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Research article

Intra-articular versus intravenous administration of dexmedetomidine in arthroscopic knee surgeries under local anesthesia: A prospective randomized study

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ABSTRACT

Background: An intra-articular injection is considered the leading method for postoperative analgesia after knee surgery. Dexmedetomidine has peripheral and central analgesic effect. The study was conducted to compare between the analgesic effect of intra-articular and intravenous dexmedetomidine in arthroscopic knee surgery.
Methods: One hundred patients underwent elective arthroscopic knee surgery had randomly allocated into two equal groups. **(Group IA)** the patients had received 1 μg/kg dexmedetomidine added to local anesthetic bupivacaine intra-articularly while **(Group IV)**: the patients had received 1 μg/kg dexmedetomidine added to 20 ml saline over 10 min starting with local intra-articular anaesthesia. Pain VAS, heart rate, mean arterial blood pressure, total requirement for analgesic, the first request for it, and first time to mobilize within the first 24 h were assessed.
Results: The VAS were significantly lower in IA group at 4 and 6 h during rest and at 4, 6, 12 h during motion, Also, the duration of first analgesic request was significantly prolonged in IA group than IV group (11 h ± 2.2 vs 9.2 h ± 3.2, respectively) (p value .001). Moreover, the total analgesic consumption was significantly lesser IA group compared with that in IV group (87 ± 27.7 mg Vs 108 ± 37.6 mg, respectively) (p value .002). No postoperative adverse effects were recorded.
Conclusion: Intra-articular dexmedetomidine when added to local anaesthesia improves the postoperative analgesic profile with decrease the needs for postoperative analgesia and prolong the time for analgesic request.
Clinical trial registration: NCT02730845.

1. Introduction

In current times, arthroscopic knee surgery is becoming increasingly popular with a fundamental quest of ameliorating postoperative pain, and hopefully resulting in early rehabilitation and shortening the length of hospital stay [1].

Intra-articular anaesthesia is preferential than other forms of anaesthesia as it is easy, cost-effective, safe and devoid of systemic adverse events [2]. Additionally, it postoperatively transcends regional anaesthesia by dint of the preservation of quadriceps function which is fundamental in the early functional recovery [3]. As offering short-term analgesia, many drugs had been added to the local anesthetics as ketamine, ketorolac, magnesium, opioids, tramadol, and α_2 agonists such as clonidine and dexmedetomidine [4–9].

Dexmedetomidine, as a highly selective α_2-adenoreceptor agonist, is approximately 8 folds as potent as clonidine. Its analgesic effects have been proven in a handful of studies when given intravenously [10,11] or intra-articularly [12–15]. To the best of our knowledge, only one study compared both routes of administration under general anaesthesia [12]; nonetheless, the analgesic effect of dexmedetomidine with intra-articular anaesthesia has not been investigated yet. So in this study we hypothesis that the addition of dexmedetomidine to bupivacaine when injected intra-articularly will potentiate its analgesic effect compared with intravenous dexmedetomidine.

Therefore, this study was conducted to compare intra-articular and systemic administration of dexmedetomidine regarding potency and the duration of analgesia and its effect on patient recovery in patients undergoing elective knee arthroscopic surgery under local intra-articular anaesthesia.

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2. Methods

This prospective randomized double–blinded study was carried out for 100 patients subjected for elective primary unilateral meniscectomy done under local intra-articular anaesthesia. Patients aged from 18 to 50 years of either sex and categorized as ASA I or II were included in this study. The study had begun after receiving the approval from the local ethical board then an informed written consent was taken from the patient before enrollment. The presence of cardiovascular, renal or hepatic diseases, uncontrolled diabetes, coagulopathies, pregnancy or patients receiving β adrenergic blockers, clonidine α-methyldopa, as hypertension treatment were excluded from the study. Patients refusal, mentally retarded, or with psychiatric disease, having any contra-indication or allergy to the study drugs, or infection at the site of injection, use of opioid or non-opioid analgesics within the previous 24 h were also excluded. Moreover, patients who had prior ipsilateral knee surgery or infection at site of injection were excluded.

At the preoperative visit, all patients were thoroughly evaluated and routine laboratory investigations were done. Detailed description of anesthetic technique and visual analogue scale (VAS) with 0 = no pain, and 10 = worst pain were explained and recorded as basal reading for every patient.

Intraoperative, an intravenous line was secured with intravenous cannula (18 G) in suitable peripheral vein and standard intra-operative monitors (ECG, pulse oximeter, non-invasive arterial blood pressure) were connected to each patient and basal hemodynamics were recorded. All patients were premedicated using IV midazolam 0.03 mg/kg ten minutes before starting the operation. Both intra-articular and intravenous solutions were prepared by a nurse not participating in the study or data recording by aspiration of (1 ml) dexmedetomidine which contain 100 mcg of dexmedetomidine by insline syringe. Therefore each one unit of syringe contain 1 mcg of dexmedetomidine. The solutions were added to local anesthetic according to the body weight of the patient and randomization. Then the prepared syringes delivered to the anesthetist who sharing in the study to perform the intra-articular anaesthesia. Under complete aseptic conditions the skin at each arthroscopic portal sites were anaesthetized by injecting a mixture of 2% lidocaine 5 ml with 1:200,000 epinephrine.

3. Randomization

By using a computer –generated randomization program, the eligible patients were randomized into two equal groups. Each group had 50 patients. The randomization was done by a third person who were not involved in the anesthetic procedure or outcome assessment.

The intra-articular group **(Group IA)**: The patients had received 19 ml bupivacaine 0.5% with1 μg/kg (1 ml) of dexmedetomidine (total volume 20 ml) intra-articularly plus IV 20 ml saline infused over 10 min starting with local intra-articular anaesthesia.

The intravenous group **(Group IV)**:The patients had received19 ml bupivacaine 0.5% with 1 ml saline (the same total volume 20 ml) intra-articularly in addition to 20 ml of IV saline containing 1 μg/kg dexmedetomidine over 10 min starting with local intra-articular anaesthesia.

Spread of intra-articular solution was helped by several times flexion and extension of the knee joint then 20 min were allowed for anaesthesia to take effect. No pump, leg, holder, tourniquet or surgical drain were used during the operation. The patients were capable to view the video monitor during the procedure. The operations were performed by the same surgeon.

After transference of the patients to the post-anesthetic care unit (PACU) whereby hemodynamics were monitored (heart rate and mean arterial pressure) at 1, 2, 4, 6, 12 and 24 h by a resident unaware of any of the study drugs or groups. The severity of pain assessed by VAS every 15 min in the first hour, then at 2, 4, 6, 12, and 24 h both at rest and at motion (active knee flexion of 0–90°). Diclofenac sodium75 mg was given IV when VAS ≥ 4. But if the pain not reduced and VAS still > 5 so 0.5–1 mg/kg pethidine was given. The first request for postoperative analgesia and the total dose of analgesic needed during the first 24 h postoperatively and the time to first mobilization were recorded. Also, Observer's assessment of alertness and sedation (OAA/S) [16] was used to assess post-operative sedation after the end of surgery and before the patient discharge to the PACU. Any intra or postoperative adverse effects such as nausea, vomiting, hypotension (known by any reduction of MAP > 25% from the baseline) and bradycardia (known by any decrease in HR < 45 beats/ min) were identified and treated. Patients' satisfaction was evaluated by using 5-grade scale ranging from 5 = very satisfied and 1 = very unsatisfied).

3.1. Sample size calculation

G power program (3.0.10) was used to calculate sample size with priory analysis. On basis of pilot study the VAS at 12 h difference was used as the priory effect. One tailed *t* test for difference between two independent means was the computed statistical test. Effect size was calculated as 0.6, α error was 0.05 and power (1-β error) of 0.95 was used. The resulted sample size was 46 patients for each group. To protect against drop out cases, 50 patients were enrolled per group.

The statistical analysis was done using SPSS version 20. Kolmogorov-Smirnov test was done to test the normality of distribution of data. The Categorical (qualitative) data were described as number and percentage. Association between these data was tested using Chi-square (x^2) or Fisher's exact test. While the Continuous (quantitative) data were described as mean ± SD and compared using student *t* test. Significance of normally distributed data was tested using Student *t*-test (unpaired); while Man-Whitney-*U* test was used to test significance of data away from normal distribution. The P-value was set at statistical significance of < .05. Additionally, the p-value supplied in the graphs are for the overall change (the slope of the two groups), and it was calculated by the Repeated measures ANOVA test.

4. Results

During the period of the study, 120 patients were selected for eligibility to been rolled in the study, 12 refused to participate and 8 hadn't met the inclusion criteria. So the remaining 100 patients were allocated and randomized according the study protocol (Fig. 1). Both groups were comparable regarding the mean age, sex, weight, duration of surgery and basal hemodynamic readings (Table 1).

There was a significant improvement of pain VAS in both groups when compared with the preoperative baseline. No statistical differences wererecorded in VAS pain scores among both groups till the fourth hour postoperatively. However, it was statistically significant better in the intra-articular group at the 4th, 6th hour postoperatively during rest and at the 4th, 6th and 12th hour at motion compared with IV group (Table 2).

The time elapsed before asking for postoperative analgesia was significantly longer in intra-articular group (11 h ± 2.2) when compared with IV group (9.2 h ± 3.2) (p = .001). Also the total analgesic consumption was significantly lower in the intra-articular group (87 ± 27.7 mg) in comparison with IV group (108 ± 37.6 mg) (p = .002) (Table 1). Moreover, the time needed for first mobilization of the limb was shorter in intra-articular group (16.2 min ± 1.7), compared with that in the IV group (19.3 min ± 1.1) (p < .001). Despite this, patient's satisfaction for the quality of analgesia during the first 24 h was comparable in both groups (Table 1).

The sedation score was significantly better in intra-articular group (5 ± 0) when compared with IV group (4.2 ± 0.3) (p = .007) as shown in (Table 3).

As regard the changes in HR readings, there were only one significant reading between the studied groups at 24 h, while there were a significant decrease in MBP in intravenous group more than the intra-

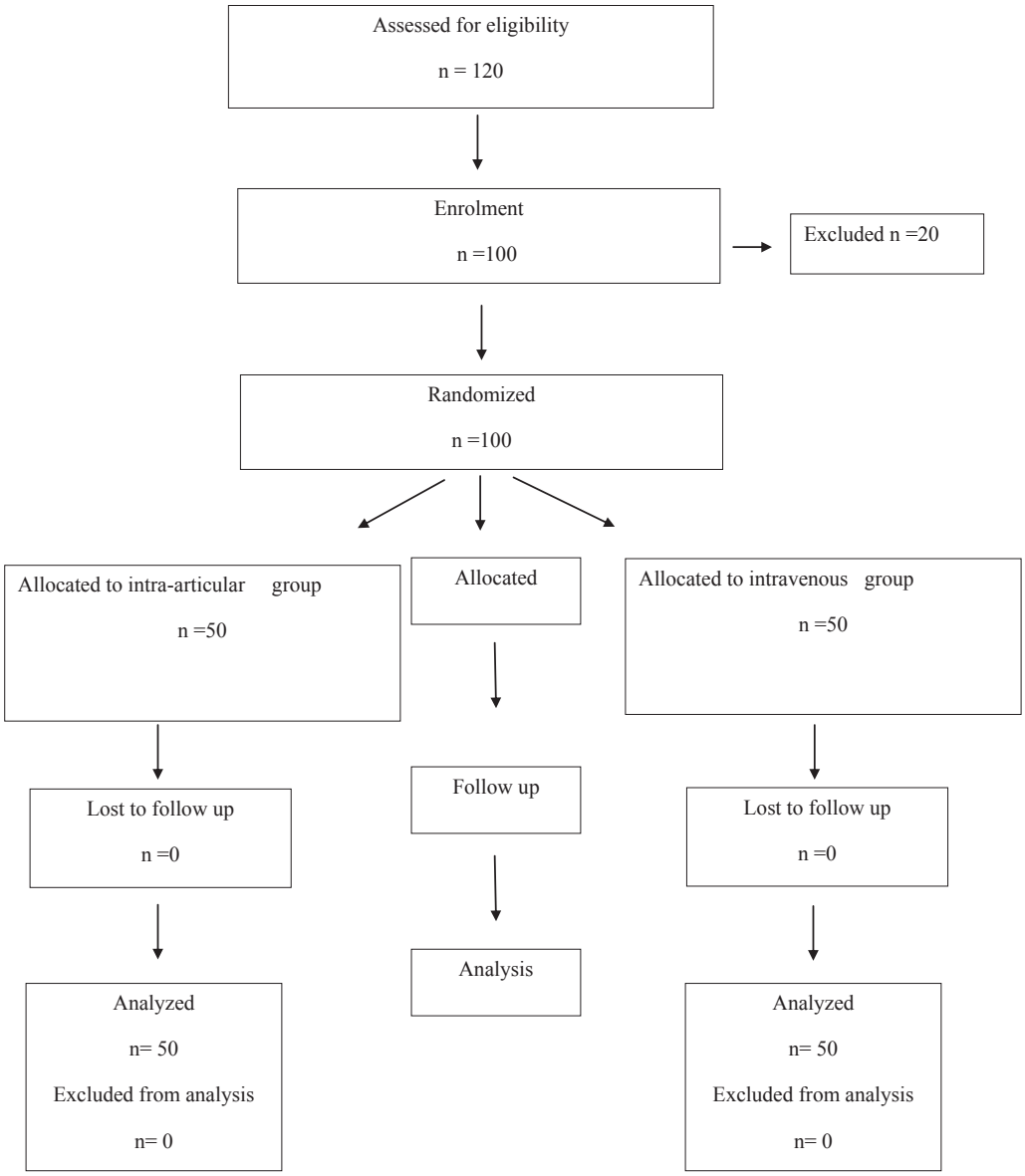

Fig. 1. CONSORT flow chart of patients through the clinical trial.

Table 1
Patient characteristics and basal hemodynamic in the studied groups. Data are expressed as Mean ± SD.

	Group IA Mean ± SD (n = 50)	Group IV Mean ± SD (n = 50)	P-value
Patient characteristics			
Age (years)	32.36 ± 10.28	31.88 ± 10.85	0.8
Sex (M/F)	26/24	30/20	0.4
Body mass index	30.38 ± 4.37	29.04 ± 5.03	0.1
Duration of surgery (min)	21.28 ± 5.51	21.64 ± 6.23	0.7
Basal hemodynamics			
Mean blood pressure (mmHg)	84 ± 5.9	82.5 ± 5.6	0.2
Heart rate (b/min)	75.4 ± 4.9	75.2 ± 4.5	0.8

articular group in all intraoperative reading (at 5, 10, and15 min) with p value (0.01, 0.005, and 0.03, respectively) (Fig. 2). No adverse effects of the drug were recorded.

5. Discussion

The main result of the study was that the presurgical intra-articular dexmedetomidine provides superior analgesic effects than presurgical intravenous drug administration regarding improved VAS, delayed time for first analgesic request, and decreased total analgesic consumption. Moreover patients were capable for earlier mobilization than IV group.

These results are comparable with the results obtained by El-Metwalli et al. [12] that intra-articular dexmedetomidine at the end of arthroscopic surgery, improved the postoperative pain and decreased the postoperative analgesic requirements from (129.3 in IV group reduced to 90.0 in IA group). Moreover the time for first analgesic request was longer in IA group 312.0 min versus 102.1. In contrast to this study the duration of analgesia lasted for the first 6 h in IA and for the first hour in the IV group.

Other investigators had added dexamedetomidine either intravenously [10,11] or intra-articularly [12–15]. Because the short duration of analgesic effect of intra-articular injection of local anesthetics nearly lasted for 4 h. Recently Panigrahi et al. [1] had tested the analgesic benefits of different doses of intra-articular dexmedetomidine. They concluded that the larger dose 2 μg/kg prolong the analgesic time (757 ± 207.6 min) against the smaller dose 1 μg/kg

Table 2
The recorded Visual Analogue Score during rest and motion in both groups. Values are presented as Median and (min–max).

	Group IA		Group IV		p-value
	Median	(min–max)	Median	(min–max)	
Basal	6	(4–9)	7	(4–10)	0.14
15 min	1	(0–2)	1	(0–2)	0.5
30 min	1	(0–2)	1	(0–2)	0.5
45 min	1	(0–2)	1	(0–2)	0.5
Rest					
1 h	1	(0–3)	1	(0–3)	0.36
2 h	1	(0–3)	1	(0–3)	0.47
4 h	1	(0–3)	2	(1–3)	0.008*
6 h	1	(0–2)	2	(1–3)	0.004*
12 h	2	(1–4)	3	(2–6)	0.6
24 h	3	(2–6)	4	(3–7)	0.7
Motion					
1 h	1	(0–2)	1	(0–2)	0.5
2 h	1	(0–2)	1	(0–2)	0.5
4 h	1	(0–3)	2	(1–3)	0.001*
6 h	1	(0–2)	2	(1–4)	0.001*
12 h	2	(0–4)	3	(1–4)	0.001*
24 h	3	(2–7)	4	(3–7)	0.9

* p value ≤ .05.

Table 3
Time of first mobilization, patient satisfaction, sedation score, first postoperative analgesic request and total analgesic consumption. Data are expressed as mean ± SD.

	Group IA Mean ± SD	Group IV Mean ± SD	P-value
Time of first mobilization (min)	16.2 ± 1.7	19.3 ± 1.1	0.001*
Patient satisfaction	4.3 ± 0.6	4.3 ± 0.7	1.0
Sedation score	5 ± 0	4.8 ± 0.3	0.007*
FPAR (h)	11 ± 2.2	9.2 ± 3.2	0.001*
TAC	87 ± 27.7	108 ± 37.6	0.002*

FPAR: first postoperative analgesic request; TAC: total analgesic consumption.
* Means p value ≤ .05.

(433 ± 54.3 min). Although our results matched with the results of larger dose, this could be attributed to the effect of spinal anaesthesia which continued nearly for (2–3 h) but after that time the patients explained pain and request analgesics.

The analgesic effect of intra-articular dexmedetomidine explained by studies done on clonidine as both being alpha 2 adrenergic receptors blockers. It mainly inhibits the transmission of painful stimuli within the posterior horn of the spinal cord [17,18] and inhibits the transmission of nerve signals through two type of fibers Aδ and C-fibers, and stimulates the release of enkephalin–like substances into the peripheral regions [19,20].

The most beneficial outcome from adequate postoperative pain control after knee arthroscopy is the early mobilization of the patient subsequently early tolerance for rehabilitation and decrease the incidence of DVT. This is the cornerstones of success of orthopedic surgery [21]. The preservation of quadriceps function in the immediate postoperative period is the main cause for early mobilization [15]. As the early functional recovery will be strengthened by functional quadriceps In spite of the equality of VAS during the first postoperative hour among both groups but, the time for first mobilization was shorter and significantly earlier in intra-articular dexmedetomidine. This could explained by the significantly better sedation score among the intra-articular group.

Although the superior analgesic effect of intra-articular dexmedetomidine, however the patient's satisfaction in both groups were comparable. This is attributed to the satisfaction of the patients with the technique itself.

The haemodynamic stability with intra-articular dexmedetomidine rather than the intravenous injection, due to the difference of absorption of drug from poorly vascular articular surface or systemic. This is in compatible with the other studies [10,11].

Since Pevey et al. [22], were the first to report knee arthroscopy under local anaesthesia in 1978; then there has been a shifting trend from the administration of the local anesthetics from regionally towards its usage locally. Because the intra-articular route of drug administration is an example for management of pain after joint surgery utilizing the peripheral receptors. It provides analgesics locally with minimal systemic side effect. In addition the several advantages had been obtained from the intra-articular anaesthesia as it is easy, safe, cost-effective, patients is conscious through the whole procedure and the patients does not have to fast for several hours prior to the surgery [23]. It can be considered as a suitable alternative to other types of anaesthesia especially if it may carry a risk for the patients. So it may be considered as the gold standard anesthestic option in knee arthroscopy [24].

However some studies claims that the intra-articular injection of local anesthetics had deleterious effect to the chondrocyte. Dragoo et al. [25] showed that a single dose of 1% lidocaine in vitro resulted in significant decrease in chondrocyte viability. Breu et al. [26] showed that the local anesthetics either ropivacaine, bupivacaine or mepivacaine had toxic effects on the cartilage tissue, the toxicity depends on the method of drug administration, concentration and time. Piper et al. [27], had a review study searching for the relation between the intra-articular local anesthetics and chondrolysis and, they found single injection with caution over 10 min is recommended. Until now there is ongoing search for an ideal drug or technique characterized with simplicity and providing the patients with postoperative analgesia with prolonged duration and with no side effects.

A limitation of our study is the lack of control group. The effect of local anesthetics on chondrocyts so further studies are needed to define the optimal dose dexmedetomidine and its effect on local knee tissues.

6. Conclusion

The finding of our study suggest that the addition of dexmedetomidine to bupivacaine intra-articularly, is a better adjuvant to the local anesthetic than the usage of dexmedetomidine intravenously in patients undergoing arthroscopic knee surgery under intra-articular anaesthesia as it prolongs the duration of postoperative analgesia and enhances the quality of analgesia with reduction in rescue analgesic consumption. Moreover it enhances the early mobilization of the patients which is very fruitful in early physiotherapy.

Author contributions

Study design: Reem Abdelraouf El Sharkawy, Tarek Habeeb Ramadan and Mohamed Aboelnour Badran.

Patient recruitment: Reem Abdelraouf El Sharkawy, Tarek Habeeb Ramadan.

Surgical procedure: Mohamed Aboelnour Badran.

Data collection and analysis: Reem Abdelraouf El Sharkawy, Tarek Habeeb Ramadan.

Writing up of the first draft of the paper: Reem Abdelraouf El Sharkawy, Tarek Habeeb Ramadan.

Conflict of interest

This research received no specific grants from any funding agency in the public, commercial or not-for-profit sectors. The authors have no financial or other conflict of interest to declare and no financial or other relationships leading to conflict of interest.

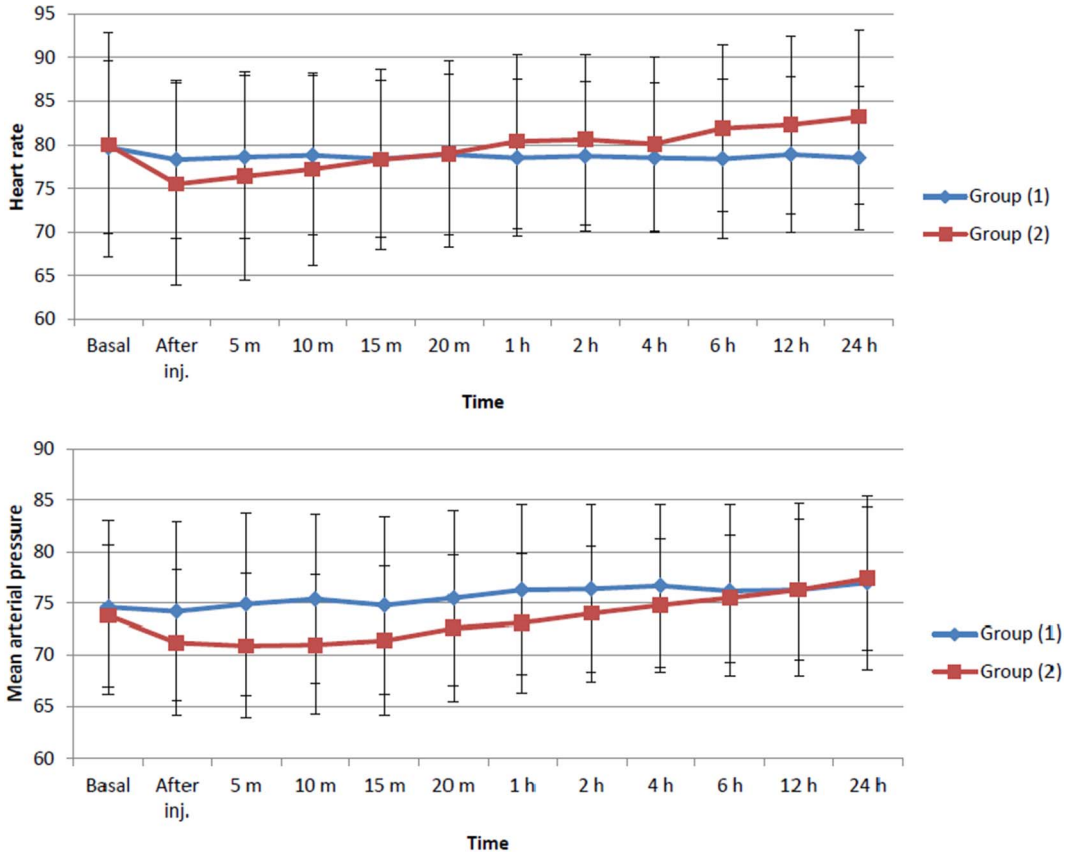

Fig. 2. Changes in HR (beat/min) and MAP (mmHg) between the two studied groups.

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