Southern African Journal of Anaesthesia and Analgesia 2018; 24(2):54–59
https://doi.org/10.1080/22201181.2018.1444443

South Afr J Anaesth Analg
ISSN 2220-1181 EISSN 2220-1173

RESEARCH

Intra-articular dexmedetomidine with bupivacaine versus bupivacaine alone for postoperative analgesia after knee arthroscopy

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Background: Optimal relief of pain after knee arthroscopy is essential for early rehabilitation and mobilisation and to minimise postoperative morbidity. This study's aim was to assess dexmedetomidine as an additive to intra-articular (IA) bupivacaine in terms of analgesic duration and postoperative rescue analgesic consumption following arthroscopic knee surgery.
Methods: A total of 70 patients, ASA physical status I and II, undergoing knee arthroscopy under general anaesthesia were enrolled in this double-blinded randomised controlled study, after Pan African Clinical Trial Registry (PACTR201507001048242) approval was obtained. Patients were randomly assigned into two groups; the bupivacaine group (B) received IA 19 ml bupivacaine 0.5% + 1 ml normal saline, bupivacaine dexmedetomidine group (BD) received IA injection of 19 ml bupivacaine 0.5% + dexmedetomidine 100 µg (1 ml). Postoperative visual analogue pain score (VAS), duration of analgesia and postoperative analgesic requirement were assessed.
Results: VAS scores at rest and on mobilisation were significantly lower in the BD group at 4 h, 6 h and 8 h postoperatively in comparison with group B ($p < 0.05$). VAS scores were comparable between studied groups during the first 2 h, and at 12 h and 24 h postoperatively. Duration of analgesia was significantly longer in group BD (458.9 ± 93.5 min) than in the B group (229.1 ± 83.7 min) ($p < 0.05$). Postoperative analgesic consumption was lowered in the BD group compared with the B group ($p < 0.05$).
Conclusions: Adding dexmedetomidine to IA bupivacaine after knee arthroscopy prolongs analgesic duration and decreases postoperative analgesic requirement.

Keywords: arthroscopy, dexmedetomidine, intra-articular, postoperative pain

Introduction

Knee arthroscopy is a well-established minimally invasive procedure. Arthroscopic surgery is often associated with a considerable degree of postoperative pain, usually caused by stimulation of the synovial tissue free nerve endings, anterior fat pad and capsule of the joint by either surgical excision or resection.[1]

Although arthroscopic knee procedures are less traumatic than open surgery, considerable postoperative pain can prevent early mobilisation and rehabilitation and reduce patient satisfaction.[2] Many techniques for postoperative analgesia have been studied (for example, systemic analgesia, neuraxial analgesia, peripheral nerve blocks and intra-articular (IA) injections) in an attempt to establish the best modality for control of postoperative pain.[3]

A single IA injection of local anaesthetic (LA) has been used to adequately provide analgesia after arthroscopic knee surgery and to reduce consumption and possible side effects of systemic analgesics. IA bupivacaine is commonly used due to its prolonged analgesic effect[4] as well as its established ability to reduce rescue analgesic consumption.[1]

Many studies have used different IA agents such as opioids, ketamine, NSAIDS and α_2 adrenergic agonists for pain management after knee surgeries.[5,6] Dexmedetomidine is a potent and highly selective α_2 adrenoreceptor agonist that binds the α_2-receptors up to eight times more avidly than clonidine, with well-recognised sedative-hypnotic, anxiolytic, analgesic, anaesthetic and sympatholytic effects.[7] Intravenous and intra-articular dexmedetomidine have been used in several studies to enhance postoperative analgesia after knee arthroscopy and have demonstrated an increased time to first analgesic request and a decreased need for postoperative analgesia.[5,6]

IA dexmedetomidine has been used before in doses of 50 µg and 80 µg. So, we hypothesised that IA dexmedetomidine at 100 µg would result in satisfactory prolongation of analgesic duration without increased adverse effects.

Our aim was to assess dexmedetomidine as an adjuvant to IA bupivacaine on analgesic duration and postoperative analgesic consumption after arthroscopic surgical procedures of the knee.

Material and methods

After obtaining approval from the Institutional Review Board, Tanta University, Faculty of Medicine, Tanta, Egypt (2971/12/14), the Pan African Clinical Trial Registry (PACTR201507001048242) and patients' informed written consent, a prospective double-blinded randomised controlled study was carried out on 70 adult patients aged > 18 years, of either gender, with American Society of Anesthesiologists physical status (ASA) I–II undergoing knee arthroscopy. The study was carried out between January and July 2015.

All patients' data were kept confidential with secret codes and in a private file for each patient. All given data were used for the current research only. Any unexpected adverse effects occurring during the research were explained to the patients and reported to the ethical committee at the time. The study protocol and the

VAS for pain assessment were explained to each patient preoperatively.

The exclusion criteria comprised patients with prolonged intake of NSAIDs, opioids, calcium channel blockers, corticosteroids, tricyclic antidepressants, or those with psychiatric disorders, patients who received analgesics up to 24 h prior to surgery, liver or renal disease, or allergy to studied medications were excluded.

Computer-generated randomisation numbers were used to allocate patients into two groups using sealed opaque envelopes chosen by each patient. In the bupivacaine group (B), patients had an IA injection of 19 ml bupivacaine 0.5% + 1 ml normal saline. In the bupivacaine dexmedetomidine group (BD), patients had an IA injection of 19 ml bupivacaine 0.5% + dexmedetomidine 100 µg (1 ml).

The studied medications were prepared by an anaesthesiologist with no subsequent role in the study to ensure blinding.

Premedication with 0.05 mg/kg IV midazolam was given 15 min before induction of anaesthesia. Monitoring included five-lead ECG, pulse oximetry, non-invasive blood pressure and capnography. Induction of general anaesthesia was with IV propofol 2 mg/kg, fentanyl 1 µg/kg, and intubation was facilitated with cisatracurim 0.15 mg/kg. Anaesthesia was maintained with 1:1 O_2:air mixture, isoflurane 1.2–1.5% and patients were mechanically ventilated.

Once the patient was anaesthetised, inflation of the tourniquet and sterilisation of the surgical field were performed. Subsequently, a standard arthroscopy technique was performed by the same surgeon through two portals, one anterolateral and one anteromedial. At the end of surgery and 10 min before tourniquet deflation, the study drug was injected into the joint after stitching the portals to prevent extravasation. This was taken as the start time to determine time to first request for analgesia. The tourniquet was removed after application of a compression bandage.

Inhalational anaesthesia was discontinued, and muscle relaxant was reversed by neostigmine sulphate 0.05 mg/ kg and atropine sulphate 0.02 mg/ kg. Patients were transferred to the Post Anaesthesia Care Unit (PACU) where VAS was assessed on admission to PACU, and at 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 12 h and 24 h both at rest (VASr) and on mobilisation (VASm) (bending of the operated knee). A dose of 1 g IV paracetamol was administered to all patients if VAS was ≥ 4 then repeated 6 h later. Rescue analgesia of 30 mg IV pethidine was administered if, 20 min after paracetamol injection, VAS was still ≥ 4. Total paracetamol and pethidine consumption was recorded.

Our primary outcome was the duration of analgesia defined as the time elapsed from IA injection to time of first analgesic request. Secondary outcome was the total 24 h rescue analgesic consumption. Adverse events including nausea, vomiting, hypotension, bradycardia, depression of respiration and sedation were recorded, as well as patients' satisfaction levels. Local adverse effects such as haematoma were recorded. Nausea and vomiting were treated with ondansetron 4 mg IV. Hypotension (defined as a decrease in mean arterial pressure more than 20% of the baseline value) was treated with intravenous fluids and intravenous ephedrine 10 mg boluses as needed. Bradycardia (defined as heart rate less than 50 beat/min) was treated by atropine 0.01 mg/kg IV. Patients were discharged 24 h postoperatively.

Statistical analysis

Sample-size calculation was based on the prolongation of time of first analgesic request. Based on the results of previous study[5] at least 29 patients in each group were needed to detect a significant prolongation of 90 min at α error of 0.05 and study power of 80%.

We used the Statistical Package for the Social Sciences (SPSS®) 16 software (SPSS Inc., Chicago, IL, USA) for statistical analysis. A Kolmogorov–Smirnov test was performed for verification of the assumption of normality. Quantitative data were described as mean ± SD and independent sample *t*-test was used for comparison between the two groups. Categorical data were described as number or frequencies (%) and chi-square test or Fisher's exact test were used as appropriate for comparison between both groups. A p-value < 0.05 was considered significant.

Results

Seventy-eight patients were evaluated for enrolment in the study. Seventy patients were randomly allocated into one of two groups after exclusion of eight patients (Figure 1).

Demographic data including age, weight, gender and duration of surgical procedure were comparable among the two studied groups ($p > 0.05$) (Table 1).

Time to first request for analgesia was significantly longer in the BD group (458.9 ± 93.5 min) in comparison with the B group (229.1 ± 83.7 min) ($p < 0.05$) (Table 2).

Total postoperative paracetamol consumption was significantly decreased in the BD group (2.57 ± 0.44 g) compared with the B group (3.11 ± 0.47 g) ($p < 0.05$) (see Table 2).

Nine patients requested postoperative rescue analgesia in the BD group, which was significantly lower compared with the B group (22 patients) ($p < 0.05$) (see Table 2).

Total postoperative rescue analgesia consumption was significantly lower in the BD group (21.40 ± 38.90 mg) compared with the B group (61.70 ± 52.90 mg) ($p < 0.05$) (see Table 2).

VAS scores at rest and on mobilisation were statistically comparable among the two studied groups from time of admission to PACU up to 2 h postoperatively ($p > 0.05$). VAS scores were significantly lower in the BD group than the B group at 4 h, 6 h and 8 h postoperatively ($p < 0.05$). No statistically significant difference was detected between the two studied groups at 12 h and 24 h ($p > 0.05$) (Table 3).

No significant complications were detected in either groups. Patient satisfaction was significantly higher in the BD group in comparison with the B group (Table 4).

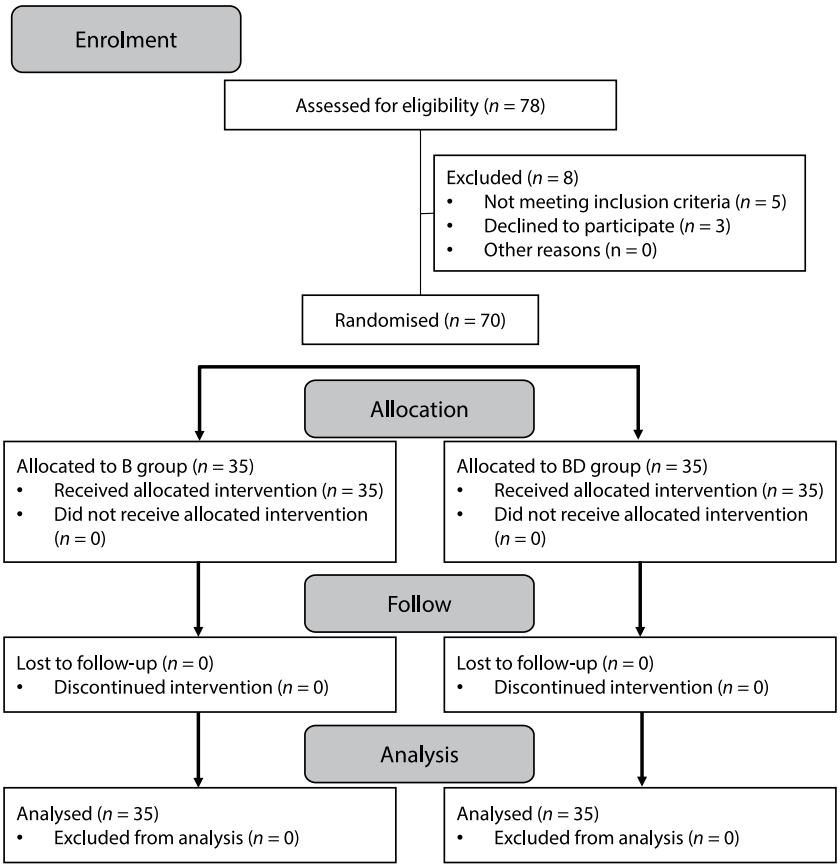

Figure 1: CONSORT flow diagram of participants through each stage of the randomised trial

Table 1: Demographic data and duration of surgery in studied groups

Item	B group	BD group	*p*-value
Age (years)	35.17±9.78	34.89±9.22	0.90
Gender (M/F)	32/3	31/4	0.69
Body weight (kg)	80.26±9.09	81.60±8.73	0.53
Duration of surgery (min)	52.1±11.3	54.3±11.5	0.44

Notes: Data are expressed as mean ± SD or patient number.
*$p < 0.05$ denotes statistical significance.

Discussion

Results of this study showed that adding dexmedetomidine 100 µg to IA bupivacaine results in prolongation of analgesia as well as reduction of postoperative analgesic requirements and better patient satisfaction than bupivacaine alone.

Single IA injection of LA has been suggested to provide adequate pain management after arthroscopy of the knee joint and to reduce consumption and possible adverse effects of systemic analgesics. IA bupivacaine is frequently used because of its extended duration of action.[4]

The duration of analgesia provided by a single dose of IA bupivacaine is not well defined. Møiniche *et al*.[8] stated that the lower pain score due to bupivacaine was short in duration, and some studies[9,10] have demonstrated bupivacaine to be superior to placebo for the first 2–4 h only. In contrast, other studies[11,12] showed bupivacaine to have an enhanced and longer analgesic effect than placebo in the first 24 h.

In other studies,[13,14] bupivacaine dose and concentration were augmented with epinephrine to obtain a longer analgesic effect. A meta-analysis by Wei *et al*.[4] stated that a single IA dose of bupivacaine is superior to placebo in providing pain relief

Table 2: Analgesic requirements in studied groups

Item	B group	BD group	*p*-value	95% CI
Paracetamol consumption (g)	3.11 ± 0.47	2.57 ± 0.44	0.000*	0.639–1.075
Number of patients requiring rescue analgesia	22/35	9/35	0.002*	
Total consumption of rescue analgesia (mg)	61.70 ± 52.90	21.40 ± 38.90	0.001*	18.1–62.5
Time of first analgesic request (min)	229.1 ± 83.7	458.9 ± 93.5	0.000*	57.2–349.0

Notes: Data are expressed as mean ± SD and patient number.
*$p < 0.05$ denotes statistical significance.
CI = confidence interval.

Table 3: Visual analogue scale (VAS) at rest and on mobilisation in studied groups

Item		B	BD	*p*-value	95% CI
VAS at rest	On admission	1.62 ± 0.59	1.42 ± 0.60	0.170	(–0.088; 0.488)
	30 min	1.54 ± 0.61	1.48 ± 0.70	0.717	(–0.257; 0.371)
	1 h	1.51 ± 0.61	1.45 ± 0.56	0.685	(–0.223; 0.337)
	2 h	1.45 ± 0.65	1.34 ± 0.48	0.410	(–0.161; 0.390)
	4 h	3.00 ± 0.80	1.77 ± 0.87	0.000 *	(0.827; 1.630)
	6 h	3.20 ± 0.58	1.71 ± 0.86	0.000 *	(1.134; 1.837)
	8 h	4.02 ± 0.70	2.37 ± 0.77	0.000 *	(1.305; 2.010)
	12 h	2.17 ± 0.74	1.88 ± 0.86	0.144	(–0.100; 0.672)
	24 h	1.54 ± 0.61	1.45 ± 0.61	0.559	(–0.206; 0.377)
VAS on mobilisation	On admission	2.09 ± 0.74	1.97 ± 0.92	0.570	(–0.286; 0.514)
	30 min	2.17 ± 0.71	1.94 ± 0.84	0.222	(–0.141; 0.599)
	1 h	2.11 ± 0.63	2.00 ± 0.73	0.485	(–0.211; 0.439)
	2 h	2.20 ± 0.53	2.03 ± 0.62	0.218	(–0.104; 0.446)
	4 h	4.31 ± 0.83	2.31 ± 0.79	0.000 *	(1.611; 2.389)
	6 h	4.20 ± 0.79	2.29 ± 1.07	0.000 *	(1.463; 2.366)
	8 h	4.91 ± 0.91	2.80 ± 1.18	0.000 *	(1.608; 2.620)
	12 h	2.60 ± 0.73	2.31 ± 1.08	0.200	(–0.156; 0.727)
	24 h	1.88 ± 0.67	1.91 ± 0.78	0.871	(–0.377; 0.320)

Notes: Data presented as mean ± SD.
*$p < 0.05$ denotes statistical significance.
CI = confidence interval.

Table 4: Adverse events and patient satisfaction

Item		B group	BD group	*p*-value
Complications	Hypotension	0 (00%)	2 (5.7%)	0.493
	Bradycardia	0 (00%)	3 (8.5%)	0.239
Satisfaction	Satisfied	17 (48%)	29 (82%)	0.007*
	Fair	11 (31%)	5 (14%)	
	Dissatisfied	7 (20%)	1 (2%)	

Notes: Data are presented as number (%).
*$p < 0.05$ denotes statistical significance.

following knee arthroscopy. Analgesic properties including greater duration of postoperative analgesia, rescue analgesic reduction and lower postoperative VAS scores after IA bupivacaine administration were also documented in other studies.[15–18]

Dexmedetomidine is an α_2 agonist with spinal, supraspinal and peripheral actions. The IA analgesia produced by dexmedetomidine may be attributed to direct local action. A central analgesic effect caused by systemic absorption may also be possible.[19]

The analgesic effect of IA dexmedetomidine might be similar to that of IA clonidine. Clonidine inhibits peripheral norepinephrine release at afferent nociceptors through its effect on α_2 adrenergic presynaptic receptors.[20] Dexmedetomidine has been shown to inhibit the conduction of nerve signals in C and Aδ fibres and promotes the release of encephalin-like substances at peripheral sites thereby producing local anaesthetic effects.[21,22] Opioid-analgesic pathway modulation may be an alternative explanation for the analgesic effect of dexmedetomidine.[23]

Consistent with our study, El-Hamamsy *et al*. compared dexmedetomidine versus fentanyl as additives to IA bupivacaine and found similar efficacy when compared with bupivacaine alone.[24] They reported that IA dexmedetomidine 1 µg/kg when added to bupivacaine resulted in significant improvement of postoperative analgesia after knee arthroscopy, with longer time to first analgesic requirement (450 ± 85 min) compared with bupivacaine alone (230 ± 85 min), and decreased meperidine requirement during the first 24 h.[24]

Paul *et al*. demonstrated that the addition of dexmedetomidine to ropivacaine local anaesthetic enhances both the quality as well as the duration of postoperative analgesia after knee arthroscopy and reduces fentanyl consumption, with an average of 10.84 ± 2.6 h between IA injection and supplementary analgesic administration by PCA pump.[25]

In a study by Reuben and Connelly,[26] the mean time to first analgesic request following knee arthroscopy was 500 min after IA clonidine, 325 min after IA bupivacaine and 700 min after combined IA clonidine and bupivacaine.

In another study by Joshi and colleagues,[27] the mean time to first analgesic request after knee arthroscopy was 280 min after IA bupivacaine, 600 min after IA clonidine, 720 min after IA bupivacaine and morphine and 950 min after combined IA clonidine, bupivacaine and morphine. Al-Metwalli *et al*.[5] concluded that IA dexmedetomidine alone provided around 312 min mean time of postoperative analgesia after knee arthroscopy. No systemic side effects were observed in any of the study groups. The lack of systemic effects in the IA injections may be

attributed to the relatively small dose used and the poorly vascular articular surface.[5]

Ismail *et al*.[28] recruited 90 patients undergoing unilateral elective knee arthroscopy and concluded that IA was superior to intrathecally administered dexmedetomidine due to prolonged analgesia (413 ± 34 min) in the IA group compared with 359 ± 30 and 224 ± 36 min in the intrathecal and control groups respectively, in addition to 24 h less analgesic consumption than the other groups.

This study has some limitations. First, we did not measure the plasma concentrations of the drugs and second, chondrotoxic effects of the drugs were not tested. A systematic review and meta-analysis by Sun *et al*.[2] reported the safety of IA bupivacaine during short-term observation. Moreover, they stated that compared with continuous IA infusion of analgesics, which is associated with large effusion of the surgical wound and direct access for infectious agents with catheter placement, single-administration IA bupivacaine maximises the safety of postoperative pain relief in the early postoperative period. Dragoo *et al*.[29] suggested that toxicity could be due to adrenaline, the preservative sodium metabisulphite and the low pH of such solutions. Bogatch *et al*.[30] did not find toxicity due to adrenaline or low pH. They suggested an alternative hypothesis of an incompatibility between the synovial fluid and the LA causing intra-articular crystal formation. In clinical practice, the toxicity of LAs has mainly been seen with continuous infusions via pain pumps.

In addition, Akça *et al*.[31] reported no adverse effects of dexmedetomidine on rat knee cartilage but little is known about any effects in humans.

Conclusion

Dexmedetomidine 100 µg when used as an adjuvant to IA bupivacaine prolongs duration of analgesia, decreases postoperative analgesic consumption, decreases VAS scores and improves patients' satisfaction without increased adverse effects.

Disclosure statement – No potential conflict of interest was reported by the authors.

Funding – This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Meetings where the work has been presented – None.

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Received: 27-08-2017 Accepted: 21-02-2018