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Comparative study of dexmedetomidine and fentanyl as an adjuvant to epidural bupivacaine for postoperative pain relief in adult patients undergoing total knee replacement: a randomized study

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Abstract

Background: Epidural analgesia is a common method for the management of postoperative pain after total knee replacement. The aim of the study was to compare the postoperative analgesic effect of dexmedetomidine and fentanyl as an adjuvant to epidural bupivacaine in adult patients undergoing total knee replacement.

Material and methods: The study included 460 cases classified randomly into two groups (each=230): Dexmedetomidine group: Dexmedetomidine 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml and infused epidurally at a rate of 5ml/hr for the postoperative 72 hours. Group F (fentanyl group): Fentanyl 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml and infused epidurally at a rate of 5ml/hr for the postoperative 72 hours.

Results: The quality of analgesia was better with dexmedetomidine than fentanyl group ($p<0.05$), and the requirement for opioids was significantly lower with dexmedetomidine than fentanyl group ($p<0.05$). The incidence of motor block, bradycardia, hypotension and dry mouth was significantly higher with dexmedetomidine than fentanyl group ($p<0.05$). The incidence of sedation was significantly higher with dexmedetomidine compared to fentanyl group ($p<0.05$), but after opioids administration, the incidence of sedation was significantly higher with fentanyl compared to dexmedetomidine group ($p<0.05$). The incidence of nausea and vomiting, pruritis, urinary retention, and respiratory depression was significantly lower with dexmedetomidine compared to fentanyl ($p<0.05$).

Conclusion: Dexmedetomidine is an ideal adjuvant to epidural bupivacaine for postoperative analgesia compared to fentanyl in patients undergoing total knee replacement.

Keywords: Dexmedetomidine, fentanyl, epidural bupivacaine, total knee replacement

Introduction

Total knee replacement is associated with intense early postoperative pain [1], and associated with high demand for analgesics [2-4]. Improving the pain management techniques and rehabilitation programs has a significant impact on postoperative outcome [1]. The incidence of pain is 55 to 60% at rest and up to 70% upon mobilization; high or very high intensity, and the peak of at 3 to 6 hours after surgery and continues for the following 72 hours [5,6].

The use of epidural analgesia is the preferred technique of postoperative analgesia for total knee replacement [7]. Epidural opioids with and without local anesthetics provides a postoperative pain relief, but it is associated with many side effects [8-11].

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, and it has a sedative, anxiolytic, analgesic, antihypertensive and sympatholytic properties [12]. It improves the quality of perioperative anesthesia and analgesia [13]. Dexmedetomidine has been shown to enhance the postoperative analgesia after arthroscopic knee surgery, and associated

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with a decreased need for postoperative analgesia [14].

The aim of the present study was to compare the postoperative analgesic effect of dexmedetomidine and fentanyl as an adjuvant to continuous infusion of epidural bupivacaine in adult patients undergoing total knee replacement.

Outcome

The primary outcome was the adequacy of postoperative analgesia and the secondary outcome was the safety of the intervention. The safety was assessed by the occurrence of any adverse events to the patients.

Material and methods

After obtaining informed consent and approval of local ethics and research committee in Aldar hospital, Almadinah Almonwarah, Saudi Arabia, a study included 544 patients ASA physical status II–III patients with osteoarthritis and scheduled for either unilateral or bilateral total knee arthroplasty [2011-2015]. The exclusion criteria included patients with coagulopathy, cardiac diseases or patients who refused the postoperative continuous infusion of analgesia, presence of neuropathic pain, previous knee joint surgery and patients with hypersensitivity to bupivacaine, dexmedetomidine or fentanyl. Eighty four cases were excluded according to the exclusion criteria and the other 460 cases were classified randomly (by simple randomization) into two groups(each=230): Dexmedetomidine group: Dexmedetomidine 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml. The rate of epidural infusion through the syringe pump was 5ml/hr for the postoperative 72 hours.

Fentanyl group: Fentanyl 2 ml (100 µg) was mixed with 48 ml bupivacaine 0.125% in a syringe 50 ml. The rate of epidural infusion through, the syringe pump was 5ml/hr for the postoperative 72 hours. The intervention was discontinued if there were untolerated side effects of the study medications in the two groups.

The sensory block was assessed by pin prick and cold application every 5 minutes until the onset of sensory block using a 3-point scale: 0=normal sensation, 1=loss of sensation of pin prick (analgesia), and 2=loss of sensation of touch (anesthesia). The motor block was assessed by Bromage three point score for the lower extremity (0-3), 0: no motor impairment (able to move the hip, knee, and ankle joints); 1: unable to raise either extended leg (able to move joints of knee and ankle); 2: unable to raise extended leg and flex knee (able to move joint of ankle); 3; unable to move knee and foot [15]. The pain relief was assessed by the pain verbal scale from 0 to 4(0: complete pain relief; 1: only slight pain; 2: a lot of pain relief, 3: little pain relief; 4: no pain relief) [16]. The level of sedation was assessed by a modified Wilson sedation scale from 1 to 4 [17].

Anesthetic technique

In the preoperative waiting room, intravenous line G 18 was inserted in all patients and an infusion of 500 ml Ringer lactate solution was started. In the operative room, monitors such as ECG, pulse oximetry, and blood pressure cuff were attached to the patients. Under complete sterilization and local anesthesia, all patients received combined spinal(L4-5 interspace) and epidural anesthesia(L3-4 interspace). The anesthesia was started with spinal anesthesia [bupivacaine 3.5 ml 0.5% plus fentanyl 25 µg, Polymed spinal needle G22 Poly Medcure Ltd, India]. After surgery, epidural analgesia [Perican® needle G18, catheter G 27, B. Braun Melsungen AG Germany] was started according to the protocol of the study.

Postoperative care

The epidural infusion was continued for the postoperative 72 hours. The hypotension(mean arterial blood pressure<20% of the baseline reading) was managed by fluid administration, and bolus doses of ephedrine(5-10mg). The bradycardia (heart rate <60 bpm) was managed with bolus doses of atropine(0.02 mg/kg). The monitors included the heart rate, arterial blood pressure, arterial oxygen saturation, the total dose of postoperative pethidine and morphine. If the patients had a pain, opioid such as meperidine or morphine was given. In the ward and after the first 12 hours postoperatively, the patients received low molecular weight heparin (clexane) 40 mg daily as a prophylaxis against deep venous thrombosis. The epidural catheter was removed after 12 hours of the last clexane dose.

Sample size calculation

Power analysis was performed using Chi square test for independent samples on frequency of patients complaining of post-operative pain after total knee replacement, because it was the main outcome variable in the present study. A pilot study was done before starting this study to compare the analgesic effect of epidural dexmedetomidine and fentanyl and the narcotic requirements for analgesia. The results of the pilot study showed that dexmedetomidine has analgesic effect than fentanyl and the narcotic requirement was of 16.6% in dexmedetomidine group, and 27.5% in fentanyl group. Taking power 0.8 and alpha error 0.05, a minimum sample size of 226 patients was calculated for each group. A total of patients in each group 230 were included to compensate for possible dropouts.

The statistical analysis

Data were statistically described in terms of range; mean± standard deviation (±SD), frequencies (number of cases) and relative frequencies (percentages) when appropriate. Comparison of quantitative variables between the study groups were done using Mann Whitney *U* test and repeated measures ANOVA for normally distributed variables. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered

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statistically significant. All statistical calculations were done using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Results

Figure 1 shows the CONSORT diagram for the flow of participants through each stage of the present study. Eighty four cases were excluded and 460 patients completed the study. There was no statistical difference regarding the demographic data, ASA class, and co-morbidities, type of surgery (unilateral or bilateral knee replacement), and duration of surgery ($p>0.05$) (**Table 1**). During the study, 16 patients were excluded in group D as a result of hemodynamic instability and also 22 patients were excluded in group F because of the nausea, vomiting and pruritis.

Table 2 shows the outcome of the epidural block. The number of patients with a verbal pain score 0, 1, 2 was significantly higher in dexmedetomidine than fentanyl group, while the number of patients with the verbal pain score 3, 4 was significantly lower in dexmedetomidine than fentanyl group ($p<0.05$). There was no difference in the levels of sensory block between the patients of both groups ($p>0.05$). The incidence of motor block was higher in dexmedetomidine than fentanyl group ($p<0.05$). Before opioids administration, the incidence of sedation was higher in the dexmedetomidine group than the fentanyl group ($p<0.05$), but after opioids administration,

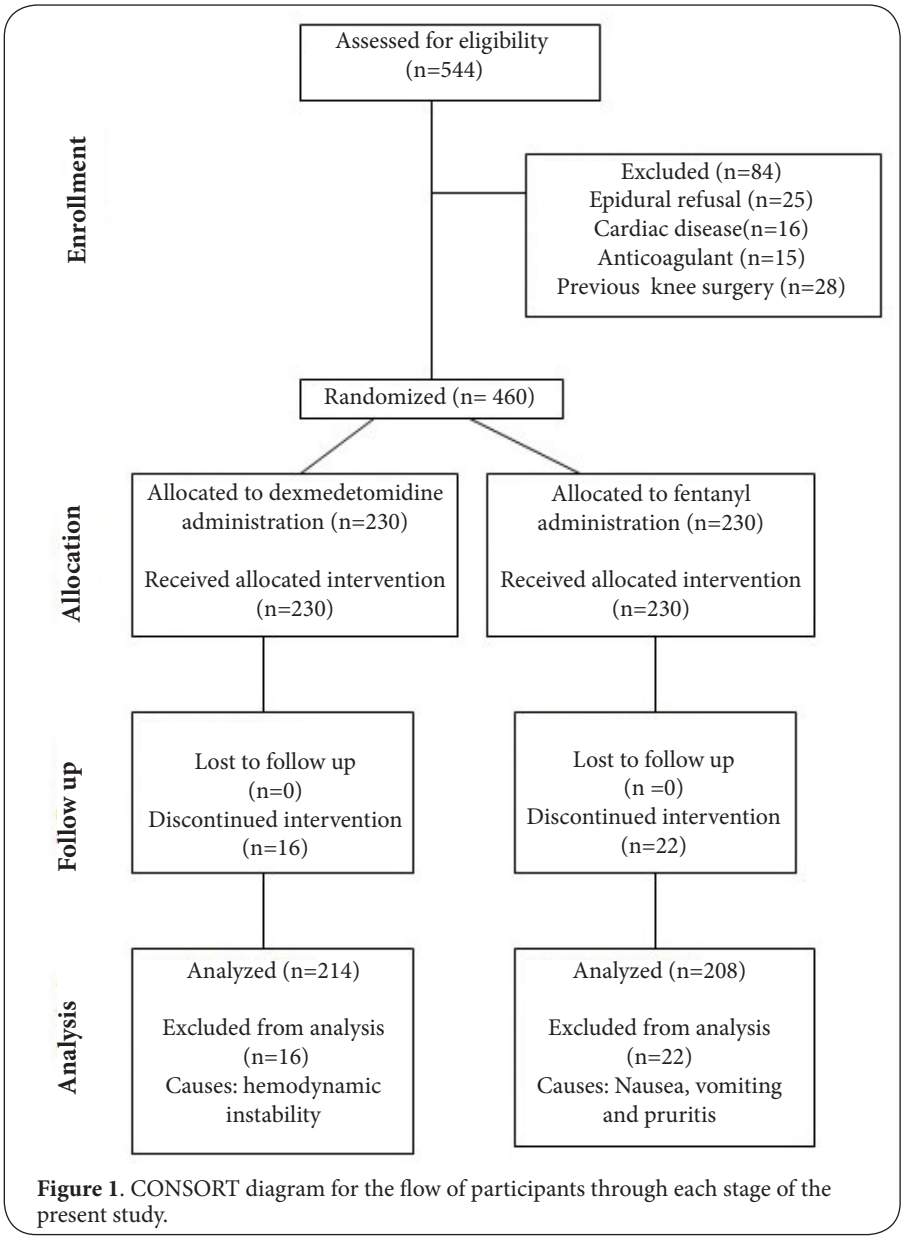

Figure 1. CONSORT diagram for the flow of participants through each stage of the present study.

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Table 1. Demographic data of the patients (data are presented as mean±SD, number).

Variables	Group D (n=214)	Group F (n=208)	P-value
Age(year)	54.18±8.40	55.76±11.62	0.111
Gender			
Female	171	166	0.979
Male	43	42	0.983
Weight(kg)	88.32±10.31	86.99±9.64	0.171
Height (cm)	169.10±8.54	168.45±7.70	0.411
ASA			
II	135	128	0.743
III	79	80	0.825
Diabetes mellitus	102	98	0.694
Hypertension	124	132	0.246
Type of surgery			
Unilateral TKR	188	184	0.846
Bilateral TKR	26	24	0.863
Mean duration of surgery (min)	258.36±47.52	255.49±46.49	0.530

ASA: American Society of Anesthesiologists physical status classification system
TKR: Total knee replacement
Group D: Dexmedetomidine group,
Group F: Fentanyl group

Table 2. Outcomes of the epidural block (data are presented as mean±SD, number).

Variables	Group D (n=214)	Group F (n=208)	P-value
Pain verbal scale			
0	135	110	0.033
1	33	18	0.033
2	27	14	0.041
3	12	35	0.001
4	7	31	0.001
Sensory block level			
T5	29	35	0.348
T6	55	49	0.609
T7-T10	130	124	0.812
Motor block	44	10	0.001
Sedation			
Before opioids	18	0	0.001
After opioids	38	66	0.001
Postoperative opioids			
Morphine	12	48	0.001
Pethidine	8	18	0.035

Group D: Dexmedetomidine group,
Group F: Fentanyl group

the incidence of sedation was higher in the fentanyl group than the dexmedetomidine group ($p<0.05$). The number of patients required for postoperative analgesia (morphine or pethidine), was significantly lower in dexmedetomidine than fentanyl group ($p<0.05$).

Table 3 shows that the heart rate and mean arterial blood pressure decreased in both groups, but the decrease was more in patients of dexmedetomidine group than fentanyl group and the comparison was significant between the two groups ($p<0.05$). The decrease was less than 20% of the baseline values.

Table 4 shows the side effects of the epidural block. The incidence of side effect such as motor block, bradycardia, hypotension, and dry mouth was higher in the dexmedetomidine group compared to fentanyl group ($p<0.05$). But the side effect such as nausea and vomiting, pruritis, urinary retention, and respiratory depression were significantly lower in the dexmedetomidine group compared to fentanyl group ($p<0.05$). There was no difference in the incidence of headache or shivering between the two groups ($p>0.05$).

Discussion

The present study showed that adding dexmedetomidine as an adjuvant to postoperative epidural bupivacaine 0.125% in patients undergoing total knee replacement significantly reduced the incidence postoperative pain, with a better quality of sensory block and a significant reduction in postoperative opioids (morphine and pethidine) compared to the addition of fentanyl to bupivacaine. Eskandar et al., [18] assessed the postoperative effect of dexmedetomidine as an adjuvant to bupivacaine for 48 hours after total knee arthroplasty. They found that the visual analogue scale and the total dose of nalbuphine decreased significantly in the dexmedetomidine group compared to the control group. Bajwa et al., [19], evaluated the addition of dexmedetomidine or fentanyl to epidural ropivacaine in patients undergoing lower limb orthopedic surgeries and they found that the onset of sensory analgesia and the establishment of the complete motor blockade was significantly earlier in the dexmedetomidine group. The postoperative analgesia was prolonged significantly in the dexmedetomidine group and consequently the low dose consumption of local anesthetic was used in dexmedetomidine group, and the same result was shown by other studies [20-23].

The present study showed that the heart rate and the mean arterial blood pressure decreased with dexmedetomidine compared with fentanyl. The decrease in heart rate and mean arterial blood pressure was less than 20% of the baseline and may be significant as a result of a large number of the study. These findings correlate with the result of other studies and the decrease in heart rate and mean arterial blood pressure can be explained by the central action of dexmedetomidine in decreasing the sympathetic outflow and catecholamines release [24,25]. Eskandar et al., [18] found that the heart rate

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Table 3. Heart rate and mean arterial blood pressure of patients (data are presented as mean±SD).

Time points	Heart rate			Mean arterial blood pressure		
	Group D (n=214)	Group F (n=208)	P-value	Group D (n=214)	Group F (n=208)	P-value
T0	79.35±6.18	78.24±6.62	0.075	96.45±9.72	95.39±8.58	0.235
T1	73.50±5.46	76.82±6.71	0.001	92.36±7.61	94.87±8.15	0.001
T2	72.46±4.33	76.21±5.91	0.001	91.57±6.90	94.70±7.84	0.001
T3	71.82±4.19	75.30±4.74	0.001	90.79±5.39	93.93±6.55	0.001
T4	71.56±3.94	74.82±4.11	0.001	89.63±4.70	93.40±4.36	0.001
T5	70.48±3.61	74.23±3.78	0.001	88.87±3.95	92.76±4.12	0.001
T6	68.15±3.75	73.41±3.34	0.001	88.28±3.40	91.80±4.10	0.001
T7	67.38±3.24	72.57±3.40	0.001	89.31±4.57	91.20±4.07	0.001
T8	68.74±3.10	72.20±3.27	0.001	89.74±4.68	92.48±4.50	0.001

T0: Baseline reading; T1:Reading 6 hours after study medication administration; T2: Reading 12 hours after study medication administration; T3: Reading 18 hours after study medication administration;T4: Reading 24 hours after study medication administration; T5: Reading 36 hours after study medication administration; T6: Reading 48 hours after study medication administration; T7: Reading 60 hours after study medication administration; T8: Reading 72 hours after study medication administration. Group D: Dexmedetomidine group, Group F: Fentanyl group

Table 4. Complications of the epidural block (data are presented as number).

Complications	Group D (n=214)	Group F (n=208)	P-value
Motor block	44	10	0.001
Hypotension (Decrease in MAP >20%)	47	19	0.001
Bradycardia(Heart rate<60 bpm)	41	13	0.001
Dry mouth	62	16	0.001
Nausea and vomiting	19	52	0.001
Pruritis	0	23	0.001
Respiratory depression	0	17	0.001
Urine retention	0	14	0.001
Headache	7	9	0.570
Shivering	8	13	0.235

MAP: Mean arterial blood pressure
Group D: Dexmedetomidine group, Group F: Fentanyl group

decreased significantly with dexmedetomidine, but the mean arterial blood pressure decreased significantly in the control group compared to dexmedetomidine. Kaur et al., [20] found that no significant changes in the heart rate and blood pressure by adding dexmedetomidine as an adjuvant to ropivacaine compared to the control group and the same result was shown by other studies [21,26-28].

The incidence of side effects such as motor block, bradycardia, hypotension, and dry mouth was higher in the dexmedetomidine group compared to fentanyl group. Bajwa et al., [19] found that no difference in the incidence of bradycardia or hypotension between epidural fentanyl and dexmedetomidine to ropivacaine, but the dry mouth was associated with dexmedetomidine more than fentanyl and also the dexmedetomidine induces motor block than fentanyl and the same result was shown other studies [11,21,29,30] by Gupta et al., [21], and Forster et al., [11]. Lee et al., [29] found that the addition of fentanyl to epidural ropivacaine was associated with continuous hypotension, serious nausea/vomiting, and dizziness. Thimmappa et al., [30] showed that the addition of dexmedetomidine to epidural ropivacaine was associated with significant bradycardia compared to clonidine and control group.

The incidence of sedation before opioid administration was higher in dexmedetomidine compared to fentanyl group, but after opioid administration it was higher in the fentanyl group compared to dexmedetomidine group, and this may be related the sedative effects of opioids required in the fentanyl group more than dexmedetomidine group. Eskandar et al., [18] showed the same result in spite of the required nalbuphine was higher in the control group and the same result was found by Kurr et al., [20], and Gupta et al [27].

The side effects such as nausea and vomiting, pruritis, urinary retention, and respiratory depression were significantly lower in the dexmedetomidine group compared to fentanyl group and a similar result was shown by Gupta et al [21]. Bajwa et al., [19] found that nausea and vomiting was associated with epidural fentanyl more than dexmedetomidine and no difference in the incidence of pruritis, respiratory depression or urinary retention between the two groups.

Conclusion

Dexmedetomidine is an ideal adjuvant to epidural bupivacaine for postoperative analgesia compared to fentanyl in patients undergoing total knee replacement. Dexmedetomidine provides a better postoperative analgesia and reduces

the postoperative narcotics requirements and complication such as nausea and vomiting, pruritis, urinary retention, and respiratory depression compared to fentanyl. But the epidural dexmedetomidine is associated with a higher incidence of motor block, bradycardia, hypotension, and dry mouth compared to epidural fentanyl.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	RS	ME
Research concept and design	✓	✓
Collection and/or assembly of data	✓	✓
Data analysis and interpretation	✓	✓
Writing the article	✓	--
Critical revision of the article	✓	✓
Final approval of article	✓	--
Statistical analysis	--	--

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