administered dexmedetomidine on sympathetic activity and postoperative pain in man. Anesth Analg 1996;82:S121.
19. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anaesthesia for cesarean section. BMC Anesthesiol 2005;5:5.
20. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly reduces the vasoconstriction and shivering thresholds. Anesthesiology 1997;87:835-41.

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