Original Research *doi: 10.5455/medscience.2015.04.8240*

Comparative Study of two Doses of Intrathecal Dexmedetomidine Versus Fentanyl as Adjuvant to Hyperbaric Bupivacaine Spinal Anesthesia

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Abstract

The aim of this study was to evaluate the effect of addition two different doses of dexmedetomidine or fentanyl to intrathecal hyperbaric bupivacaine on spinal block characteristics, intraoperative hemodynamics, the blood glucose level and postoperative pain. 100 patients ASA I and II, ages 20 -60 years old undergoing elective surgeries below the umbilicus under spinal anesthesia were divided into four groups (n=25 each): Patients were randomly allocated into four equal groups (n= 25, each): Group I: received 3 mL of 0.5% hyperbaric bupivacaine +0.5ml normal saline. Group II: received 3 mL of 0.5% hyperbaric bupivacaine plus 3 μg dexmedetomidine (diluted in 0.5ml of normal saline) intrathecal. Group III: received 3 mL of 0.5% hyperbaric bupivacaine plus 5 μg dexmedetomidine (diluted in 0.5ml of normal saline) intrathecal. Group IV: received 3 mL of 0.5% hyperbaric bupivacaine plus 25 μg fentanyl (0.5ml) intrathecal. intraoperative heart rate and mean arterial blood pressure showed no statistical significant differences between the study groups, patients in group II, III and IV had significantly longer sensory and motor block times than patients in group I. The time of first request of postoperative analgesia was statistically significantly shorter in group I compared to the other groups. Pain scores were higher in group I compared to the other groups. Postoperative blood glucose level was only statistically significantly higher in group II compared to the other groups. Both intrathecal dexmedetomidine and fentanyl are associated with prolongation of sensory and motor block, with stable hemodynamics, minimal effect on blood glucose level, and better postoperative analgesia, compared to intrathecal bupivacaine alone.

Key Words: Spinal anesthesia, bupivacaine, dexmedetomidine, fentanyl

Rec.Date: Dec 22, 2014 Accept Date: Jan 26, 2015)

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Introduction

Spinal anesthesia is the most commonly used neuraxial anesthetic technique for operations of the lower limbs and lower abdomen [1,2]. Spinal anesthesia has some the advantages (e.g. Preservation of spontaneous respiration, relaxation in the bowel and abdominal wall thus facilitating surgery) [3], these advantages are limited by the short duration of action of local anesthetics when used alone and by side effects as hypotension and bradycardia [2,4], many adjuvants can been used to prolong the anesthetic and analgesic effect of local anesthetics [5]. The quality of spinal anesthesia can be enhanced by the addition of fentanyl when added to hyperbaric bupivacaine [6].

Dexmedetomidine, a highly selective alpha2 adrenoreceptor agonist, has been approved by Food and Drug Administration (FDA) in1999 for analgesia and sedation in the intubated patients at the intensive care [7], when used intrathecally in animals it provided potent antinociceptive effect [8,9]. It prolongs the sensory block by acting on presynaptic C fibers and decrease the neurotransmitter release, it prolongs the motor block by binding to motor neurons in the spinal cord [10,11].

Alpha-2 adrenoceptor agonists can cause hyperglycemia in humans through postsynaptice alpha 2-adrenoceptor stimulation of pancreatic B cells, thus inhibiting insulin release [12].

The aim of this study was to evaluate the effect of adding two different doses of dexmedetomidine versus fentanyl to intrathecal hyperbaric bupivacaine on the onset and duration of motor and sensory block, intraoperative hemodynamics, the blood glucose level, postoperative pain and complications.

Patients and Methods

After approval of the review board of department of anesthesia and SICU at Beni Suef University Hospital and the local ethics and research committee, a written informed consents were obtained from each patient before the operation.

This study enrolled 100 patients of both sex undergoing elective surgical procedures below the umbilicus under spinal anesthesia (e.g. lower abdominal and lower limb surgeries) at Beni Suef University Hospital, Egypt, from March 2012 to February 2014.

Exclusion Criteria

1. ASA>II Patients

2. Diabetes mellitus, neuromuscular, hepatic, ,adrenal gland abnormality or major renal disease

3. Known allergy. to amide local anesthetics, dexmedetomidine or fentanyl.

4. Patients using steroids, alpha 2 receptor antagonists, calcium channel blocker

5. Contraindication to spinal anesthesia (e.g. patient refusal, coagulation disorder, infection at the puncture site and tight valvular heart lesion).

Preparation of the Patients

The study protocol and the visual analogue scale (VAS) for pain were explained to the patients preoperatively.

In the operating room, a wide bore intravenous cannula was inserted, preload with 10 ml/kg Ringer solution.

Electrocardiogram, pulse oximetry, and non-invasive arterial blood pressure cuff were applied, blood glucose level measured by glucometer.

Patients were randomly allocated by closed envelope technique for randomization into four equal groups (no=25, each), to maintain the blind nature of the study, the studied drug were given by a well-trained senior anesthesiologist according to the instructions written in a sealed envelope as follows:

Group I: received 3 mL of 0.5% hyperbaric bupivacaine.

Group II: received 3 mL of 0.5% hyperbaric bupivacaine plus 3 μg dexmedetomidine (diluted in 0.5ml of normal saline) intrathecal.

Dexmedetomidine (Precedex 100 μg/ml; Hospira, Inc., Lake Forest, IL 60045 USA).

Group III: received 3 mL of 0.5% hyperbaric bupivacaine plus 5 μg dexmedetomidine (diluted in 0.5ml of normal saline) intrathecal.

Group IV: received 3 mL of 0.5% hyperbaric bupivacaine plus 25 μg fentanyl (0.5ml) intrathecal. Fentanyl (Fentanyl-Janssen 50 μg/ml; Janssen-Cilag).

For all groups, the used hyperbaric bupivacaine is (Sunnybupivacaine 20mg/4ml; Sunny Pharmaceutical). Normal saline 0.5ml was added to the hyperbaric bupivacaine in group I to make the volume 3.5ml

Spinal anesthesia was performed under strict aseptic technique in the sitting position, 2ml lidocaine 2% for local infiltration of the skin at L3-L4 or L4-L5 space, then insertion of 22-G Quincke type spinal needle by midline approach, when free flow of CSF was obtained the study drug was injected spinal needle was withdrawn and the patients were put in the supine position immediately, supplemented with oxygen 3 L/min by face mask.

At the end of surgery, all patients were transferred to PACU where they were monitored and discharged from the PACU to the ward, after achieved complete reversal of sensory and motor block.

The following parameters were evaluated and recorded

1-Demographic data: age, sex, weight, height

2-Hemodynamic parameters: heart rate, mean arterial blood pressure were recorded before anesthesia. After performing the spinal block the mean arterial blood pressure and heart rate were recorded every 5 minutes for the first 20 minutes and then every 15 minutes intraoperative and before the patient discharge from the PACU to the ward. Hypotension was defined as a decrease of systolic blood pressure by more than 30% from baseline or a fall below 90 mmHg and if maintained, was treated with IV fluid, incremental doses of intravenous ephedrine 5 mg as required. Bradycardia defined as a heart rate<50 beats/min, was treated with 0.5 mg of intravenous atropine.

3-Number of patients who required atropine or ephedrine intraoperatively

4- The highest level of sensory blockade assessed by pin prick.

5-Time to reach the maximum sensory level in minutes

6- Time to sensory regression to S1 in minutes

7- Onset time to modified Bromage3 in minutes

The motor block was assessed and recorded using Modified Bromage Scale [(13)] **:** Bromage 0= the patient is able to move the hip, knee and ankle; Bromage 1= the patient is unable to move the hip, but is able to move the knee and ankle; Bromage 2= the patient is unable to move the hip and knee, but is able to move the ankle; Bromage3= the patient is unable to move the hip, knee and ankle every 2 minutes for the first l0 minutes and there after every 5 minutes until Brormage 3 is reached

8- The motor block duration: the time for regression to Bromage 0 in minutes

9-The level of sedation using ***Ramsay sedation scale***: scale l=patient anxious, agitated, or restless; scale 2=patient cooperative, oriented, and tranquil alert; scale 3=Patient drowsy butresponsive to commands; scale 4= Asleep, but with brisk response to light glabellar tap or tactile stimulation; scale 5=asleep with a sluggish response o light glabellar tap or tactile stimulation and scale 6= asleep and no response [14].

10- Blood glucose level: preoperative, one hour after the onset of the operation and immediately postoperative by glucometer.

11- The severity of postoperative pain for 24 hours at l, 6, 12, l8, and 24 h postoperatively using VAS

12- Time to first request of postoperative analgesia in minutes: the time from the end of surgery to the time of first request for analgesia

13-Number of patients required postoperative analgesia (Tramadol hydrochloride 1mg/kg IV) in 24 hours

14-Postoperative complications: sedation, hyperglycemia, hypotention, pruritus.

Statistical Analysis

Data are presented as mean ±SD, median and range, mode, number and percentage as appropriate. Parametric data were analyzed using One way ANOVA, Kruskal-Wallis test was used for analysis of non-parametric data. P value <0.05 value was considered statistically significant. Statistical Package for Social Science (SPSS) software version 17 was used.

Results

All patients completed the study, there were no statistical significant differences between the studied groups as regards to the patient characteristics and operative data, (Table1).

Table 1. Patient characteristics and operative data in the studied groups. Data presented as mean ±SD, numbers.

Variables	Group I (n=25)	Group II (n=25)	Group III (n=25)	Group IV (n=25)
Age (Years)	44.7±11.9	41.8±14.5	44.3±11.5	42.0±13.1
Height (cm)	167.2±3.3	168.6±4.6	167.4±4.3	169.9±5.7
Wight (kg)	84.2±10.3	80.3±10.2	79.04±10.02	83.56±7.00
Gender (M/F)	15/10	17/8	14/11	17/13
ASA (I/II)	21/4	19/6	16/9	20/5
Duration of surgery (min)	80.6±20.1	78.4±22.9	95.4±30.6	86.3±25.6

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ug dexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

No statistical significant differences between the studied groups, P values >0.05

Intraopeartive heart rate showed no statistical significant differences between the study groups, (Table2).

Table 2. Intraopeartive heart rate(Bpm). Data presented as mean ±SD.

Time	**Group I (n=25)**	**Group II (n=25)**	**Group III (n=25)**	**Group IV (n=25)**
Preanesthesia	83.3±13.0	80.0±10.8	80.2±7.0	82.2±8.6
After anesthesia 5 min	86.3±12.9	83.1±12.8	79.0±8.4	81.6±13.0
10 min	82.8±14.0	84.8±9.9	78.7±10.8	78.2±11.1
15 min	77.0±10.8	81.4±9.8	76.1±13.5	76.1±9.7
20min	77.9±8.7	80.9±8.9	76.0±14.6	78.1±10.9
35 min	76.9±10.7	79.4±8.6	75.4±14.7	77.5±9.5
50 min	74.0±8.1	77.2±9.2	74.8±15.2	76.6±7.3
65 min	79.2±8.1	76.9±8.0	75.4±15.1	77.0±7.1
80min	77.3±9.2	79.2±9.0	76.7±16.2	79.4±6.9
95 min	76.7±1.1	79.3±9.2	71.9±7.8	78.0±7.3
Before discharge from PACU	78.1±7.9	76.0±7.0	75.5±14.1	77.8±7.1

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ug dexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

No statistical significant differences between the studied groups, P values >0.05

As regards to intraopeartive mean arterial blood pressure no statistical significant differences between the study groups except at 95 minutes, (Table3).

Table 3. Intraopeartive mean arterial blood pressure (mmHg).Data presented as mean ±SD.

Time	**Group I (n=25)**	**Group II (n=25)**	**Group III (n=25)**	**Group IV (n=25)**
Preanesthesia	89.5±9.7	91.7±11.2	88.5±11.6	93.3±11.6
After anesthesia 5 min	87.5±10.9	89.1±8.3	84.4±10.6	90.5±11.7
10 min	82.8±17.7	89.9±15.4	82.7±10.3	84.4±9.7
15 min	79.6±16.3	85.2±15.3	82.2±10.1	79.8±9.0
20min	78.0±11.0	85.0±9.9	80.1±9.0	80.8±9.6
35 min	79.8±10.5	81.1±9.1	78.8±8.7	79.3±7.3
50 min	80.8±7.4	82.2±9.9	78.6±8.8	76.6±6.8
65 min	80.3±6.8	82.2±11.6	78.7±8.2	76.8±7.2
80min	82.3±6.4	76.9±10.4	77.2±8.7	78.8±5.0
95 min	80.7±6.7*	75.7±12.6	75.7±7.5	77.4±9.4
Before discharge from PACU	78.1±7.9	82.9±7.8	77.3±9.9	79.1±8.4

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ug dexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

*P value <0.05 is statistically significant

Regarding the spinal block characteristics, no statistical significant differences between the study groups in the highest sensory level, time to reach the maximum sensory level, but time to sensory regression to S1was statistically significant lower in group I compared to the other groups, onset time to modified Bromage 3 was statistically significantly lower in group IV compared to the other groups, regression to modified Bromage 0 was statistically significant lower in group I compared to the other groups (Table 4).

Table 4. Spinal block characteristics (Highest sensory level, onset and regression time of sensory and motor blocks in minutes), data were expressed as mean ±SD, median and range

Variable	**Group I (n=25)**	**Group II (n=25)**	**GroupIII (n=25)**	**GroupIV (n=25)**
Highest sensory level	4 (3-6)	5 (4-6)	4 (4-6)	4 (4-6)
Time to reach the maximum sensory level (min)	13.6±6.2	10.6±4.6	10.8±4.0	10.5±3.7
Time to sensory regression to S1 (min).	263.8±42.7*	329.4±25.8	392.0±43.1	324.8±73.0
Onset time to modified Bromage 3(min)	7.3±5.5	6.9±5.4	6.7±1.9	4.2±1.9*
Regression to modified Bromage 0(min)	205.7±49.0*	257.4±35.4	266.6±49.9	227.8±58.2

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ug dexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

*P values <0.05 is statistically significant.

Blood glucose level was only statistically significantly higher in group II compared the other groups (Table5).

Table 5. Blood glucose level mg/dl data expressed as mean ±SD

Variable	**Group I (n=25)**	**Group II (n=25)**	**Group III (n=25)**	**Group IV (n=25)**
preoperative	94.7±18.7	92.4±18.1	83.7±10.2	88.6±11.3
1 hour	89.8±18.8	97.4±25.4	86.4±9.6	87.3±11.9
postoperative	88.4±15.3	99.0±22.3*	86.6±8.1	90.6±10.4

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ugdexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

*P values <0.05 statistically significant.

No statistical significant differences between the study groups in the number of patient required atropine, ephedrine, patients required tramadol hydrochloride 50mg IV in 24 hours, complications, but the time of first request of postoperative analgesia was statistically significantly shorter in group I compared to the other groups (Table 6).

Table 6. Number of patients required atropine or ephedrine, TFA additional analgesia, complications, Data presented as mean ±SD, number (%)

Variable	**Group I (n=25)**	**Group II (n=25)**	**Group III (n=25)**	**Group IV (n=25)**
patients required atropine No.(%)	1(4)	2(8)	3(12)	2(8)
patients required ephedrine No(%)	3(12)	1(4)	2(8)	1(4)
TFA (min)	184.4±31.5*	227.5±25.2	278.8±53.6	218.0±61.3
Patients required Tramadol hydrochloride 50mg IV in 24 hours	19(76)	18(72)	16(61)	16(61)
Hyperglycemia	0(0)	0(0)	0(0)	0(0)
Hypotension	4(16)	3(12)	3(12)	1(4)
Sedation	0(0)	0 (0)	0(0)	0(0)
Pruritus	0(0)	0(0)	0(0)	0(0)

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ug dexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ug dexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

TFA =Time to first request of postoperative analgesia (min)

*P values <0.05 statistically significant.

The visual analogue scale was statistically significantly higher in group I compared to the other groups at 6,12 hours. Pain scores were statistically significantly lower with dexmedetomidine 3µg and 5µg than group I and group VI at 24 hours (Table7).

Table 7. Postoperative Visual Analogue Scale, Data presented as mode

VAS	Group I (n=25)	Group II (n=25)	Group III (n=25)	Group IV (n=25)
1h	0	0	0	0
6h	6*	4	4	4
12h	5*	3	3	4
18h	5	4	3	4
24 h	4	2*	2*	3

Group I: hyperbaric bupivacaine

Group II: 0.5% hyperbaric bupivacaine +3 ugdexmedetomidine

Group III: 0.5% hyperbaric bupivacaine + 5 ugdexmedetomidine

Group IV: 0.5% hyperbaric bupivacaine +25 ug fentanyl

*P values <0.05 is statistically significant.

Discussion

The results of the present study showed that addition of intrathecal dexmedetomidine 3 µg and 5 µg or 25 µg fentanyl to hyperbaric bupivacaine was associated with prolongation of sensory and motor block, with stable hemodynamics and minimal effect on blood glucose level, prolongation of time to first request of postoperative analgesia, reducing the postoperative pain score compared to bupivacaine alone, no postoperative complications or heavy sedation reported.

Kanazi GE and his coworkers [7] concluded that 3ug dexmedetomidine when added to intrathecal bupivacaine resulted in rapid onset of motor block, prolongation in the duration of motor and sensory block, hemodynamic stability and no sedation. Similarly It was shown that the addition of dexmedetomidine3 µg to intrathecal 0.5% hyperbaric bupivacaine 6 mg in patients undergoing transurethral prostatectomy produced fast onset and a prolonged duration of sensory block and postoperative analgesia [15].

In this study the addition of dexmedetomidine 5 ug to intrathecal heavy bupivacaine was associated with prolongation of the time to postoperative analgesic requirements and reduction in the VAS, less number of patients needed postoperative analgesia. Similar to our results, a study by *Vidhi Mahendru et al* [1] showed that dexmedetomidine 5 ug with 12.5 mg bupivacaine leads to prolongation of motor and sensory block, preserved hemodynamics and decreased postoperative analgesic consumed compared to clonidine 30 ug, fentanyl 25 ug, or 12.5 mg hyperbaric bupivacaine alone in patients undergoing lower limb surgery, also 5 μg dexmedetomidine as adjuvant to heavy bupivacaine 3.5 ml 0.5% provided earlier sensory and motor blockade, increase in time to first analgesic request, less postoperative analgesic requirements, with no complications in patients undergoing lower abdominal surgery under spinal anesthesia [4,16] concluded that intrathecal dexmedetomidine 5 ug prolonged the duration of sensory and motor block of bupivacaine in adult patients undergoing surgeries below the level of umbilicus.

A meta-analysis by *Xiao-Yin Niu et al* [17] showed that dexmedetomidine prolonged the duration of spinal anesthesia and enhance postoperative analgesia without increasing the incidence of side effects. In this study the addition of dexmedetomidine 3 μg or 5 μg to hyperbaric bupivacaine had minimal effect on the blood glucose level, dexmedetomidine can increase blood glucose level during video gynecologic surgeries [18] and may cause hypoinsulinemia when used as sedative in icu [19] due to its effect on postsynaptic α2 adrenoreceptors on β cells of the pancreas which results in decease insulin secretion [20].

Conclusion

The addition of intrathecal dexmedetomidine 3ug and 5ug or 25ug fentanyl to hyperbaric bupivacaine was associated with prolongation of sensory and motor block, with stable hemodynamics and minimal effect on blood glucose level, prolongation of time to first request of postoperative analgesia, and reduction of the postoperative pain scores compared to bupivacaine alone with no postoperative complications or heavy sedation reported in patients undergoing elective surgical procedures below the umbilicus.

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