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Research Article

Effects of intrathecal bupivacaine–fentanyl versus bupivacaine–dexmedetomidine in diabetic surgical patients

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KEYWORDS

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Abstract *Background:* Diabetes mellitus is the most common endocrine disorder encountered during anesthesia. Experimental researches showed that the functional μ opioid receptors in the dorsal horn of spinal cord in diabetics are either reduced or impaired in their function. This prospective study was postulated to differentiate between the effects of either opioid like fentanyl versus nonopioid like dexmedetomidine agents added to spinal bupivacaine in diabetic patients.

Methods: Sixty diabetic patients of either sex were submitted for elective lower limb orthopedic surgery. Patients were randomly allocated into three equal groups (each group 20 patient): bupivacaine group in which patients received 2.5 ml of hyperbaric bupivacaine 0.5% plus 0.5 mL of normal saline, bupivacaine–fentanyl group in which patients received 2.5 ml of hyperbaric bupivacaine 0.5% plus 25 μ g fentanyl in 0.5 mL of normal saline and bupivacaine–dexmedetomidine group in which patients received 2.5 ml of hyperbaric bupivacaine 0.5%, plus 10 μ g dexmedetomidine in 0.5 mL of normal saline. Duration and quality of sensory and motor block were assessed.

Results: The duration of sensory and motor block as well as duration of effective analgesia was significantly longer in the bupivacaine–dexmedetomidine group as compared with both bupivacaine–fentanyl and control bupivacaine groups.

Conclusion: Addition of intrathecal dexmedetomidine to heavy bupivacaine 0.5% was more advantageous than fentanyl with special regard to its analgesic properties in diabetic surgical patients.

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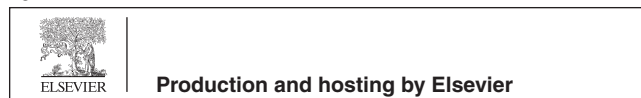
1. Introduction

The prevalence of diabetes mellitus in both adults and children has been steadily rising throughout the world for the past 20–30 years. Recent changes in diagnostic criteria, if widely adopted, will probably also lead to more patients being classified as having diabetes. Diabetic patients undergoing surgery with neural blockade will usually resume oral intake earlier than after general anesthesia, which confers a benefit in the diabetic surgical patients [1].

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Chen et al. [2] suggested in their experimental work that the functional μ opioid receptors in the dorsal horn of spinal cord in diabetics are either reduced or impaired in their function. This may constitute one of the mechanisms underlying the reduced spinal analgesic effect of μ opioid in diabetic neuropathic pain.

The quality of the spinal anesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs (such as dexmedetomidine, clonidine, magnesium sulfate (Mg), neostigmine, ketamine, and midazolam). Alpha (α)-2-adrenergic receptor (AR) agonist drugs, are approved to have sedative, analgesic, perioperative sympatholytic, anesthetic-sparing, and hemodynamic-stabilizing properties [3]. Dexmedetomidine, a highly selective Alpha (α)-2 (AR) agonist drug, when compared with clonidine, the affinity of the former to α 2 receptors has been reported to be 10-times more than the latter. Kalso et al. [4] and Post et al. [5] reported a 1:10 dose ratio between intrathecal dexmedetomidine and clonidine in animals. Evidence indicates that neuraxial administration of dexmedetomidine produces spinal analgesia as efficiently as clonidine [6].

Based on the previous notion of reduction of μ opioid receptors in diabetic patients, we assumed that intrathecal dexmedetomidine adjuvant could be more advantageous than any intrathecal opioid addition for diabetic surgical patients. So, this study was designed to compare the analgesic properties of intrathecal dexmedetomidine versus fentanyl added to hyperbaric bupivacaine 0.5% in diabetic patients subjected to lower limb orthopedic surgery.

2. Patients and methods

This double-blinded randomized study was carried out on 60 diabetic patients, with long standing diabetes more than 5 years of either sex and aged more than 50 years submitted for orthopedic lower limb surgery at Mansoura University Hospitals. The exclusion criteria included patient refusal, patients with major cardiac, respiratory, renal, hepatic disorders or uncontrolled diabetes mellitus, history of chronic use of analgesic medication or hypersensitivity to drugs under investigation, any contraindication to regional anesthesia, namely; patients with coagulopathy infection at puncture site, backache, spine deformity or prior surgery, neuromuscular disorders or psychic disturbances. The protocol was approved by the responsible authorities and a written consent was secured from all patients.

2.1. Preoperative management

All patients were assessed clinically before surgery including full history, thorough clinical examination and laboratory investigations (fasting and random blood sugar, blood picture, liver functions (serum albumin, prothrombin, bilirubin, SGOT and SGPT) and kidney function (serum creatinine). All patients were kept on insulin sliding scale and received premedication with 5 mg diazepam orally at the night before surgery.

On arrival to the operating suite, the patients were monitored by a three leads ECG, noninvasive blood pressure and pulse oximetry. Basal readings of heart rate (HR) mean arterial blood pressure (MBP), arterial oxygen saturation (SpO₂)

were recorded. Intravenous access was established and each patient was preloaded with 1000 ml of normal saline (0.9%).

The patients were randomly allocated into three equal groups according to predetermined randomization code to ($n = 20$ for each):

1. Control group (group-B): patients were given 2.5 ml of hyperbaric bupivacaine 0.5%, plus 0.5 mL of normal saline.
2. Bupivacaine fentanyl group: (group-BF): patients were given 2.5 ml of hyperbaric bupivacaine 0.5%, plus 25 μ g fentanyl in 0.5 mL of normal saline.
3. Bupivacaine dexmedetomidine group (group-BD): patients were given 2.5 ml of hyperbaric bupivacaine 0.5%, plus 10 μ g dexmedetomidine in 0.5 mL of normal saline.

2.2. Anesthetic management

Under strict aseptic technique, subarachnoid block was performed in the sitting position using 22 G spinal needle at the L3–L4 interspace. The studied solution was slowly injected over 10 s then the patient was turned supine. The study was carried out in a double-blind fashion where, the attending anesthetist was not aware of the content of injected solution and not involved in the patient assessment. The time at which the injection was completed was considered the zero time of the study and all the times were recorded from this time (except times of sensory regression from the maximal level). Monitoring and assessment were carried out by a another investigator blinded to the studied solution.

Intraoperative monitoring of heart rate, mean arterial blood pressure and oxygen saturation were recorded 5 min from the zero time then every 15 min. Any decrease in heart rate below 60 beat per minute (bpm) was treated with intravenous atropine (0.4 mg) according to response. Decrease in mean blood pressure below 20% of the basal reading or below 70 mmHg was treated by fluid bolus and/or 5 mg increments of intravenous ephedrine. Any episodes of bradycardia, hypotension or desaturation were recorded. Sensory block assessment was done by pin prick every 2 min till the maximal block level was reached, then every 5 min. Degree of motor block was assessed using a six points modified Bromage scale [7]:

1. Complete motor block.
2. Almost complete blockade, the patient was able to move feet only.
3. Partial motor blockade, the patient was able to move the knee.
4. Detectable weakness of hip flexion, the patient was able to raise the leg but was unable to keep it raised.
5. No detectable weakness of hip flexion.
6. No weakness at all.

The assessment of motor block was performed at 5, 10, 15 min of the intrathecal injection and then every 15 min after surgery until recovery of motor blockade were detected. Post operative analgesia was assessed by using a visual analogue scale (VAS/from 0 to 10 (0 = no pain at all, 10 maximum in imaginable pain)).

The hemodynamic parameters including heart rate, mean blood pressure and peripheral oxygen saturation were recorded in post anesthetic care unit (PACU) every 1 h till complete recovery from anesthesia. Rescue analgesic medication was done with the use of intramuscular diclofenac 75 mg when VAS > 3 and the total analgesic requirements in the first 24 h after surgery were recorded. Duration of effective analgesia was taken from the time of intrathecal drug administration to the first supplementation with rescue analgesic. Patients who experienced pruritus, nausea, vomiting and urine retention were recorded.

3. Statistical analysis

The statistical analysis of data was done by using excel program and SPSS program (statistical package for social science; SPSS Inc, Chicago, IL). Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Data was expressed as either mean and standard deviation or numbers and percentages. One way ANOVA was used to compare more than two groups followed by post hoc LSD (least significant difference) test if subtraction between two means gives \geq LSD this means significant difference between the two means. Chi square test was used for qualitative data. Kruskal Wallis test was done to test significance difference for nonparametric values followed by Mann–Whitney test was used to test significance difference between two groups. *P* is considered significant if < 0.05 .

4. Results

The three studied groups were comparable as regard age, sex, height, and weight (Table 1). There was no significant difference in heart rate, mean arterial blood pressure and arterial oxygen saturation (SPO₂) between the three studied groups (Tables 2–4). The maximum dermatome level of sensory anesthesia and modified Bromage scale at 15 min after spinal anesthesia were comparable in the three studied groups (Tables 5 and 6).

Table 7 shows that durations of sensory blockade, as assessed by 2 segment regression and time to regression to S2 segment, were significantly longer in the bupivacaine–dexmedetomidine group as compared with both bupivacaine–fentanyl and control bupivacaine groups. Also, the table shows the duration of motor blockade (the time from intrathecal drug administration until no motor weakness could be detected means modified bromage scale = 6), was prolonged in bupivacaine–dexmedetomidine group as compared with both bupivacaine–fentanyl and control bupivacaine groups. In addition, there was a significant prolon-

gation in the duration of effective analgesic time (the time of intrathecal drug administration to the first supplementation with rescue analgesics) in BD group when compared with both BF and B groups. Also, the total analgesic requirement was significantly decreased in BF group when compared with control group.

Visual analogue score was statistically significant lower in BD group than B group at 1 h, 2 h, and 3 h postoperatively. Also VAS significantly lowers in BD group when compared with BF group at 1 h, 2 h, 3 h postoperatively (Table 8).

In the present study, the incidence of bradycardia, hypotension, nausea, vomiting, pruritus and urine retention was not statistically significant among the three groups. We did not observe any incidence of respiratory depression in the studied groups (Table 9).

5. Discussion

The results of this study demonstrated that adding 10 μ g dexmedetomidine to spinal 12.5 mg (2.5 ml) of hyperbaric bupivacaine 0.5% significantly prolonged sensory and motor block when compared with intrathecal 25 μ g fentanyl in diabetic patients subjected to lower limb orthopedic surgery.

The situation in diabetic patients may be different than nondiabetics. It was shown that the analgesic potency of morphine and fentanyl are reduced in diabetic animals and patients [8]. Chen et al. [2] observed that functional μ opioid receptors in the spinal cord was impaired in diabetes and also noticed the reduced analgesic action of spinally administered μ opioid agonists in diabetic neuropathic pain.

Addition of intrathecal fentanyl to spinal anesthesia has been evaluated by several investigators on non-diabetic patients. While, Ben-David and his associates [9] found that 10 μ g fentanyl added to bupivacaine would intensify the sensory blockade without prolonged motor recovery, Kuusiniemi et al. [10] suggested that addition of 25 μ g fentanyl to bupivacaine provided good sensory level of analgesia together with prolonged motor blockade.

In our study, the duration of sensory and motor blockade were significantly longer in the bupivacaine–dexmedetomidine group as compared with both bupivacaine–fentanyl and control bupivacaine groups. The analgesic effects of intrathecal dexmedetomidine are mediated by the hyperpolarization of noradrenergic neurons, which suppresses neuronal firing in the locus ceruleus along with inhibition of norepinephrine release and activity in the descending medullospinal noradrenergic pathway, secondary to activation of central α 2-ARs [6]. The suppression of activity in the descending noradrenergic pathway, which modulates nociceptive neurotransmission, terminates propagation of pain signals leading to analgesia [11].

Table 1 Demographic data of studied groups.

	Group-B (<i>n</i> = 20)	Group-BF (<i>n</i> = 20)	Group-BD (<i>n</i> = 20)
Age (years)	64 \pm 4	70 \pm 5	71 \pm 9
Sex (M/F)	10/10	10/10	11/9
Height (cm)	175 \pm 8	173 \pm 7	172 \pm 8
Weight (kg)	75 \pm 9	74 \pm 11	73 \pm 12

Group-B (bupivacaine group), group-BF (bupivacaine–Fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are mean \pm SD of patients number. No significant differences between groups ($P > 0.05\%$).

Table 2 Heart rate changes (bpm) in studied groups.

	Group-B (n = 20)	Group-BF (n = 20)	Group-BD (n = 20)
Intra operative			
Basal	91 ± 16	85 ± 22	88 ± 14
5min	93 ± 17	96 ± 24	93 ± 14
15 min	89 ± 16	90 ± 20	86 ± 12
30 min	88 ± 17	91 ± 20	87 ± 17
60 min	86 ± 14	90 ± 15	86 ± 17
90 min	85 ± 16	92 ± 14	86 ± 12
120 min	89 ± 12	91 ± 15	88 ± 8
Post operative			
1 h	85 ± 13	84 ± 10	79 ± 9
2 h	86 ± 14	82 ± 9	78 ± 8

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are mean ± SD. No significant differences between groups ($P > 0.05\%$).

Table 3 Mean arterial blood pressure changes (mmHg) in studied groups.

	Group-B (n = 20)	Group-BF (n = 20)	Group-BD (n = 20)
Intra operative			
Basal	96 ± 10	100 ± 9.6	99 ± 13
5 min	90 ± 17	93 ± 17	91 ± 15
15 min	84 ± 14	84 ± 13	83 ± 12
30 min	84 ± 13	85 ± 14	81 ± 14
60 min	83 ± 12	83 ± 13	81 ± 12
90 min	87 ± 12	84 ± 12	83 ± 17
120 min	85 ± 12	85 ± 14	83 ± 15
Post operative			
1 h	82 ± 13	86 ± 12	84 ± 11
2 h	89 ± 15	89 ± 12	86 ± 9

Group B (bupivacaine group), group-BF (bupivacaine–Fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are mean ± SD. No significant differences between groups ($P > 0.05\%$).

Table 4 Arterial oxygen saturation (SP02 %) changes in the studied groups.

	Group-B (n = 20)	Group-B F (n = 20)	Group-BD (n = 20)
Intra operative			
Basal	98 ± 2	98 ± 2	98 ± 2
5 min	98 ± 2	98 ± 2	98 ± 2
15 m in	99 ± 1	99 ± 1	98 ± 2
30 min	99 ± 1	99 ± 1	99 ± 1
60 min	99 ± 1	98 ± 2	99 ± 1
90 min	99 ± 1	99 ± 1	99 ± 1
120 min	98 ± 1	99 ± 1	98 ± 2
End	98 ± 2	98 ± 1	99 ± 1
Post operative			
1 h	98 ± 1	99 ± 1	98 ± 1
2 h	98 ± 1	99 ± 1	99 ± 1

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are mean ± SD. No significant differences between groups ($P > 0.05\%$).

Activation of both α_2 -C and α_2 -ARs, situated in the neurons of superficial dorsal horn especially lamina II, directly reduces pain transmission by reducing the release of nociceptive transmitter, substance P and glutamate from primary afferent terminals and by hyperpolarizing spinal inter-neurons via G-protein-mediated activation of potassium channels [12].

Our results were in agreement with another study done by Kanazi et al. [13] who found in their study that the supplementation of bupivacaine (12 mg) spinal block with a low-dose dexmedetomidine (3 μ g) produces a significantly shorter onset of motor block and a significantly longer sensory and motor block than bupivacaine alone. Al-Mustafa et al. [14] and Al-Ghanesm et al. [15] also, observed that the use of other doses

Table 5 Maximal sensory level obtained 15 min after spinal anesthesia.

	Group-B (<i>n</i> = 20)	Group-B F (<i>n</i> = 20)	Group-BD (<i>n</i> = 20)
T8	3 (15%)	2 (10%)	3 (15%)
T9	4 (20%)	4 (20%)	4 (20%)
T10	6 (30%)	7 (35%)	8 (40%)
T11	6 (30%)	6 (30%)	4 (20%)
T12	1 (5%)	1 (5%)	1 (5%)

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are patients number (%). No significant differences between groups ($P > 0.05\%$).

Table 6 Motor block evaluated by modified Bromage scale after 15 min in the studied groups.

Score	Group-B (<i>n</i> = 20)	Group-BF (<i>n</i> = 20)	Group-BD (<i>n</i> = 20)
1	1 (5%)	1 (5%)	1 (5%)
2	15 (75%)	16 (80%)	16 (80%)
3	4 (20%)	3 (15%)	3 (15%)
4	0 (0%)	0 (0%)	0 (0%)

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are patients number (%). No significant differences between groups ($P > 0.05\%$).

Table 7 Characteristics of sensory and motor block of the studied groups (minutes).

	Group-B (<i>n</i> = 20)	Group-BF (<i>n</i> = 20)	Group-BD (<i>n</i> = 20)
Time to 2 segment regression (min)	100 ± 25	114 ± 35	150 ± 42 ^{*#}
Time to regression to S2 (min)	165 ± 34	198 ± 52	300 ± 82 ^{*#}
Duration of motor block (min)	130 ± 54	149 ± 62 [*]	175 ± 75 ^{*#}
Time to first request of analgesia (min)	250 ± 57	280 ± 61 [*]	450 ± 84 ^{*#}

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are mean ± SD.

* Statistically significant difference when compared with group-B ($P < 0.05\%$).

Statistically significant difference when compared with group-BF ($P < 0.05\%$).

Table 8 Postoperative visual analogue scale (VAS) in the studied groups.

	Group-B (<i>n</i> = 20)	Group-BF (<i>n</i> = 20)	Group-BD (<i>n</i> = 20)
1 H	4 (1–5)	3 (2–4)	0 (0–3) ^{*#}
2 H	3 (1–4)	3 (2–4)	1 (0–3) ^{*#}
3 H	3 (0–4)	3 (0–4)	1 (0–3) ^{*#}
4 H	2 (1–3)	2 (0–3)	2 (0–3)
5 H	2 (1–4)	2 (0–2)	2 (0–2)

Group- B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are median (range).

* Statistically significant difference when compared with group-B ($P < 0.05\%$).

Statistically significant difference when compared with group-BF ($P < 0.05\%$).

of dexmedetomidine (5 µg and 10 µg), associated with shorter onset of sensory block.

The current study findings of insignificant hemodynamic changes were consistent with that reported of Kanazi and his associates [13]. They reported insignificant changes in blood pressure either intraoperatively or postoperatively with the use of 3 µg intrathecal dexmedetomidine as an adjuvant to bupivacaine. The reasons of no associated hemodynamic effects in our study could be attributed mainly to good preloading. Furthermore; the associated sympathetic block is usually near maximal with bupivacaine dose used for spinal anesthesia.

The addition of either dexmedetomidine or fentanyl as adjuvants does not further influence the near maximal action of sympathetic block of bupivacaine. The our hemodynamic findings goes parallel with that reported by Al-Ganesm and his colleagues [15] who did not find a statistical intergroup significant difference of bradycardia and/or hypotension with intrathecal addition of either dexmedetomidine or fentanyl. However, their patients were no-diabetic and no other previous studies compare intrathecal addition of fentanyl vs dexmedetomidine. Therefore, further clinical studies are needed to validate the efficacy and safety of the optimum intrathecal dose of

Table 9 Coincident events in the studied groups.

	Group-B (n = 20)	Group-BF (n = 20)	Group-BD (n = 20)
Bradycardia	1 (5%)	1 (5%)	2 (10%)
Hypotension	3 (15%)	3 (15%)	3 (15%)
Nausea	0 (0%)	1 (5%)	1 (5%)
Vomiting	0 (0%)	2 (10%)	0 (0%)
Pruritus	0 (0%)	1 (5%)	0 (0%)
Urine retention	0(0%)	2 (10%)	1 (5%)
Respiratory depression	0 (0%)	0 (0%)	0 (0%)

Group B (bupivacaine group), group-BF (bupivacaine–fentanyl group), group-BD (bupivacaine–dexmedetomidine group). Values are patient s number (%). No significant differences between groups ($P > 0.05\%$).

dexmedetomidine for supplementation with spinal local anesthetics for diabetic surgical patients.

Notes about some limitations of this study could be considered. First the design did not include nondiabetic patients to test the influence of the diabetic state and the effect of neuropathy on sensory and motor degree of block. Secondly, the extent and duration of diabetic state as well as degree of diabetic neuropathy were not evaluated which may influence the results of intrathecal adjuvants during anesthesia.

In conclusion, addition of 10 µg intrathecal dexmedetomidine to 2.5 ml heavy bupivacaine 0.5% was superior than addition 25 µg fentanyl with special regard to its analgesic effect, intensity and duration of blockade in diabetic surgical patients.

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