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Intra-articular dexmedetomidine improves outcomes of postoperative analgesia after arthroscopic meniscus surgery

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ABSTRACT

Objectives: The evaluation of the outcomes of patients undergoing arthroscopic unilateral meniscus repair on receiving intra-articular injection (IAI) of dexmedetomidine (DXM) alone in dose of 2 µg/kg or in dose of 1 µg/kg with other analgesics.

Patients & Methods: 150 patients were randomly distributed between 5-groups: C-Group received saline, Study Group I (SI-Group) received DXM 2 µg/kg, SII, SIII and SIV groups received DXM 1 µg/kg with ketamine 0.5 mg/kg, dexamethasone (DXA) 8-mg or ketorolac 30-mg, respectively, with bupivacaine. Bupivacaine spinal anesthesia was provided, and IAI was injected through an arthroscopic port as a single shot. The study outcome is the efficacy of IAI of DXM as judged by pain scores, duration till requesting morphine, times of requesting, and total dose of morphine used during 12-h after IAI.

Results: Pain scores and the cumulative scores were significantly lower in the study groups with lower frequency of requests and the total dose of morphine compared to the C-Group with insignificant difference between study groups. The incidence of adverse events was significantly lower in SIII-Group than in other groups. Patients' and surgeons' satisfaction was higher in the study groups than C-Group.

Conclusion: The IAI of DXM alone or in combination with any other analgesic is an effective and safe analgesic modality for post-arthroscopic surgeries. All additives were effective in terms of reduction of pain score and opioid consumption, but the side effects of ketamine and duration of analgesia of ketorolac are questionable. However, DXA is an efficient analgesic with minimal side effects.

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Intra-articular analgesia; arthroscopic surgery; dexmedetomidine; ketamine; dexamethasone; ketorolac

1. Introduction

Dexmedetomidine (DXM) is an α_2-adrenoreceptor agonist that is widely used as a sedative drug. However, retrospective studies and clinical trials have demonstrated its effectiveness and safety for surgery patients, so DXM is becoming more attractive in clinical applications [1]. Moreover, DXM was regarded as neuroprotective in several studies mostly through its ameliorative effects on inflammatory cytokines, apoptosis, and oxidative stress in central nervous system [2].

The role of DXM as an analgesic adjuvant was extensively examined as an adjuvant to intravenous (IV) analgesics and was found to provide superior effects than the use of these analgesics alone [3]. Also, as a part of opioid-free analgesia in conjunction with various blocks, DXM improved outcomes with a reduction of pain scores and opioid consumption after major abdominal surgeries [4,5]. As an adjuvant for regional blocks, DXM added to local anesthetics and other analgesics for postoperative (PO) regional analgesia provided prolonged PO analgesia, and better functional outcomes with a reduction of rescue PO analgesia [6].

Arthroscopy in the setting of joint fracture surgery affords direct visualization of reduction and facilitates the identification of associated injuries of cartilage and soft tissue [7]. Arthroscopy provided several advantages for patients undergoing joint surgeries with better outcomes not only for surgeries of large joints [8,9] but also for small or compound joints [7,10].

However, post-arthroscopy pain was associated with anxiety, induced depression and showed bad impacts on patients' quality of life, thus various analgesic manipulations were provided to alleviate apprehension and relieve PO pain to improve patients' quality of life and movement ability [11].

2. Objectives

This study tried to evaluate the short-term outcomes of patients undergoing arthroscopic meniscus repair on receiving intra-articular injection (IAI) of DXM in dose of 2 µg/kg alone or in dose of 1 µg/kg as adjuvant to

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other analgesics for post-arthroscopy pain in comparison to IAI of saline as a Placebo.

3. Design

Prospective comparative study

4. Setting

Anesthesia, ICU, Pain Department, Faculty of Medicine, Benha University

5. Ethical consideration

The study protocol was approved by the departmental committee before case collection. The protocol was discussed with patients before enrolment, and those accepted to participate in the study signed the written fully informed consent. After completing case collection and obtaining the results, the final approval was obtained from the Local Ethical Committee, Benha University.

6. Sample size calculation

Previously, **Moeen et al**. [12] compared the IAI of DXM, dexamethasone (DXA) versus placebo in a study of 20 patients per group and failed to detect a significant difference between DXM and DXA, despite the significant difference versus placebo. However, **Agarwal et al**. [13] in comparison of IAI of morphine, DXM and placebo in 26 patients per group detected a significant difference between morphine and DXM versus placebo with a significant difference between morphine and DXM. The null hypothesis of the current study is the insignificant difference in pain scores between DXM received alone in dose of 2 µg/kg and in dose of 1 µg/kg in a mixture with either DXA, ketamine (KET) or ketorolac (KTR). Using the G*Power (Version 3.1.9.2) [14], the sample size that was calculated to provide a study power of 80% using α-error of 5%, and considering the effect size of 0.20, the F-test model defined 30 patients per group is the suitable number to ensure the certainty of the null hypothesis.

7. Blindness

One author, Abouseeda MM, was responsible for preoperative evaluation and assurance of fulfillment of inclusion criteria and preparation of medications for IAI and was blinded about the randomization process or grouping. The duties of the 2nd author; Amer NE were randomization process, patients' grouping and the provision of the IAI but she was blinded about the drugs or dose to be used. The 3rd author; Elafifi EM was responsible for PO care with registration of pain scores and need for rescue analgesia, but she was blinded about the medication used for IAI. At the end of the case collections, the data collected by the authors was interpreted and compared to fulfill the outcome.

8. Preliminary evaluation

Patients' age, gender, weight and height for calculation of body mass index (BMI) as weight (kg) divided by height (m^2), ASA grade, laterality of the lesion, and presence of other orthopedic or medical diseases were determined.

9. Exclusion criteria

The presence of intra-articular injuries other than meniscus injury, bilateralism, presence of manifestations of osteoarthritis or other forms of arthritis, ASA grade >II, allergy to the study drugs, refusal to receive IAI, and shift to open surgery are the exclusion criteria.

10. Inclusion criteria

Patients of ASA I-II grade and assigned for unilateral meniscus repair under spinal anesthesia and were free of exclusion criteria were included in the study.

11. Randomization

Randomization was achieved using a software program to generate a sequence for cases with even number dropping and the developed sequence was translated to numbered cards carrying the abbreviation for the groups and the patient was asked to choose a card and introduce it to the anesthetist in charge.

12. Grouping

All patients received IAI of bupivacaine 0.25%; 18 ml in addition to one of the following adjuvants in 2 ml to complete the amount injected to 20 ml: Control group (C-Group): received 2 ml saline as a placebo additive to bupivacaine; Study group I (SI-Group) received DXM 2 µg/kg, SII-Group received DXM 1 µg/kg in combination with ketamine 0.5 mg/kg, SIII-Group received DXM 1 µg/kg in combination with DXA 8 mg and SIV-group received DXM 1 µg/kg in combination with ketorolac 30 mg.

13. Anesthetic technique

Preoperative heart rate (HR), and mean arterial pressure (MAP) were non-invasively determined and monitored during surgery. All patients were preloaded with 500 ml of lactated Ringer's solution. The patient was adjusted in the sitting position,

after sterilization of the back, a 25-gauge spinal needle was inserted at the level of L4–5 or L3–4 and an intrathecal injection of 12.5 mg of bupivacaine 0.5% was performed. After completion of injection and needle withdrawal a sterile sponge was applied to the injection site, and the patient was turned to a supine position. The level of sensory block at T8–10 was assured and a pneumatic tourniquet was applied to the thigh and was inflated up to 250–350 mmHg and pressure was maintained till the end of surgery. After the surgery, intra-articular administration of the study drugs was aseptically accomplished through the arthroscopy ports by the anesthetist in charge, and the tourniquet was deflated 10-min after IAI of the study drug.

14. Monitoring

(1) Intraoperative (IO) HR and MAP were continuously non-invasively monitored till the end of surgery.
(2) The need for a shift to general anesthesia, duration of surgery, duration of tourniquet application, need for supplemental IO analgesia and development of IO complications were recorded.
(3) PO monitoring included the following points
   a. HR and MAP measures were determined at 1-h, 2-h, 4-h, and 8-h after IAI.
   b. PO pain data
      – Pain severity was assessed using an 11-point numeric rating scale (NRS) with 0 indicating no pain, and 10 indicating the worst pain imaginable[15].
      – Times of pain assessment: pain was assessed at PACU transfer and hourly for four hours and at 8-h and 12-h PO.
      – Type of the assessed pain: pain scores were determined at rest with knees in the neutral position and at flexion and extension movement of the knee when the effect of spinal anesthesia faded away; mostly at 4-h PO.
      – Duration of PO analgesia as defined by the duration since IAI till pain sensation defined as NRS of ≥4.
      – Rescue PO analgesia was provided at NRS of ≥4 in the form of morphine 5 mg diluted in 10-ml saline and given slowly intravenously as 2-ml till pain relief, and the total dose of morphine used was determined.
   c. PO Sedation: the Ramsey sedation scale (RSS) was used to assess PO sedation[16] at 1-h, 2-h, 4-h and 8-h after IAI
   d. The frequency of PO adverse events especially hypotension, bradycardia, nausea and vomiting, anxiety, and hallucination.
   e. Patients' satisfaction with the provided PO analgesia using IAI was evaluated by asking the patients about how much they evaluated their experience with the analgesia provided by IAI. Patients' satisfaction was assessed using a 4-point Likert scale with 1 indicating very satisfied, and 4 indicating very unsatisfactory [17].
   f. Surgeon satisfaction by the applied PO analgesia through IAI was assessed at the time of patient discharge using a 100-point satisfaction visual analogue score (VAS) with 0 indicating the surgeon was not satisfied and 100 indicating the surgeon was entirely satisfied [18].

15. Study outcomes

(1) The primary outcome is the efficacy of IAI of DXM for post-arthroscopic meniscus repair analgesia in comparison to IAI bupivacaine as judged by NRS pain scores.
(2) Secondary outcomes include
   – The analgesic efficacy of DXM (1 µg/kg) used in a mixture with other analgesics as judged by the duration till requesting 1st PO rescue analgesia and times of requesting the rescue analgesia.
   – Patients' and surgeons' satisfaction scorings by the applied IAI analgesia.

16. Statistical analysis

The intergroup differences were evaluated for significance using the One-way ANOVA test, the intra-group differences were tested for significance using the paired t-test and differences in data presented as percentages were analyzed using the Chi-square test. Statistical analyses were conveyed using the SPSS software Ver. 26; 2019 (IBM, NY, USA). A P-value of 0.5 was used as the cutoff point for significance.

17. Results

Throughout the study duration, 171 patients who had meniscus injuries requiring operative interference were evaluated and 21 patients were excluded; 5 patients refused to receive neuraxial anesthesia, 3 patients had a bilateral injury, 4 patients were ASA III, 5 patients were obese grade II, 3 patients had osteoarthritis, and one patient refused to participate in the study. The remaining 150 patients were randomly distributed between the study groups; 30 patients per group (Figure 1). The enrolment data of the studied patients showed insignificant differences as shown in Table 1.

The recorded HR and MAP measures during surgery showed insignificant intergroup differences compared to

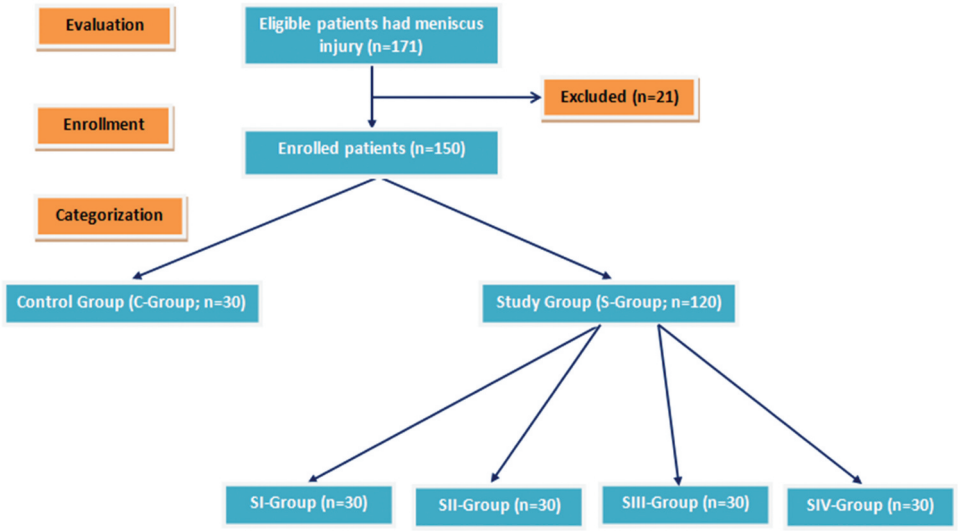

Figure 1. Study patients' flow sheet.

Table 1. Enrolment data of the studied patients.

Data	Group	C	SI	SII	SIII	SIV	P
Age (Years)	Mean (± SD)	40.9 ± 5.8	42.4 ± 9.9	40 ± 7.2	40.3 ± 11	40 ± 8.7	0.807
Gender	Male	19 (63.3%)	23 (76.7%)	20 (66.7%)	17 (56.7%)	21 (70%)	0.558
	Female	11 (36.7%)	7 (23.3%)	10 (33.3%)	13 (43.3%)	9 (30%)	
BMI (kg/m^2)	Average	2 (6.6%)	3 (10%)	0	0	0	0.095
	Overweight	17 (56.7%)	11 (36.7%)	10 (33.3%)	16 (53.3%)	14 (46.7%)	
	Obese-I	11 (36.7%)	16 (53.3%)	20 (66.7%)	14 (46.7%)	16 (53.3%)	
	Mean (± SD)	28.86 ± 2.5	29.6 ± 2.9	30.2 ± 2	29.49 ± 1.9	28.8 ± 2.7	0.347
ASA	Grade-I	21 (70%)	24 (80%)	20 (66.7%)	21 (70%)	23 (76.7%)	0.771
	Grade-II	9 (30%)	6 (20%)	10 (33.3%)	9 (30%)	7 (23.3%)	
Side	Right	13 (43.3%)	12 (40%)	16 (53.3%)	10 (33.3%)	12 (40%)	0.622
	Left	17 (56.7%)	18 (60%)	14 (46.7%)	20 (66.7%)	18 (60%)	

BMI: Body mass index; ASA: American Society of Anesthetisits.

each other and to the C-Group. Operative and tourniquet times also showed insignificant differences between the studied groups. Moreover, no need for a shift to general anesthesia was recorded, no additive systemic IO analgesia was required by all patients and no complications were encountered during surgery (Table 2).

The mean HR and MAP measures recorded after IAI showed insignificant intergroup differences throughout the observation period for 8-h (Table 3).

Pain scores were progressively increased during the PO observation period during rest and on joint movement. Pain scores showed insignificant differences between the four study groups, despite being in favor of patients who received DXM in dose of 2 µg/kg (SI-Group). Further, the determined pain scores of patients of the study groups were significantly lower in comparison to the pain scores of patients of the C-Group. Moreover, the cumulative pain scores of patients of the study groups were significantly lower in comparison to those of patients of the C-Group, but the intergroup differences between the study groups showed insignificant differences (Figure 2).

The frequency of requesting rescue analgesia after IAI was significantly lower in all the study groups in comparison to the C-Group. Sixty-five patients of the study groups (54.2%) did not

Table 2. Operative data of the studied patients.

Data	Group	C	SI	SII	SIII	SIV	P
IO heart rate (beats/min)	Preoperative	86.6 ± 4.6	85.3 ± 3.3	86.3 ± 5.3	85.4 ± 3.1	86.5 ± 4.8	0.644
	15-min	81.2 ± 4	78.8 ± 3.5	79.7 ± 4.7	79.3 ± 2.2	80 ± 3.4	0.126
	30-min	79.4 ± 4.5	76.6 ± 4.6	77.6 ± 4.4	77.4 ± 3.3	79.2 ± 4.5	0.054
	45-min	81 ± 7.4	76.3 ± 5.9	78.5 ± 5.4	78 ± 4.7	78.2 ± 6	0.051
	End of surgery	79.6 ± 3.3	77 ± 4.9	77.5 ± 4.6	77.2 ± 4.1	78.3 ± 3.2	0.091
IO mean arterial pressure (mmHg)	Preoperative	84.8 ± 2	82.9 ± 3	82.5 ± 5.2	81.8 ± 5	82.3 ± 4.3	0.055
	15-min	79.4 ± 2.5	78.1 ± 3.9	78.2 ± 4.9	78.1 ± 3	78 ± 4.2	0.582
	30-min	75 ± 2.4	74.4 ± 3.5	76 ± 4.4	74.9 ± 3	74.8 ± 4	0.492
	45-min	79.3 ± 2.9	78.5 ± 3.7	79.7 ± 4.6	79 ± 2.4	79.7 ± 4.8	0.706
	End of surgery	81 ± 2	81.9 ± 3.1	82.2 ± 4.7	83 ± 2.8	82.5 ± 4.1	0.238
Operative time (min)		56.6 ± 7.8	55.6 ± 4.7	55 ± 6.8	58.5 ± 6	56.7 ± 7.3	0.306
Tourniquet time (min)		66.9 ± 7.5	64.8 ± 7.1	67.2 ± 8	68.2 ± 7.5	66 ± 9.6	0.524

Table 3. Mean (± SD) of HR and MAP measures recorded after IAI.

		C	SI	SII	SIII	SIV	P
Heart rate (beats/min) after IAI	1-h	84.3 ± 4.2	83.7 ± 4.5	83.4 ± 5.1	83.9 ± 3.4	84 ± 5.2	0.964
	2-h	81.6 ± 5.4	79 ± 5.2	81.4 ± 6.3	81.6 ± 4.7	82.7 ± 7.2	0.166
	4-h	79.9 ± 7	77 ± 6	78.7 ± 6.3	78.5 ± 5.4	79 ± 7	0.518
	8-h	82.4 ± 3.6	79.1 ± 5.4	80.8 ± 6.5	80.2 ± 6.6	80 ± 7.5	0.593
Mean arterial pressure (mmHg) after IAI	1-h	78.3 ± 6.8	74.9 ± 7.2	75.5 ± 6.1	76.7 ± 4.6	76.8 ± 5.3	0.235
	2-h	76.7 ± 5.6	73.8 ± 7.2	74.6 ± 6.6	75.7 ± 6	76 ± 6.2	0.414
	4-h	78.8 ± 6.2	74.1 ± 8.2	76.3 ± 7.4	76.2 ± 8.1	76.6 ± 7.7	0.215
	8-h	80.7 ± 5.3	76.8 ± 5.2	78.6 ± 7.2	79.5 ± 6	77.1 ± 4.8	0.051

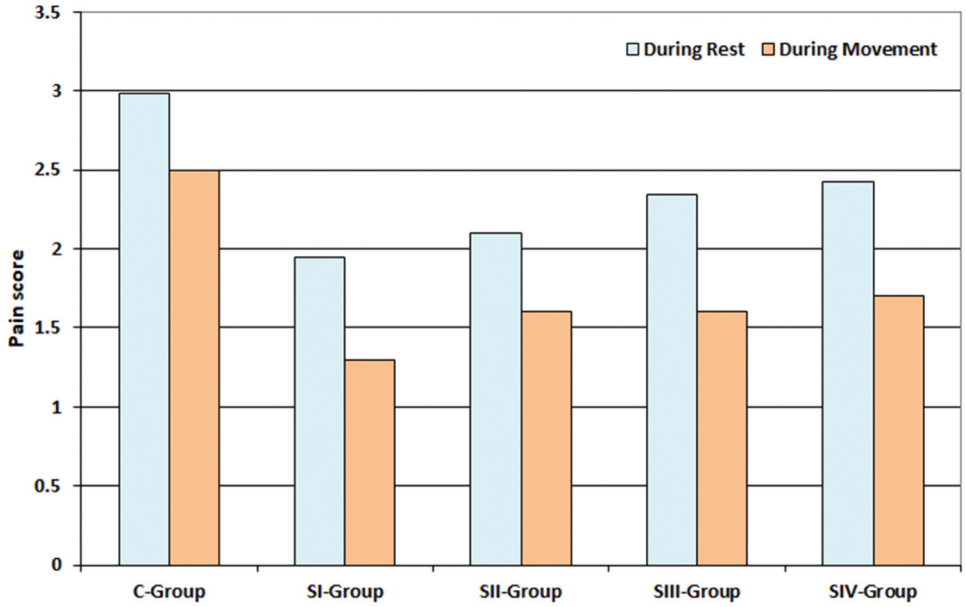

Figure 2. The cumulative NRS PO pain score of patients of the studied groups.

request rescue analgesia, while 55 patients (55.8%) requested it once with insignificant intergroup differences. However, the difference in the frequency of requesting rescue analgesia after IAI was significant between the C-Group and the study groups (Figure 3).

Duration till the 1st request of rescue analgesia after IAI showed insignificant differences between the study groups, while was significantly shorter in the C-Group in comparison to each of the study groups. The mean value of the total dose of morphine consumed by patients of C-Group after IAI was significantly higher

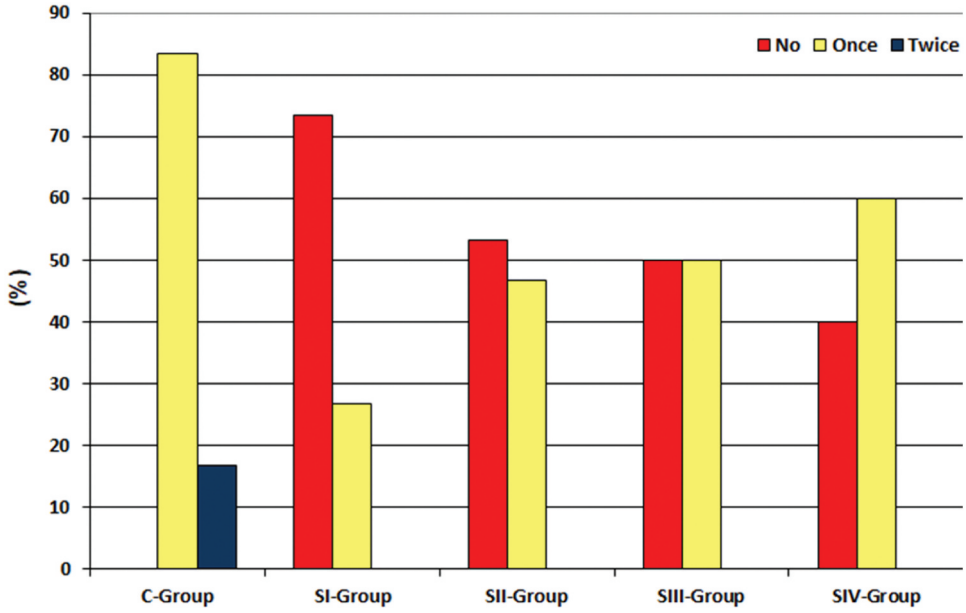

Figure 3. Patients' distribution according to times of requesting rescuse analgesia.

in comparison to that consumed by patients of each of the study groups with insignificant difference between study groups (Table 4, Figure 4).

At the time of PACU admission, all patients had RSS of 2, but the frequency of patients who had RSS = 3 among the study groups started to increase since 4-h after IAI ($n = 3$; 2.5%) and peaked at 8-h where 23 patients (19.2%) had RSS = 3, while 94 patients (78.3%) had RSS = 2 and 3 patients of SII-group had RSS = 1. The frequency of patients who had RSS of 2 at 8-h IAI was significantly lower in all groups in comparison to the frequency at PACU admission. During the PO period, 38 patients developed adverse events that were maximal in C-Group ($n = 12$; 40%) and SII-Group ($n = 11$; 36.7%) and were minimal in SIII-Group ($n = 2$; 6.7%). The incidence of adverse events was significantly lower in SIII-Group in comparison to C-Group ($p = 0.0022$), SI-Group ($p = 0.037$) and SII-Group ($p = 0.0048$) and was significantly lower in SIV-Group in comparison to C-Group ($p = 0.045$), while differences between other groups were insignificant (Table 5).

Table 4. PO pain data of the studied patients.

Data	Group	C	SI	SII	SIII	SIV	P
NRS pain scores during rest at	Admission	1 ± 0.7	0.8 ± 0.8	0.9 ± 0.9	1.1 ± 0.8	0.9 ± 0.9	0.595
	1-h PO	1.5 ± 0.9	0.9 ± 0.8	0.9 ± 0.9	1.2 ± 0.8	1.1 ± 1	0.492
	Significance vs. C-Group		0.009	0.004	0.231	0.097	
	2-h PO	2.1 ± 0.8	1.1 ± 0.8	1.2 ± 0.8	1.4 ± 0.8	1.5 ± 0.9	0.253
	Significance vs. C-Group		<0.001	<0.001	0.004	0.022	
	3-h PO	2.4 ± 0.9	1.3 ± 0.8	1.7 ± 0.9	1.6 ± 0.9	1.8 ± 1	0.159
	Significance vs. C-Group		<0.001	0.001	0.004	0.017	
	4-h PO	2.4 ± 1.4	1.4 ± 0.9	1.8 ± 1	1.7 ± 0.9	1.9 ± 1.1	0.236
	Significance vs. C-Group		0.001	0.048	0.017	0.105	
	8-h PO	2.3 ± 1.6	1.8 ± 1	2.1 ± 0.9	2.3 ± 1.1	2.5 ± 1.1	0.085
	Significance vs. C-Group		0.184	0.576	0.804	0.569	
	12-h PO	3.2 ± 0.8	2.4 ± 0.9	1.9 ± 1.3	2.7 ± 1.5	2.4 ± 1.7	0.385
	Significance vs. C-Group		0.001	<0.001	0.011	0.024	
	Cumulative	2.98 ± 0.4	1.95 ± 1	2.1 ± 0.8	2.34 ± 0.7	2.42 ± 0.6	0.067
	Significance vs. C-Group		<0.001	<0.001	<0.001	<0.001	
Pain scores on joint movement	4-h PO	2.2 ± 0.9	0.7 ± 0.6	0.9 ± 0.6	1 ± 0.6	1.1 ± 0.8	0.123
	Significance vs. C-Group		<0.001	<0.001	<0.001	<0.001	
	8-h PO	2.7 ± 0.9	1.3 ± 1	1.5 ± 0.8	1.8 ± 0.7	1.8 ± 1	0.083
	Significance vs. C-Group		<0.001	<0.001	<0.001	0.002	
	12-h PO	2.5 ± 1.6	1.5 ± 1	2.3 ± 1	2 ± 1.2	2.4 ± 1.3	0.424
	Significance vs. C-Group		0.089	0.601	0.219	0.506	
	Cumulative	2.5 ± 0.4	1.3 ± 0.7	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.8	0.137
	Significance vs. C-Group		<0.001	<0.001	<0.001	<0.001	
Times of requesting rescue analgesia	No	0	22 (73.3%)	16 (53.3%)	15 (50%)	12 (40%)	0.069
	Once	25 (83.3%)	8 (26.7%)	14 (46.7%)	15 (50%)	20 (60%)	
	Two	5 (16.7%)	0	0	0	0	
	Significance vs. C-Group		<0.001	<0.001	<0.001	0.0001	
Duration of analgesia (h)		7.4 ± 3.7	10 ± 3	8.1 ± 3.8	8.9 ± 3.4	8.8 ± 3.7	0.755
	Significance vs. C-Group		0.0003	0.0046	0.032	0.0022	
	Mean (± SD)	5.5 ± 1.2	3.5 ± 0.8	4 ± 1	4.2 ± 0.8	3.8 ± 0.8	0.262
			<0.001	0.0004	0.0004	<0.001	

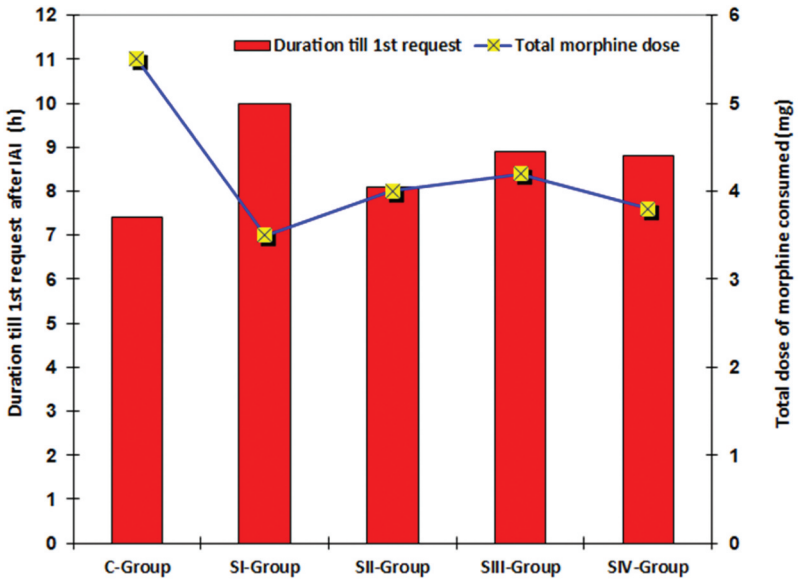

Figure 4. Mean values of duration till the 1st request of rescue analgesia & the total dose consumed after IAI by patients of the study groups.

Table 5. Adverse events encountered during PO observation of the studied patients.

Data	Group			C	SI	SII	SIII	SIV
Ramsay sedation score	Admission		1:2:3	0:30:0	0:30:0	0:30:0	0:30:0	0:30:0
	Time after IAI	1-h	1:2:3	0:30:0	0:30:0	0:30:0	0:30:0	0:30:0
		2-h	1:2:3	0:30:0	0:30:0	2:28:0	0:30:0	0:30:0
		4-h	1:2:3	0:25:5	0:30:0	3:27:0	0:27:3	0:30:0
		8-h	1:2:3	0:23:7	0:27:3	3:19:8	0:25:5	0:23:7
	A p-value of difference of admission vs. 8-h score			0.0049	0.076	0.0012	0.019	0.0049
Incidence of PO hypotension				5 (16.7%)	3 (10%)	2 (6.7%)	1 (3.3%)	2 (6.7%)
Incidence of PO bradycardia				4 (13.3%)	3 (10%)	3 (10%)	1 (3.3%)	1 (3.3%)
Incidence of PONV				3 (10%)	2 (6.7%)	3 (10%)	0	2 (6.7%)
Total PO adverse events	Incidence			12 (40%)	8 (26.7%)	11 (36.7%)	2 (6.7%)	5 (16.7%)
	Significance versus	C-Group			0.273	0.791	0.0022	0.045
		SI-Group				0.405	0.037	0.347
		SII-Group					0.0048	0.079
		SIII-Group						0.228

Patients' distribution according to satisfaction grade showed a significantly higher frequency of very satisfied patients among IAI groups in comparison to the C-Group with insignificant differences between patients who received IAI according to the frequency of very satisfied patients. Satisfaction score was significantly lower in the study groups except for the SII-Group which showed an insignificantly lower score in comparison to the score of patients of C-Group with insignificant differences between the study groups. Surgeons' satisfaction scores by the effect of DXM IAI were significantly higher than by placebo with significantly higher scores by the effect of IAI applied for SI-Group than that applied for SII ($p = 0.0002$) and SIV ($p < 0.001$) groups, while the difference was insignificant ($p = 0.065$) in comparison to SIII-Group. Moreover, surgeons' satisfaction score by outcomes of IAI applied for patients of SIII-Group was significantly higher than their satisfaction by SII-group ($p = 0.017$) and SIV-Group ($p < 0.001$) with insignificant difference between the latter groups (Table 6).

18. Discussion

The obtained results could assure the null hypothesis of the current study that the use of DXM alone in dose of 2 µg/kg or 1 µg/kg mixed with other analgesics for analgesia after therapeutic knee arthroscopy via intra-articular injection would provide analgesia with insignificant difference in pain scores during rest or with knee movement. Further, all the provided preparations for DXM IAI allowed reduction of pain scores and the requests for morphine as rescue analgesia with significant differences versus placebo IAI.

In line with the efficacy of DXM as the sole IAI, a systemic review and meta-analysis demonstrated the efficacy of IAI of DXM and documented improved pain outcomes in the early PO period after knee arthroscopy versus placebo [19]. In line with the obtained results, previous comparative studies of the additive effect of DXM (1 µg/kg) versus DEX (8 mg) [12] or DXM (0.5 µg/kg) versus magnesium (10 mg/kg) [20] to bupivacaine IAI reported significantly lower pain scores, lower consumption of PO rescue analgesia and longer duration of analgesia than bupivacaine alone. Then, **El Baz & Farahat** [21] found adding DXM to the IAI of levobupivacaine after knee arthroscopy provided lower pain scores, prolonged time to the 1st request for systemic PO analgesia with reduction of the dose used than levobupivacaine alone. Also, **Diab et al**. [22] compared the efficacy of adding 1 mg morphine versus 1 µg/kg DXM to IAI of a mixture of local anesthetics with epinephrine for anesthesia and PO analgesia after knee arthroscopy and detected comparable analgesic efficacy of both additives.

Recently, **Salem et al**. [23] compared the analgesia yield of IAI using bupivacaine with 100 µg DXM or with 50 µg fentanyl versus placebo and found both adjunctive provided significantly lower PO static and dynamic pain scores till 8-h PO. Also, **Amer & Al-Ahwal** [24] detected comparable outcomes of IAI of DXM (1 µg/kg) or tramadol with significant differences versus placebo as regards the time to the 1st request of analgesia, the incidence of PO pain and PO morphine requirements

Table 6. Patients' and Surgeons' satisfaction with the effect of IAI.

Data	Group		C	SI	SII	SIII	SIV
Patients' satisfaction	Grade	Very satisfied (Score=1)	6 (20%)	17 (56.6%)	15 (50%)	15 (50%)	15 (50%)
		Satisfied (Score=2)	20 (66.7%)	11 (36.7%)	11 (36.7%)	14 (46.7%)	12 (40%)
		Unsatisfied (Score=3)	4 (13.3%)	2 (6.7%)	4 (13.3%)	1 (3.3%)	3 (10%)
	Significance vs. C-Group			0.014	0.039	0.034	0.048
	Score		1.93 ± 0.6	1.5 ± 0.6	1.63 ± 0.7	1.53 ± 0.6	1.6 ± 0.7
	Significance vs. C-Group			0.0076	0.081	0.0095	0.045
Surgeons' satisfaction	Score		71 ± 9.7	86.5 ± 7.2	79 ± 7.5	83.3 ± 6	75.7 ± 5
	Significance versus	C-Group		<0.001	0.0007	<0.001	0.022
		SI-Group			0.0002	0.065	<0.001
		SII-Group				0.017	0.050
		SIII-Group					<0.001

and **Nesioonpour et al**. [25] using IAI of DXM (2 μg/kg) after knee arthroscopy, reported significant PO pain relief with reduced analgesic consumption and increased the time till the 1st analgesic request compared to placebo. Thereafter, **Paul et al**. [26] documented that the use of DXM (1 μg/kg) for IAI increased the duration of PO analgesia, offered improved quality of analgesia and reduced the total dose of rescue analgesics needed versus placebo in patients undergoing arthroscopic knee surgeries.

In support of the higher analgesic efficacy of using IAI of a cocktail of DXM with other analgesics than DXM or other analgesics when used solely, **Avci et al**. [27] tried IAI of DXM (1 μg/kg) or levobupivacaine alone or in combination versus placebo after knee arthroscopy and found pain scores at rest were significantly lower till 24-h PO, time to take the 1st analgesia was significantly longer and total analgesic consumption was significantly lower in combination group compared to other groups. Also, **Ülgey et al**. [28] reported significantly lower PO morphine requirements and consumption, and pain scores during the 24-h PO period with the use of IAI of a cocktail of DXM 100 μg and levobupivacaine IAI than levobupivacaine alone, and found the time to start PO rehabilitation was significantly shorter with a cocktail than with levobupivacaine alone.

The reported analgesic effects of DXM might be attributed to its local suppressive effect on the trauma-induced local release of nociceptive cytokines within the joint cavity and in joint cartilage and synovial membrane and for the surgically induced cytokines' release. This attribution coincided with **Gomes et al**. [29], who used an animal model of osteoarthritis and found IAI of DXM in doses of 1 and 3 μg/kg significantly improved pain threshold throughout the entire experiment and reduced levels of tumor necrosis factor-α levels on day 28 compared with the osteoarthritis group without causing any additional damage to the synovial membrane.

Unfortunately, the literature review failed to detect a comparative study of IAI of combinations similar to that used in the current study. However, multiple studies documented the efficacy of the used additives for IAI, where **Salman et al**. [30] reported a better analgesic effect, early mobilization and less need for additional analgesics with IAI of ketamine compared to tramadol or magnesium and **Xu et al**. [31] found patients who received ketorolac as additive to multimodal IAI injection experienced lower VAS scores for 48-h PO, with significantly longer duration till receiving the initial analgesic dose and significant reduction of the total dose used. Furthermore, **Sağir et al**. [32] compared the IAI of ketamine in dose 0.5 or 1 mg/kg versus saline and reported significantly lower pain scores at rest and during movement with ketamine versus saline with the comparable effect of both doses, but higher dose decreased opioid requirement in the early PO period, but at the end of 24-h PO the total consumed dose of morphine was comparable between the three groups. Recently, **Niaz et al**. [33] tried ketorolac 30 mg IAI versus lidocaine after arthroscopic knee surgery and detected significantly better analgesia after ketorolac IAI at 4-h PO.

The reported insignificant differences in the incidence of adverse events between patients who received combination IAI as intergroup difference and in comparison to placebo indicated the safety of these drugs. Regarding hypotension, the most common post-spinal complication, DXM did not significantly increase the incidence of hypotension compared to placebo with insignificant MAP measures. This could be attributed to the minimal or non-absorption of the constituents of IAI from the joint cavity. In support of this assumption, **Knych et al**. [34] using an animal model, detected DXM plasma concentrations fell below the limit of quantification; i.e., 0.005 ng/ml, 2.5 and 8-h after IAI of 1 and 5 μg/kg, respectively, and DXM was not detected in urine samples at any time after IAI, while synovial fluid concentrations of DXM were higher than 0.1 ng/ml. Clinically, **Diab et al**. [22] reported more hemodynamic stability with DXM than morphine as additives to IAI of local anesthetics.

All patients were managed as day-case surgery and were discharged to home at 12-h after IAI. This might be attributed to the effectiveness of IAI for the reduction of pain and consumption of PO narcotics with subsequent reduction of side effects. In support of the efficacy of IAI, **Mittal et al**. [35] reported no significant difference in pain scores and analgesic requirement between IAI and ultrasound-guided adductor canal block in arthroscopic knee surgeries, but IAI was easier and did not require proficiently needed for nerve block under US guidance.

Also, the reported outcomes of IAI through the arthroscopic port as a single-shot injection spared the need for an intra-articular catheter for continuous joint flushing and thus reduced the procedure costs and preserved resources and went in hand with **Fitz et al**. [36] who documented that the intra-articular catheter does not improve 48-h pain scores or opioid consumption despite of the very low overall pain scores.

19. Conclusion

The IAI of DXM alone or in combination with any other analgesic is a feasible, effective and safe analgesic modality for post-arthroscopic surgeries. DXM (2 μg/kg) provided superior analgesia despite being comparable to DXM (1 μg/kg) with another additive. DXM (1 μg/kg) with ketamine is the best combination in terms of reduction of pain score and opioid consumption, but side effects may limit its use. DXM (1 μg/kg) with DEX is an efficient

analgesic combination with the best PO course and minimal side effects. Combined DXM (1 µg/kg) and ketorolac provide efficient analgesia with cost reduction, but the duration of analgesia is a limitation for its use.

20. Limitation

The lack of previous research to compare the effect of IAI on similar combinations is the limitation of this study.

21. Recommendations

Wider scale multicenter studies are mandatory to establish the best combination to be recommended for similar cases.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Availability of data and material

Data is available when required.

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