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Spinal anesthesia for lengthy lower limb orthopedic surgeries: dexmedetomidine plus fentanyl versus dexmedetomidine

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Abstract

Background: Spinal anesthesia is efficient but of limited duration. Intrathecal dexmedetomidine prolongs the sensory and motor blockade of bupivacaine. Dexmedetomidine-opioids combination displayed a clinically controversial interaction. Our proposal is that fentanyl may augment the block characteristics of dexmedetomidine using proper doses.

Patient and methods: This is a randomized double-blinded study. The included patients were scheduled for orthopedic procedures expected to extend more than 4 h. Patients were allocated into two groups each of 23. Group D received intrathecal bupivacaine 20 mg 0.5% + dexmedetomidine 10 μg. Group DF received bupivacaine 20 mg 0.5% + dexmedetomidine 10 μg + fentanyl 25 μg. The spinal block characteristics and adverse effects were determined. Data were compared by *t* test, Mann-Whitney, and chi-square tests as appropriate.

Results: There was no significant difference between the two groups as regards spinal block and hemodynamic characteristics. The addition of fentanyl provided earlier time to T10 sensory block, lower midazolam and ephedrine utilization, but occasional mild itching. Postoperatively, the time to the first analgesic request, morphine consumption, and patient's satisfaction were not different.

Conclusion: The addition of fentanyl does not prolong the sensory and motor block characteristics of dexmedetomidine. In favor of dexmedetomidine-fentanyl combination was the less hypotension and less sedative requirement.

Trial registration: Pan African Clinical Trials Registry
Trial number: PACTR201703002122189 on 28 March 2017.

Keywords: Spinal anesthesia, Dexmedetomidine, Fentanyl, Analgesia, Orthopedic

Background

The anesthetic choices for lengthy lower limbs orthopedic procedures may comprise general anesthesia and limited types of regional techniques such as epidural, continuous spinal, or combined nerve blocks. However, technical difficulties and lack of facilities including microcatheters or ultrasound machines may preclude some techniques. Despite the conflict, the regional anesthesia may be associated with lower morbidity in major orthopedic surgery than general anesthesia (Helwani et al. 2015).

Intrathecal fentanyl enhances the sensory but not the motor block duration (Zode 2015). In contrast, dexmedetomidine prolongs the duration of both sensory and motor blockade in a dose-dependent manner (Gosavi and Swami 2018). Experimentally, there is evidence of synergism between opioids and α2-adrenoceptor agonists (Ossipov et al. 1990). However, the clinical application of this interaction is not extensive (Chabot-Doré et al. 2015), and the results are controversial (Mohamed et al. 2012). For a maximum effect, we used the recommended intrathecal (IT) dose of dexmedetomidine as 10 μg (Naaz et al. 2016). While the usual IT dose of fentanyl 25 μg has longer sensory and motor block than the lower doses (Ali et al. 2018). The combination in these doses was studied for the visibility of the preferential application in

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prolonged lower limb procedures in comparison with dexmedetomidine. This study aimed to elucidate the spinal block characteristics, analgesic, and side effects of the dexmedetomidine-fentanyl combination.

Patients and methods

This prospective randomized double-blind study was done from March 2017 to July 2018. The patients were scheduled for two or more procedures of lower limb orthopedic surgery expected to exceed 4 h. The 4 h represent the duration of spinal anesthesia after 20 mg of bupivacaine (3–4 h) (Tuominen 1991). The included criteria were the American Society of Anesthesiologists (ASA) I–II, both sexes, age 25–60 years. The exclusion criteria were patient refusal; cognitive impairment; intensive care admission; hypersensitivity to the study drugs; cardiac, hepatic, renal or respiratory failure; and general contraindications to spinal anesthesia.

Sample size calculation

The sample size was determined using G*Power software, version 3.01 (Franz Faul, Christian-Albrechts-Universität Kiel, Germany). A priori test analysis was done following a preliminary study on 10 patients, and the primary outcome was the time to the first request for analgesia. Outcomes were two means of 5.5 and 6.5 h for group D and group DF, respectively, and SD was 1.1. The calculated effect size was 0.90. Assuming α (type I error) = 0.05 and β (type II error) = 0.1 (power = 90%) yields a total number of 44 patients. A dropout of 5% was suspected, so the required number is 46 patients. An anesthetist not involved in the study prepared the cocktail according to a randomization using the closed envelop method into two groups:

Group DF (n = 23) received spinal anesthesia using a cocktail of:

- Heavy bupivacaine (BUP) (Marcaine 0.5% heavy, Astra Zeneca, France); 20 mg in 4-ml volume,
- Dexmedetomidine (DEX) 10 μg (Precedex®, Hospira, 200 μg/2-ml ampule), taken as 0.1-ml volume (10 units) by 1-ml insulin syringe.
- Fentanyl (FEN) 25 μg in 0.5-ml volume (Fentanyl®, 100 μg/2-ml ampule, Janssen-Cilag Pharmaceutica, Germany), so the total volume is 4.6 ml.

Group D (n = 23) received similar doses of BUP 20 mg, and DEX 10 μg, plus normal saline 0.5 ml to the same total volume of 4.6 ml for blinding.

After the evaluation of history and investigations, patients were examined and the consent was signed. The visual analog score (VAS) 0–10 for pain assessment was explained, where 0 represents no pain and 10 is the worst pain. Preoperatively, there was no premedication, only preloading by 10 ml/kg Ringer's solution. All administered fluids were prewarmed. After attaching the standard monitors and recording basal data, the IT anesthesia was conducted in the sitting position. Propofol procedural sedation was given in patients who experienced pain in this position. A 25-G Quincke needle was used in the paramedian plane under sterile condition. The sensory block level was assessed by pinprick in the midclavicular line every 2 min until it reached the T10 level then the surgery was started. The sensory recovery was assessed to S1 dermatome level. The degree of motor blockade was assessed by the modified Bromage scale (Bromage 1965) where no paralysis = 0, no rise of extended legs = 1, no knee flexion = 2, and no ankle dorsiflexion = 3. The regression times were assessed subjectively—if feasible—every 20 min and not interfering with surgery, starting 4 h after injection time.

Hypotension was defined as a mean arterial blood pressure (MAP) < 60 mmHg, and it was managed by bolus doses of ephedrine 5 mg, fluids and blood transfusion as indicated. Bradycardia was defined as heart rate (HR) < 60 b/min, and it was managed by atropine 0.5 mg increments. Desaturation was defined as SaO2 < 90% and managed by an oxygen face mask. Vomiting was treated with metoclopramide 10 mg or granisetron 1 mg (Grantryl®, Alexandria, Egypt) if persistent.

Intraoperative complaints were managed by increments of FEN 25 μg, midazolam 1–2 mg, and propofol 50 mg in consequence as required. General anesthesia was applied using a laryngeal mask and sevoflurane inhalation if the patient still cannot tolerate pain, and the expected time to complete the procedure exceeds 15 min.

Postoperative pain was controlled by a multimodal regimen started after the first request of analgesics including ketorolac tromethamine (ketolac®, Amriya Pharmaceutical Industries, Alexandria, Egypt) 30 mg IV every 8 h + paracetamol 1-g tablets every 8 h + pregabalin (Lyrica®, Pfizer Limited), 75-mg capsule twice per day plus morphine 3-mg increments if VAS is still > 3.

The primary outcome was the time to the first request for analgesia. The secondary outcomes were the time to T10 sensory loss; the time to S1 sensory regression; the time to Bromage 3 and 0; the total morphine consumption; intraoperative consumption of anesthetic drugs; the rate of conversion to general anesthesia; VAS every 4 h for 16 h then after 24 h, perioperative hemodynamics (MAP, HR) including the frequency of atropine and ephedrine utilization; patient's satisfaction after 24 h in a score (0–10) with 0 as the worst value; and the frequencies of intraoperative adverse effects including shivering, itching, vomiting and the occurrence of spontaneous sedation > 2 using Ramsay sedation score (Ramsay et al. 1974), provided that no intravenous sedative or analgesic drugs were added after intrathecal injection. Ramsay

scale level 1: patients are anxious and agitated; level 2: patients are cooperative, oriented, and tranquil; level 3: patients only respond to commands; level 4: patients are asleep with a brisk response to glabellar tap; level 5: patients are asleep with a sluggish response to tap; and level 6: patients have no response.

Statistical analysis

The data were analyzed by the SPSS program statistical package version 17 (SPSS, Inc., Chicago, IL, USA). The normality of distribution was tested by the Shapiro-Wilk test. The parametric data display was in mean and standard deviation (SD) after the comparison by Student's *t* test. The non-parametric data display was in median and range after using the Mann-Whitney test. Categorical data presentation was in frequency and percentage and its comparison was by chi-square test. Data are significant if the *P* value is ≤ 0.05.

Results

In this study, 46 patients were analyzed (Fig. 1). Demographic data showed no significant difference between the groups (Table 1). The surgical procedures were mainly bilateral total knee arthroplasty. The other procedures were for polytrauma, non-union, plate removal, Ilizarov application, and bone grafting. The mean duration of surgery was 5 h (Table 1).

The sensory block to T10 level was faster in group DF. The time to S1 sensory regression extended around 7 h with no difference between the groups (Table 2). The motor block extended about 6 h without intergroup difference (Table 2). The motor recovery preceded the sensory recovery, that patients may move the legs but tolerate the surgery. The iliac graft pain was earlier than femoral or tibial pain.

The time to the first request for analgesia—as determined from the onset of IT injection—and the total morphine consumption were not different between the groups (Table 2). VAS also showed no significant differences (Fig. 2).

There were no significant differences in perioperative HR and MAP values (Fig. 3). Hypotension was less frequent in group DF in association with less consumption of ephedrine (Table 3). The hypotension occurred frequently

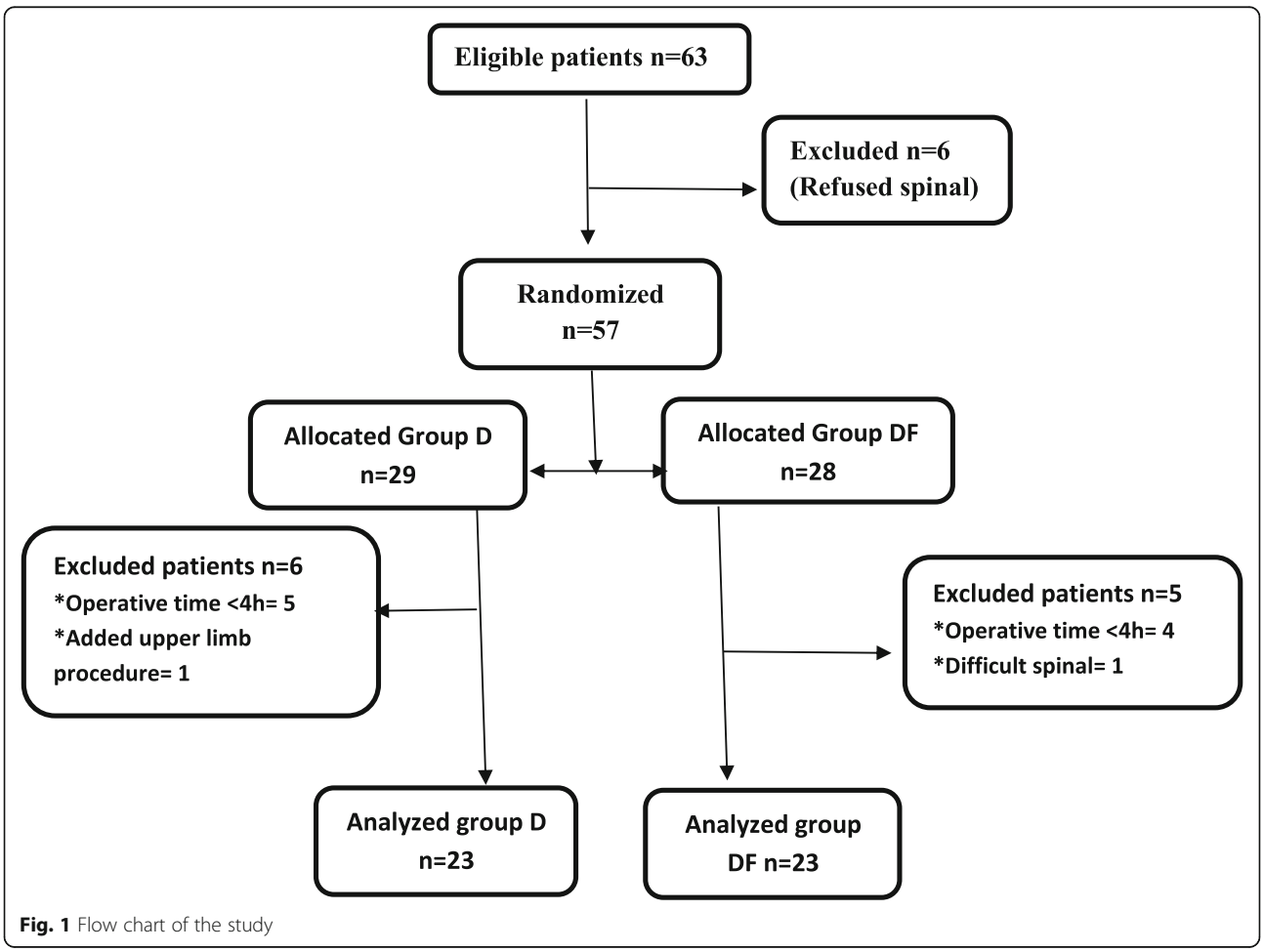

Fig. 1 Flow chart of the study

Table 1 Demographic and surgical data

	Group D	Group DF	*P*
Age (year)	49 ± 16	53 ± 15	0.670
BMI (kg/m^2)	30 ± 7	31 ± 7	0.750
Male *n* (%)	8 (36%)	4 (17%)	0.248
Female *n* (%)	15 (65%)	19 (83%)	0.493
Duration of surgery (h)	5.1 ± 1.2	4.8 ± 1.0	0.617
Surgical procedures *n* (%)			
1. Bilateral total knee arthroplasty	11 (48%)	9 (40%)	0.556
2. Polytrauma, plates, interlocking nails	8 (35%)	7 (30%)	0.756
3. Non-union, plate removal, Ilizarov, bone graft	4 (17%)	7 (30%)	0.305

Data are in mean ± SD or number (percent). ($n = 23$)
BMI body mass index, *D* dexmedetomidine, *DF* dexmedetomidine plus fentanyl

following IT injection and tourniquet release and sometimes presented at the recovery room. Bradycardia demanding atropine occurred in about half of the patients (Table 3). Drug consumption was not different between the groups except for lower midazolam and ephedrine in group DF (Table 3). Six of all the patients required general anesthesia after about 6 h, the pain related to iliac bone graft or upper thigh incisions late in the procedures. The incisional and arm positional pain was mostly relieved by FEN, midazolam, and propofol sedation (Table 3). The oxygen face mask was required for 30% of patients in both groups mostly following sedatives.

The adverse effects were not different except for occasional mild facial itching in group DF (Table 4). Most of the patients presented with a mild sedation (Ramsay scale 2–3) (Table 4). The patient's satisfaction was not different between the groups (Table 2).

Discussion

This study evaluated the intrathecal DEX-FEN interaction with BUP in utmost recommended doses. The two most impressive aspects of this interaction are the block characteristics and side effects. The results showed no potentiation of the sensory or motor block times or analgesia in group DF, only the onset was enhanced. The side effects were not increased except for mild itching and more sedation, but there was less hypotension.

Table 2 Spinal block (sensory, motor) and postoperative analgesia data

Time variables in mean ± SD	Group D	Group DF	*P*
T10 sensory level (min)	5.1 ± 1.4	4.1 ± 1.4*	0.028
S1 sensory regression (h)	6.8 ± 1.3	7.8 ± 1.1	0.737
Time to Bromage 3 (min)	7.5 ± 1.3	7.4 ± 1.2	0.870
Time to Bromage 0 (h)	6.1 ± 1.0	6.8 ± 1.0	0.068
Time to first analgesia request (h)	6.7 ± 1.1	7.3 ± 1.3	0.118
Morphine consumption (mg)	7 (3–18)	6 (3–15)	0.453
Patient satisfaction (score 0–10)	7 (5–9)	8 (5–9)	0.366

Data are in mean ± SD or median (range). $n = 23$
*Significant difference between the groups. $P \leq 0.05$

In an agreement to our results, there was no clinical benefit using DEX-FEN combination in major abdominal cancer surgery. The opioid consumption decreased 8% only after adding FEN 25 μg to DEX 5 μg and 10 mg BUP compared with DEX/BUP. Also, there was no significant difference in the time to the first analgesic request (5.41 h vs. 3.3 h) despite being equal to 64% difference (Mohamed et al. 2012). Another opioid + DEX interaction revealed that IT morphine 0.5 mg was not potentiated by the addition of DEX 5 μg. The duration of analgesia increased by 1.3 h only accounting for 6% difference, where the duration of IT morphine analgesia was 22 h (Abdel-Ghaffar et al. 2016).

In contrast to this study results, some studies showed a potentiation of spinal block characteristics. Megalla showed a mean time to the first analgesic request of 8.7 h. This analgesic potentiation followed the combination of FEN 20 mcg and DEX 6 μg as adjuvants to BUP 12.5 mg in elderly patients undergoing orthopedic surgery. However, the comparison was against FEN and not DEX (Megalla 2018). Another two studies showed a potentiation of DEX-FEN combination for labor analgesia. Mohamed et al., using DEX 5 μg plus FEN 10 μg without BUP showed a faster onset and longer duration of analgesia (144 min), while DEX 10 μg provided 130 min of analgesia. This accounts for 11% difference (Mohamed and Salem 2015). Also, Shah et al. provided a matching comment with the same combination (Shah et al. 2018). Although, the difference between the first analgesic request times was non-significant, accounting for 10% in this study. Esmat et al. showed also a long block duration of 6.6 h in DEX-FEN group with minimal side effects for knee arthroscopy, but they compared the combination against FEN and not DEX (Esmat et al. 2016).

The comparison with other studies is difficult due to the few numbers of studies about DEX/FEN combination; the primary outcome varied between the first analgesic

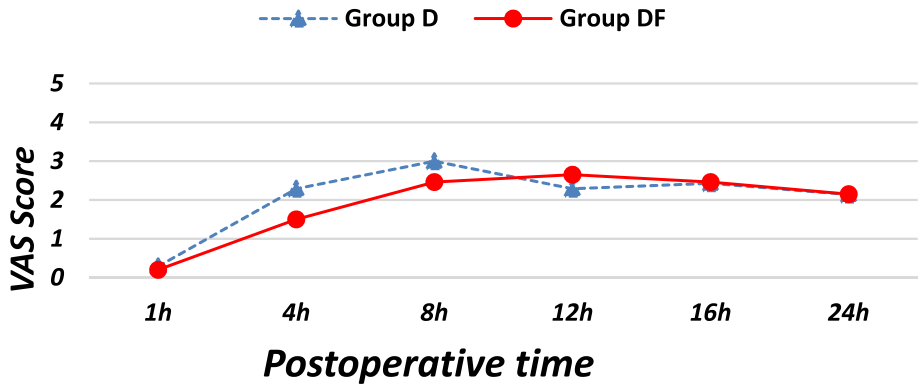

Fig. 2 Postoperative mean VAS of both groups through the first 24 h. No significant differences

request, duration of analgesia, opioid consumption, and sensory and motor block times; and different types of procedures such as orthopedic and abdominal surgery and labor analgesia; there are no comparative studies using the same doses of this study.

Using a lower dose of BUP (12.5 mg) added to DEX 10 μg provided a time to S1 regression of 5.7 h (Al-Mustafa et al. 2009). While using a lower dose of DEX (5 μg) added to BUP produced a shorter time of 4.6 h (Al-Ghanem et al. 2009). The extent of sensory and motor block by BUP is dose-dependent also. However, the magnitude of the sympathetic blockade and subsequent hemodynamic depression was not correlating with BUP dose (Liu et al. 1996). The action of DEX and local anesthetics may be synergetic (Mohamed et al. 2012). Beneficially, DEX protects against neurotoxicity of local anesthetics (Zhang et al. 2013). Furthermore, DEX reduces the cardiovascular and central nervous manifestations of BUP overdose in animals (Eisenach et al. 1996).

In this study, the dose of 20 mg BUP and DEX 10 μg provided a sensory block time of about 7 h in both groups. In association, there was a motor block time of about 6 h. Therefore, the utilized doses in this study may be recommended for long procedures. In practice, bilateral total knee arthroplasty—for example—became mostly done under this spinal technique as the first anesthetic choice in our center, offering rapid onset, long block duration, sedation, low postoperative opioid analgesia, low side effects, and high patient satisfaction rate.

The low VAS (≤ 3) and low opioid consumption (6–7 mg) in this study through 24 h can be explained by the extended analgesic effect of DEX. The half-life of DEX is short (2–3 h); however, it has long-lasting analgesic properties (24 h) (Zhang et al. 2013) or 17 h in another study (Qi et al. 2016). In addition, the α2-adrenoceptor agonists may ameliorate the hyperalgesia and mechanical allodynia (Kingery et al. 2000). Fentanyl has a short time of action relative to DEX, so a potentiation

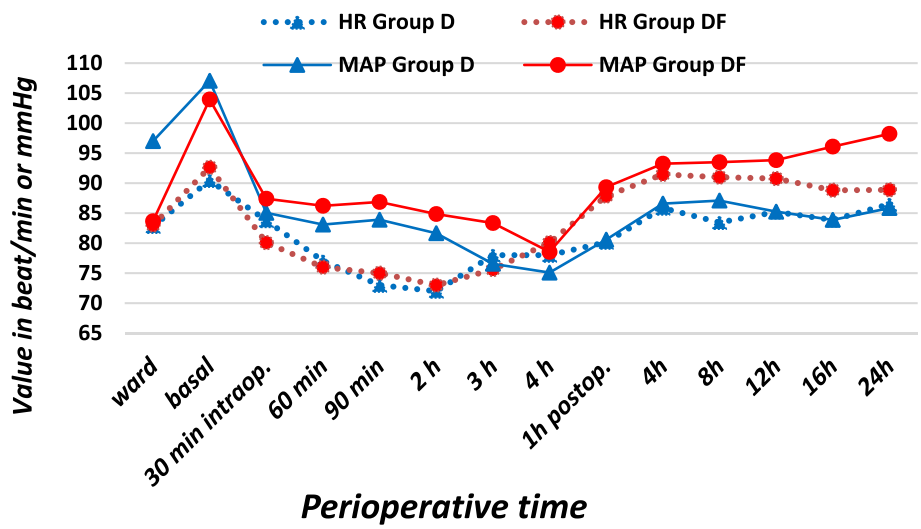

Fig. 3 The perioperative mean heart rate (HR) and mean blood pressure (MAP). No significant differences

Table 3 Intraoperative drug consumption frequencies

	Group D	Group DF	*P*
Fluids administered (ml)	3094 ± 688	2979 ± 477	0.530
Urine output (ml)	677 ± 420	646 ± 290	0.180
Blood Loss (ml)	635 ± 332	536 ± 261	0.250
Blood transfusion (units)	1 (0–3)	0 (0–2)	0.217
Drug consumptions:			
Midazolam *n* (%) (dose 1–5 mg)	4 (18%)	0 (0%)*	0.001
Fentanyl *n* (%) (dose 25–100 μg)	4 (18%)	4 (18%)	0.971
Propofol *n* (%) (dose 30–150 mg)	5 (23%)	3 (13%)	0.432
General anesthesia *n* (%)	4 (18%)	2 (9%)	0.386
Atropine *n* (%) (dose 0.5–1.5 mg)	12 (52%)	10 (44%)	0.502
Ephedrine *n* (%) (dose 5–50 mg)	19 (82%)*	16 (62%)	0.035

Data are in mean ± SD, median (range), or number (percent)
*Significant difference, $P \leq 0.05$

may not be expected. However, the matched long-acting combination of morphine and DEX showed also no potentiation (Abdel-Ghaffar et al. 2016).

Intrathecal DEX produces analgesia by binding to presynaptic C-fibers inhibiting the release of C-fiber transmitters, and postsynaptic by dorsal horn neuron hyperpolarization that inhibits nerve signal firing and propagation (Birnbaumer et al. 1990). The enhanced motor effects of IT DEX may result from the binding to α2-adrenoceptor to motor neurons in the dorsal horn (Saadawy et al. 2009). The synergism between opioids and DEX may be related to the abundance of α2-adrenergic and opioid receptors in the spinal cord (Coggeshall and Carlton 1997).

The hemodynamic values for MAP and HR were not different after DEX-FEN combination in this study. However, ephedrine consumption was lower in the combination group. That may indicate less hemodynamic effects of this combination, especially there was no difference in fluid and blood transfusion. Pharmacologically, that was not expected nor explained, as IT DEX administration is associated with significant reduction in HR and MAP (Mohamed et al. 2012),(Al-Ghanem et al. 2009). Saikia et al. reported a 60% incidence of hypotension and 27% of bradycardia in patients given DEX 3 mcg plus BUP 12.5 mg (Saikia et al. 2016). But in controversy, the hemodynamic stability is reported when adding DEX to BUP (Gupta et al. 2011). Fentanyl increases also the hypotensive episodes of IT BUP threefolds (43% vs. 14%) (Singh et al. 1995). However, adding BUP to FEN reduced the incidence of side effects as pruritus (36.4% vs. 95%) (Asokumar et al. 1998). Nevertheless, clinically, many studies showed blood pressure conservation and decreased side effects using the DEX-FEN combination. Mohamed et al. showed a higher systolic blood pressure in the DEX-FEN combination group than the DEX group. While bradycardia was longer in the combination group (120 min vs. 90 min in DEX group) (Mohamed et al. 2012). Mohamed and Salem found also less hypotension, more itching, and lower side effects in the combination group (Mohamed and Salem 2015). Megalla found an enhanced analgesia with no more complications, and hemodynamic stability using the DEX-FEN combination in high-risk elderly patients (Megalla 2018). Similarly, Shah et al. reported decreased side effects with this combination (Shah et al. 2018).

Table 4 The incidence of intraoperative adverse effects

	Group D	Group DF	*P*
Sedation (Ramsay scale > 2)	11 (48%)	17 (75%)	0.172
Shivering	6 (27%)	3 (13%)	0.268
Vomiting	1 (4%)	3 (13%)	0.301
Itching	0 (0%)	2 (9%)*	0.001

Data are in number (percent). $n = 23$
*Significant difference, $P \leq 0.05$

The statistical bias or individual and procedural variations may contribute to the apparently reduced side effects with DEX/FEN combination. However, The IT DEX-morphine combination in various doses in an animal study produced a synergistic interaction as regards antinociception with extremely lower side effects (sedation, motor weakness, and urine retention) than either drug alone (Kabalak et al. 2013). Moreover, the addition of α2-adrenoceptor agonist to opioids reduced the withdrawal symptoms in addicts (Imani et al. 2011). Similarly, DEX reduces the withdrawal effects of opioid/benzodiazepine used for sedation during mechanical ventilation (Phan and Nahata 2008).

In this study, sedation scores were not different among the groups, but midazolam utilization was significantly lower in the combination group. That may be an indirect measure of enhanced sedation. In addition to cost saving of extended spinal anesthesia during long operations, sedation may be beneficial in this situation. The hypnotic effect of DEX is like normal sleep. It is mediated by triggering of neurotransmitters that decrease histamine due to inhibition of the descending noradrenergic inhibitory pathway (Carollo et al. 2008). In addition, this sedation was not associated with respiratory depression, where the incidence of oxygen utilization was similar in both groups. Unequivocally, there is no potentiation of respiratory depression using opioid-α2-adrenoceptor agonist combination (Eisenach et al. 1996).

The incidence of shivering in this study was 14% in group DF with no significant difference in group D (27%). Saikia et al. reported an incidence of 13% in patients given DEX 3 μg plus BUP 12.5 mg (Saikia et al. 2016). However, there was no shivering using DEX-FEN combination in other studies (Mohamed and Salem

2015; Shah et al. 2018). The higher incidence in our patients may be related to heat loss during the long operative time.

The limitations of this study may comprise un-unified surgical procedures and difficulties in the subjective assessment of block due to occasional interference with the running surgery or patient sedation. Further clinical studies and larger sample size are required to verify the efficacy of DEX-FEN combination.

In the future, the on-demand photo-triggered tetrodotoxin (a natural Na^+ channel blocker with potent local anesthetic properties) and DEX may provide the protracted analgesia (Zhan et al. 2017).

Conclusion

Intrathecal dexmedetomidine 10 μg and bupivacaine 20 mg with or without Fentanyl 25 μg were suitable for long orthopedic procedures within 6 h duration. The addition of fentanyl does not prolong the sensory and motor block characteristics of dexmedetomidine. In favor of DEX-FEN combination was the less hypotension and less sedative requirement.

Abbreviations

BUP: Bupivacaine; DEX: Dexmedetomidine; FEN: Fentanyl; HR: Heart rate; IT: Intrathecal; MAP: Mean arterial blood pressure; VAS: Visual analog score

Acknowledgements

Not applicable.

Availability of data and materials

The analyzed data are included in the tables. The details are available from the corresponding author upon a reasonable request.

Authors' contributions

The idea, design, and data analysis were prepared by the corresponding author. Literature search and manuscript editing were done by the first two authors. All authors shared the clinical data acquisition and the final manuscript review and approval.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board with the reference number (R/17.01/97). A written consent was signed by all participants. The clinical trial registration number is (PACTR201703002122189).

Consent for publication

A consent for publication of personal data was not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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