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Research Article

A dose reduction study of local anesthetic with addition of dexmedetomidine on postoperative epidural analgesia after total knee arthroplasty

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KEYWORDS

Bupivacaine;
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Abstract *Background:* Epidural analgesia is still the preferred method of postoperative analgesia for total knee arthroplasty in many countries. Dexmedetomidine is a new alpha-2 agonist which had many beneficial effects when administered epidurally. The aim of study was to provide effective postoperative analgesia with hemodynamic stability through reduction of the amount of epidural local anesthetic by adding dexmedetomidine.

Methods: 75 patients, 50–70 years old, ASA physical status I–III undergoing total knee arthroplasty were randomly divided into three equal groups, group I received 0.125% bupivacaine 5 ml/h for postoperative analgesia, group II received 4 ml of a mixture of bupivacaine 0.125% and dexmedetomidine 0.2 μg/kg/h and group III received 3 ml of a mixture of bupivacaine 0.125% and dexmedetomidine 0.2 μg/kg/h. Postoperative pain were scored by visual analog scale (VAS), sedation score, postoperative nalbuphine consumption and hemodynamic parameters were recorded every 4 h for 48 h postoperatively.

Results: The demographic data were comparable in all groups. VAS (visual analog scale) of pain showed a significant reduction between the two groups II, III and group I with insignificant difference between groups II and III at both rest and movement. The mean of nalbuphine consumption during the study period was significantly reduced in group II, III than in group I with insignificant difference between groups II and III. Sedation scores were significantly higher in groups II and III compared to group I. Heart rate was more reduced in groups II and III than in group I with insignificant difference between the groups. The mean arterial blood pressure was significantly reduced in group I than groups II and III from hour 8 till the end of the study.

Conclusion: Dexmedetomidine is an effective adjuvant to epidural bupivacaine for postoperative analgesia after total knee arthroplasty through reducing the amount of local anesthetic.

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1. Introduction

Total knee arthroplasty is associated with sever early postoperative pain which remains the major factor that limits patients seeking TKA [1]. Improving the pain management techniques has significant impact on stress response and postoperative outcome [2,3]. The use of epidural analgesia is the preferred technique of analgesia in many European countries for total knee arthroplasty, as revealed by a declarative European survey [4]. Epidural techniques are commonly used in postoperative analgesia for elderly patients, with the combination of a local anesthetic and an opioid being preferred [5,6]. However, the occurrence of serious adverse effects (eg, hypotension, respiratory depression, deep bradycardia) and unwanted adverse events (eg, nausea, vomiting, motor block) with these analgesic regimens make it necessary to continue research about different and more optimal analgesia methods [6,7]. The α-2 agonists, particularly the combination of clonidine with local anesthetics administered via the epidural or spinal route, have been found to be effective in pain management [8–10]. Dexmedetomidine, another α-2 receptor agonist, is firstly used in ICUs for sedation of patients [11–13]. The effective analgesia obtained with dexmedetomidine has been widely discussed [14–16]. However, clinical studies on its spinal and epidural use are limited, also it has got numerous beneficial effects when used epidurally [17].

Hence, in the present study we have hypothesised that adding epidural adjunct dexmedetomidine to low volumes of bupivacaine, aiming to reduce the complications of epidural local anesthetics and opioids, and provide suitable postoperative analgesia for patients undergoing total knee arthroplasty without hemodynamic instability.

2. Materials and methods

After approval of the institutional ethics committee and Pan African Clinical Trial Registry (www.pactr.org) PACTR 201503001068335. Written consents of 75 patients, 50–70 years old, American Society of Anesthesiology (ASA) physical status I–III, admitted to Menoufiya University Hospitals, undergoing elective total knee arthroplasty were included in this prospective, double-blinded, randomized controlled study. Exclusion criteria included morbid obese, age older than 70 years, known allergy to bupivacaine or dexmedetomidine, renal or hepatic insufficiency, cardiac conduction disturbances, neurological or psychiatric diseases and coagulation disorders. Patients were randomly classified into three parallel groups (20 patients in each group) using closed envelope technique. A good intravenous line was accessed by 18 gauge intravenous cannula and Ringer's solution infused at a rate of 6–15 ml/kg/hour. All patients received midazolam 2 mg IV five minutes before epidural anesthesia was performed. Routine monitoring was applied pre-operatively including ECG, NIBP and pulse oximetry and the baseline measurements were recorded. A combined spinal and epidural technique was used for anesthesia and postoperative analgesia. A 16 G Tuohy needle was used to insert an epidural catheter at the L3–4 or L4–5 interspaces. In all patients, a midline approach was used, with the epidural space identified using loss of resistance then the epidural catheter was introduced into epidural space for 3–4 cm and a test dose of 2 ml of lidocaine 2% containing adrenaline 1:200,000 was given to exclude both intrathecal and intravenous injection. Then spinal anesthesia was given by 15 mg 0.5% heavy bupivacaine. Patients in group I (control group) received only 5 ml/h of bupivacaine 0.125%, group II received 4 ml/h of a mixture of bupivacaine 0.125% and dexmedetomidine 0.2 μg/kg/h and group III received 3 ml/h of a mixture of bupivacaine 0.125% and dexmedetomidine 0.2 μg/kg/h. Post-operative pain scores were assessed using a 10 cm visual analog scale (VAS) (0 = no pain and 10 = worst pain imaginable) during rest (primary outcome) and movement (secondary outcome). According to the patient's request to analgesia when VAS $\geqslant$ 4, post-operative incremental doses of I.V. 4 mg nalbuphine were given and recorded. The patient's level of sedation was assessed using the inverted observer's assessment of alertness/sedation scale [18], with a score of 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, and 5 = asleep and not responsive to any stimuli. The post-operative data (e.g. pain, sedation) and cardio-respiratory parameters (heart rate, blood pressure and SpO_2) were monitored and recorded every 4 h for 48 h.

2.1. Statistical analysis

A power analysis was performed using a power of 85% and an α value 0.05. We assumed that the minimum difference of pain scores at rest (primary outcome of the study) was 20% and standard deviation 20%. The sample size was calculated to be 23 patients so we decided to include 25 patients in each group in the study. We used GraphPad Stat Mate version 2 statistics program for power analysis.

Statistical analysis was done using SPSS program. Descriptive statistics were expressed as mean + SD unless otherwise stated. One way analysis of variance (ANOVA) with Student Newman–Keuls post-hoc test was used for comparison of the means of continuous variables and normally distributed data. The Chi-square test was used otherwise. P-value < 0.05 was considered statistically significant.

3. Results

The demographic data of the patients in the three groups were comparable with regards to age, sex, weight and height (Table 1). During the course of the study, VAS (visual analog scale) of pain at rest showed a significant reduction between group I and both groups II and III with insignificant difference between groups II and III at rest during the first 24 h and insignificant reduction between the studied groups during the rest of the study (Table 2), while VAS of pain at movement, showed significant reduction between group I and the other 2 group with insignificant difference between groups II and III all over the study period (Table 3). The mean of nalbuphine consumption during the study period was significantly reduced in group II and group III more than in group I with insignificant difference between groups II and III (Table 4). The sedation score was significantly higher in groups II and III (which received dexmedetomidine) compared to group I with insignificant difference between the two groups II and III (Table 5). Whereas heart rate was reduced in both groups II, III used

Table 1 Demographic data.

Character	Group I	Group II	Group III	*P*-value
Age (years)	58.88 ± 4.77	60.2 ± 3.89	59.12 ± 4.87	0.55
Sex (F/M)	14/11	13/12	10/15	0.5
Weight (kg)	86.64 ± 6.82	86.16 ± 6.99	85.76 ± 6.53	0.9
Height (cm)	159.08 ± 6.99	161 ± 6.89	163.12 ± 8.83	0.18

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine, F: Female, and M: Male.
Data were expressed as mean ± SD and number of patients.

Table 2 VAS at rest.

Time (h)	Group I	Group II	Group III	*P*-value
4	4.2 ± 2.15*†	2.5 ± 1.4	2.6 ± 1.3	< 0.001
8	3.48 ± 1.45	2.3 ± 1.6	2.4 ± 1.5	0.009
12	3.04 ± 1.1*†	2.05 ± 1.14	2.07 ± 1.13	0.003
16	2.85 ± 0.91*†	1.87 ± 1.0	1.89 ± 1.1	< 0.001
20	2.77 ± 0.85*†	1.77 ± 0.98	1.8 ± 1.0	< 0.001
24	2.68 ± 0.76	2.15 ± 0.84	2.16 ± 0.85	0.038
28	2.46 ± 0.83	2.16 ± 0.76	2.18 ± 0.87	0.358
32	2.43 ± 0.81	2.13 ± 0.74	2.16 ± 0.75	0.320
36	2.4 ± 0.87	2.11 ± 0.72	2.13 ± 0.73	0.342
40	2.39 ± 0.89	1.99 ± 0.9	2.1 ± 0.72	0.228
44	2.36 ± 0.91	1.94 ± 0.8	1.92 ± 0.7	0.101
48	2.34 ± 0.81	1.87 ± 0.75	1.88 ± 0.73	0.052

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.
* Significance between group I and group II.
† Significance between group I and group III.

Table 3 VAS at movement.

Time (h)	Group I	Group II	Group III	*P*-value
4	5.08 ± 1.41*†	4.11 ± 1.36	4.14 ± 1.38	0.023
8	4.92 ± 1.29*†	3.88 ± 0.98	4.04 ± 1.27	0.006
12	4.76 ± 1.3*†	3.82 ± 0.97	3.84 ± 0.99	0.004
16	4.7 ± 1.36*†	3.68 ± 0.86	3.72 ± 0.94	0.001
20	4.6 ± 1.35*†	3.6 ± 0.88	3.65 ± 0.86	0.001
24	4.32 ± 1.28*†	3.52 ± 0.76	3.48 ± 0.77	0.004
28	4.12 ± 1.09*†	3.2 ± 0.74	3.4 ± 0.79	0.001
32	3.98 ± 1.03*†	3.15 ± 0.75	3.36 ± 0.81	0.003
36	3.88 ± 0.97*†	3.1 ± 0.74	3.16 ± 0.75	0.002
40	3.68 ± 0.85*†	3.09 ± 0.77	3.1 ± 0.73	0.013
44	3.54 ± 0.73*†	3.02 ± 0.72	3.08 ± 0.76	0.029
48	3.36 ± 0.64*†	2.66 ± 0.7	2.76 ± 0.6	< 0.001

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.
* Significance between group I and group II.
† Significance between group I and group III.

Table 4 Nalbuphine consumption.

Time (h)	Group I	Group II	Group III	*P*-value
4	3.76 ± 0.66*†	2.96 ± 1.02	3.2 ± 1.0	0.008
8	3.6 ± 0.82*†	2.88 ± 1.01	3.04 ± 1.02	0.024
12	3.28 ± 0.98*†	2.56 ± 0.92	2.72 ± 0.98	0.025
16	2.8 ± 1.0*†	2.16 ± 0.55	2.32 ± 0.75	0.015
20	2.48 ± 0.87*†	1.84 ± 0.55	2.0 ± 0.58	0.004
24	3.38 ± 0.95*†	2.64 ± 0.95	2.8 ± 1.0	0.021
28	3.12 ± 1.01*†	2.4 ± 0.82	2.56 ± 0.92	0.018
32	3.04 ± 1.02*†	2.32 ± 0.75	2.48 ± 0.87	0.014
36	2.8 ± 1.0*†	2.16 ± 0.55	2.32 ± 0.75	0.015
40	2.48 ± 0.87*†	1.84 ± 0.55	2.0 ± 0.58	0.004
44	2.4 ± 0.82*†	1.76 ± 0.66	1.92 ± 0.4	0.002
48	2.56 ± 0.92*†	1.92 ± 0.4	2.08 ± 0.4	0.001

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.
* Significance between group I and group II.
† Significance between group I and group III.

Table 5 Sedation score.

Time (h)	Group I	Group II	Group III	*P*-value
4	1.27 ± 0.45	1.54 ± 0.73	1.52 ± 0.7	0.257
8	1.28 ± 0.46*†	1.72 ± 0.68	1.7 ± 0.66	0.019
12	1.3 ± 0.47*†	1.79 ± 0.83	1.78 ± 0.77	0.024
16	1.32 ± 0.48*†	1.88 ± 0.83	1.87 ± 0.82	0.011
20	1.24 ± 0.44*†	1.78 ± 0.85	1.78 ± 0.84	0.014
24	1.21 ± 0.42*†	1.69 ± 0.81	1.68 ± 0.79	0.025
28	1.13 ± 0.34*†	1.67 ± 0.77	1.65 ± 0.75	0.006
32	1.14 ± 0.35*†	1.68 ± 0.8	1.69 ± 0.9	0.012
36	1.17 ± 0.37*†	1.76 ± 0.88	1.77 ± 0.89	0.008
40	1.18 ± 0.38*†	1.88 ± 0.93	1.86 ± 0.92	0.003
44	1.12 ± 0.33*†	1.68 ± 0.8	1.66 ± 0.7	0.004
48	1.07 ± 0.27*†	1.42 ± 0.41	1.41 ± 0.39	0.001

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.
* Significance between group I and group II.
† Significance between group I and group III.

dexmedetomidine more than in bupivacaine group I, there was no significant difference between the three groups and none of the heart rate values were found to be outside the normal range (Table 6). On contrast, the mean arterial blood pressure was significantly reduced in group I than groups II, III with significant difference between group II and group III from hour 8 till the end of the study (Table 5). There was insignificant difference between the two groups in relation to SpO_2 (see Table 7).

Table 6 Heart rate.

Time (h)	Group I	Group II	Group III	*P*-value
Base	77.08 ± 8.65	77.52 ± 9.28	72.24 ± 9.37	0.082
4	76.2 ± 8.63	76.56 ± 9.15	76.52 ± 8.94	0.988
8	75.92 ± 8.8	75.64 ± 8.3	75.88 ± 8.6	0.992
12	75.2 ± 8.54	75.08 ± 7.68	74.88 ± 8.09	0.990
16	74.52 ± 8.21	73.96 ± 6.62	74.2 ± 7.8	0.966
20	74.08 ± 7.6	73.32 ± 5.71	72.84 ± 6.87	0.809
24	73.88 ± 5.62	73.64 ± 7.48	73.16 ± 6.9	0.928
28	74.24 ± 5.67	72.16 ± 6.2	73.36 ± 6.82	0.501
32	72.44 ± 6.1	774.4 ± 5.61	73.04 ± 6.75	0.521
36	73.84 ± 5.34	71.2 ± 5.22	72.6 ± 6.45	0.267
40	73.12 ± 5.29	70.36 ± 4.38	70.4 ± 4.41	0.066
44	72.36 ± 5.01	70.92 ± 3.91	70.92 ± 4.11	0.409
48	72.68 ± 5.97	71.72 ± 3.9	71.56 ± 4.14	0.669

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.

Table 7 Mean arterial blood pressure.

Time (h)	Group I	Group II	Group III	*P*-value
Base	97.92 ± 8.11	93 ± 6.89	94.88 ± 10.42	0.132
4	92.4 ± 7.97	90.27 ± 4.26	91.08 ± 6.93	0.516
8	82.44 ± 5.9[*†]	85.45 ± 5.01	88.96 ± 8[‡]	0.003
12	80.92 ± 3.35[*†]	85.1 ± 4.49	88.6 ± 8.01[‡]	< 0.001
16	80 ± 3.43[*†]	85 ± 4.38	88.2 ± 5.79[‡]	< 0.001
20	77.88 ± 4.3[*†]	82.6 ± 4.73	86.16 ± 5.25[‡]	< 0.001
24	76 ± 4.69[*†]	82.2 ± 4.69	86.6 ± 5.19[‡]	< 0.001
28	76.56 ± 4.79[*†]	82.5 ± 5.02	87.12 ± 5.09[‡]	< 0.001
32	77.04 ± 5.02[*†]	83.2 ± 5.23	87.68 ± 5.03[‡]	< 0.001
36	79.04 ± 4.12[*†]	84.09 ± 4.23	88.52 ± 4.91[‡]	< 0.001
40	81.2 ± 4.69[*†]	85.32 ± 5.3	89.24 ± 4.64[‡]	< 0.001
44	83.08 ± 4.13[*†]	86.01 ± 5.35	90.28 ± 4.27[‡]	< 0.001
48	84.76 ± 5.64[*†]	87.88 ± 4.97	91.68 ± 4.47[‡]	< 0.001

Group I: Bupivacaine (5 ml/h), Group II: Dexmeditomidine + 4 ml/h bupivacaine, Group III: Dexmeditomidine + 3 ml/h bupivacaine.
Data were expressed as mean ± SD.
[*] Significance between group I and group II.
[†] Significance between group I and group III.
[‡] Significance between group II and group III.

4. Discussion

The present study has found that adding dexmedetomidine as an adjuvant to postoperative epidural bupivacaine 0.125% in patients undergoing total knee replacement significantly reduced local anesthetic volume from 5 ml/h to 3 ml/h (40%), postoperative pain during both rest and movement, with significant reduction in postoperative nalbuphine consumption and cardiorespiratory stability.

Total knee arthroplasty (TKA) is a successful procedure to improve the quality of life in patients with degenerative joint disease [19]. Severe postoperative pain is a significant concern for patients and can affect the physiological, psychological status and clinical outcomes of these patients. Most of the candidates for TKA are elderly and have medical comorbidities that can worsen when subjected to stress. As a result, postoperative pain management has become an essential part of the perioperative care program for TKA [20,21].

Epidural analgesia is the most commonly recommended method for postoperative pain management of this age group [5]. However, choosing the optimal epidural drug is still the subject of many investigations [5,22]. Using only local anesthetics at effective doses raises concerns about adverse events, such as hypotension, bradycardia, motor weakness, and elevation in block level [22]. Opioid combinations may not provide satisfactory results, as they are associated with respiratory depression, nausea, vomiting and pruritus [6,22]. Dexmedetomidine is a new opioid-sparing adjuvant to epidural administration. Dexmedetomidine is a potent and highly selective α2-adrenoceptor agonist [23]. This causes it to be a much more effective sedative and analgesic agent, with much less unwanted cardiovascular effects [24]. It acts on both pre and post-synaptic sympathetic nerve terminal and central nervous system thereby decreasing the sympathetic outflow and norepinephrine release causing sedative, anti-anxiety, analgesic, sympatholytic and hemodynamic effects [17,25].

In the present study epidural dexmedetomidine groups reduced postoperative VAS at rest and movement as found by Elhakim and colleagues [24] and also decreased postoperative analgesic (nalbuphine) requirement as was expected in the view of the established analgesic efficacy of dexmedetomidine and other centrally acting α-2 agonists [17,24,25]. Dexmedetomidine has a potent sedative effect which approved by the present study, that showed a significant increase of sedation score in dexmedetomidine groups. The sedative and analgesic effects of dexmedetomidine has been documented in several studies [26–28], after major surgical surgeries [29], after thoracic surgery [24], after vaginal hysterectomy [17] and after lower limb orthopadic surgery [29]. Dexmedetomidine exerts its sedative and analgesic sparing effects through central actions in the locus coeruleus and in the dorsal horn of the spinal cord, respectively [30,31]. In the present study, mean HR was insignificantly lower in the dexmedetomidine groups II, III than bupivacaine group I as expected in many studies [17,24,31] and remained within normal limits, as reported in other studies [32–34], which was an advantage in these geriatric patients. The decrease in heart rate caused by α-2 agonist can be explained by their central action decreasing the sympathetic outflow and norepinephrine release [35]. In contrast to heart rate results, the mean arterial pressure was significantly decreased in bupivacaine group I than the two groups II, III in which patients received dexmedetomidine with significant decrease in group II than group III which can be explained by using lower volume of local anesthetic in group III (3 ml/h) than used in group I (5 ml/h) and in group II (4 ml/h). Although there was a decrease in heart rate and mean arterial blood pressure reported in dexmedetomidine group, it never was less than 20% of the baseline values which proved that the use α-2 agonists provides a hemodynamic stability during the post-operative periods.

The present work studied the evaluation of adding dexmedetomidine to low doses of bupivacaine in patients undergoing total knee arthroplasty under combined spinal epidural anesthesia. More studies including large number of patients and measurements of efficacy of both, physical therapy and rehabilitation programs should be performed to confirm our study findings about the usage of dexmedetomidine as a safe and effective adjuvant to epidural low volume bupivacaine.

The study has established that the dose of epidural bupivacaine can be safely and significantly lowered by 40% with the addition of low-dose dexmedetomidine, thereby avoiding hemodynamic instability and providing an effective postoperative analgesia, sedation and decreased postoperative analgesic requirement in patients undergoing total knee arthroplasty.

Conflict of interest

The authors declare that there is no conflict of interest.

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