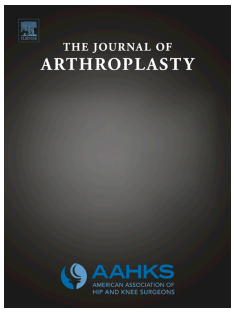

Intranasal dexmedetomidine reduces postoperative opioid requirement in patients undergoing total knee arthroplasty under general anesthesia

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What is already known: Intravenous dexmedetomidine is widely used for procedural sedation and many studies have shown its analgesic sparing effect.

What this article adds: Administration of intranasal dexmedetomidine is feasible during anesthesia and it reduces postoperative opioid requirement in patients undergoing total knee arthroplasty.

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Abstract

Background: Total knee arthroplasty (TKA) causes severe pain and strong opioids are commonly used in postoperative analgesia. Dexmedetomidine is a novel alpha-2-adrenoceptor-activating drug indicated for procedural sedation, but previous studies have shown clinically relevant analgesic and antiemetic effects. We evaluated retrospectively the effect of intranasal dexmedetomidine on postoperative opioid requirement in patients undergoing TKA.

Methods: 150 patients with ASA status 1-2, age between 35 and 80 years and scheduled for unilateral primary TKA under total intravenous anesthesia were included in the study. Half of the patients received 100 µg of intranasal dexmedetomidine after anesthesia induction, while the rest were treated conventionally. Postoperative opioid requirement was calculated as morphine equivalent doses for both groups. The effect of dexmedetomidine on postoperative hemodynamics, length of stay (LOS) and incidence of postoperative nausea and vomiting (PONV), was evaluated.

Results: The cumulative postoperative opioid consumption was significantly reduced in the dexmedetomidine group compared to the control group (- 28.5 mg, 95% CI 12-47 mg $P < 0.001$). The reduction in cumulative opioid dose was significantly different between the groups already at 2, 12, 24 and 36 h postoperatively ($p < 0.001$). LOS was shorter in the dexmedetomidine group ($p < 0.001$) and dexmedetomidine group had lower postoperative mean arterial pressure and heart rate were lower compared to control group ($p < 0.001$). The incidence of PONV did not differ between the groups ($p = 0.64$).

Conclusion: Intraoperatively administered intranasal dexmedetomidine reduces postoperative opioid consumption and may be associated with shorter hospital stay in patients undergoing TKA under general anesthesia.

Keywords: Anesthesia, Pain, Multimodal analgesia, Knee Arthroplasty

Introduction

Total knee arthroplasty (TKA) is a common operation and among the most painful elective procedures [1]. Postoperative pain concerns patients scheduled to TKA and quality of analgesia is a major factor affecting patient satisfaction [2]. Poorly controlled postsurgical pain has many negative consequences, such as risk for development of chronic pain and stiffness and even increased health care costs [3]. Moreover efficient postoperative analgesia is crucial to facilitate early mobilization and rehabilitation [3].

Spinal anesthesia is often chosen anesthesia method for TKA [4]. A recent study found no difference in acute postoperative pain, opioid consumption or recovery time between general and spinal anesthesia in patients undergoing TKA [5]. Moreover, increasing use of novel anticoagulants and antithrombotic agents may compel anesthesiologist to choose general anesthesia for safety reasons [6]. Opioids are efficient in postoperative pain treatment regardless of the anesthesia method, but awareness of the adverse issues during opioid use is growing and actions to reduce opioid use are eagerly sought after [7].

Multimodal pain management targeting different pain signalling pathways by combining two or more analgesic modalities is a good option to reduce opioid consumption. Dexmedetomidine is an alpha-2 adrenoceptor agonist indicated for procedural sedation. In addition to its sedative effect, dexmedetomidine has analgesic and antiemetic effects [8,9]. Compared to other sedative drugs with analgesic effects, dexmedetomidine causes minimal effects on respiration [10]. Analgesic effect of intravenously administered dexmedetomidine in orthopedic surgeries has been previously demonstrated [11] and intranasally administered dexmedetomidine decreased opioid consumption after total hip arthroplasty [12]. There are however no previously published studies on intranasal dosing of dexmedetomidine in patients undergoing TKA.

Our primary aim of this study was to evaluate the effect of intranasally administered dexmedetomidine on postoperative opioid consumption in patients undergoing TKA. We hypothesized that intraoperative intranasal dexmedetomidine reduces opioid consumption in patients undergoing TKA under general anesthesia. To evaluate this, we conducted a retrospective study to analyze postoperative analgesia in adults, scheduled for elective TKA.

Materials and methods

Ethics

The study protocol was approved by the local hospital district. Informed consent was not sought for this retrospective register-based study.

Patient population

A retrospective register-based study was conducted with total of 150 consecutive patients American Society of Anesthesiologists (ASA) physical status classification 1-2, age between 35 and 80 years, weight between 50 and 100 kg and scheduled for primary unilateral total knee arthroplasty under total intravenous anesthesia in tertiary university hospital. Consecutive patients operated between years 2017 and 2019 were identified and included in the study.

We excluded patients with prescribed preoperative opioid use, patients receiving other adjuvant analgesics such as ketamine, gabapentinoids, clonidine or tricyclic antidepressants pre-, intra- or postoperatively, and patients with clinically significant abnormalities in preoperative medical examination (eg. liver or kidney failure), ECG or laboratory values. Furthermore, patients with perioperative bleeding over 500 ml and patients undergoing spinal or inhalational anesthesia were excluded.

Eligible patients were identified and patient data was retrieved from the patient database and anesthesia reports of the hospital. Seventy-five consecutive patients operated between January and October 2017, who met the inclusion criteria and did not receive any dexmedetomidine were allocated to the control group (CTRL). Seventy-five consecutive patients operated between November 2017 and January 2019 who met the inclusion criteria and received intraoperatively 100 µg of intranasal (IN) dexmedetomidine were included in the dexmedetomidine group (DEX). After implementation of IN dexmedetomidine to anesthetic management of patients undergoing TKA in the end of October 2017, all patients without contraindication for dexmedetomidine received IN dexmedetomidine as part of standard care. Two surgeons took care of the majority of the cases, and altogether three surgeons were involved.

Surgical technique

The TKA procedure were done per routine via medial parapatellar approach. A unilateral cruciate retaining implant without a patella button was used in every case. Both femoral and tibial

components were cemented. All patients received an intra- and periarticular local infiltration anesthesia (LIA) -block with 145 ml of 0,125 % levobupivacaine and 5 ml of epinephrine 0.01 %. Blood loss was measured intraoperatively by taking account the amount of the blood in suction bottles and the weighted swabs. The surgical technique was the same for all patients.

Anesthetic management

All patients without contraindications for general anesthesia received the standard total intravenous anesthesia. All patients received preoperatively 1000 mg of oral paracetamol. General anesthesia was induced and maintained with propofol and remifentanil target-controlled infusions (TCI). Propofol TCI was administered with Schnider effect-site model and remifentanil with Minto effect-site model [13,14]. Depth of anesthesia was monitored with entropy (GE B850 Monitor Entropy Module, Helsinki, Finland) aiming to keep the target response entropy (RE) between 35 and 45 during the anesthesia. If RE was below target level, propofol infusion rate was lowered and if RE was above target level, propofol infusion rate was elevated. Mean arterial pressure (MAP) target was between 65 and 75 mmHg depending on the patients age and disease history. If blood pressure was below target level, patients were treated with ephedrine or etilefrine. In DEX group 100 µg of IN dexmedetomidine was administered to all patients within 10 min of anesthesia induction.

All patients received intraoperatively 4 mg of intravenous ondansetron and 4 to 8 mg of intravenous betamethasone according to the bodyweight (4 mg for patients < 75 kg and 8 mg for patients > 75 mg) for prophylaxis of postoperative nausea and vomiting (PONV). If patients received further antiemetics postoperatively, it was considered as PONV. In the end of surgery intravenous 30 mg of ketorolac and 50 µg of intravenous fentanyl were given to the patients. Vast majority of the anesthesias were managed by two senior anesthesiologists.

Pain management

In postoperative anesthesia care unit (PACU), pain was treated with 0,03-0,05 mg/kg intravenous oxycodone if the patient reported pain as moderate or intense (Visual Analog Scale; VAS >3). The dose was repeated after 15 minutes until VAS score was 3 or under. After PACU, in the ward patients received daily 3000 mg of paracetamol for postoperative pain. Stronger pain (VAS > 3) was managed with 0,05-0,1 mg/kg of oral oxycodone. From the first postoperative day onwards patients received oral naproxen/esomeprazole 500/20 mg twice a day. Pain control after hospital discharge consisted of paracetamol (on average 1 g three times a day), non-steroidal anti-inflammatory drug (on average naproxen/esomeprazole 500/20 mg twice a day) and weak opioids

for stronger pain (oral tramadol 50-300 mg a day or oral codeine 30-240 mg a day). If strong opioids were needed, a specialist was consulted.

Pharmacodynamic measurements

Heart rate (HR) and MAP were recorded preoperatively, at the time of incision, one hour after the anesthesia induction, at the end of surgery and in the postoperative anesthesia care unit (PACU) one hour after surgery. Entropy (SE) and effect site TCI target concentrations were collected at the time of incision, one hour after the anesthesia induction, and at the time of wound closure.

PACU time and time to discharge

PACU time and time to the discharge were defined as the period of time between the end of surgery until transfer to surgical ward and the time of discharge from the orthopedic inpatient ward. Clock times were obtained from the hospital's patient information system. Criteria for the transfer from PACU to surgical ward were stable vital signs (HR 50-100/min, MAP 65-90 mmHg, respiratory rate 12-20/min, SpO2 > 95 % diuresis 0,5-1ml/kg/h, sinus rhythm or other chronic rhythm), breathing without effort, patient arousable, adequately controlled pain and no signs of bleeding. Criteria for hospital discharge were ability to independently take care of basic activities of daily living (dressing, nutrition, personal hygiene etc.), ability to mobilize (walking distance > 40m) and pain that can be managed with reasonable amount of oral weak opioids (< 300 mg a day of oral tramadol or < 240 mg a day of oral codeine). If strong opioids were needed, a specialist were consulted.

Statistics

Our primary outcome measure was the cumulative amount of opioids administered to the patients in morphine equivalent dose within 2, 12, 24, 36 and 48 h after the end of surgery. A 20 % reduction in opioid consumption was considered clinically significant [15]. Secondary outcomes were incidence of postoperative nausea and vomiting (PONV), MAP and HR values recorded during the perioperative period, length of PACU and hospital stay (LOS). Sample size was based on previous experience in similar retrospective studies. [16,17] The Shapiro-Wilks test ($P > 0.05$) was used to assess normality assumptions. Student's t-test was used to compare the groups with normally distributed data, and Wilcoxon's rank sum test was used to test non-normally distributed data. Nominal data were tested using chi-square analysis. $P < 0.05$ (two-tailed) was considered statistically significant. The results are expressed as mean values with standard deviations (SD), and as medians with interquartile ranges (IQR) when the normality assumption was not met. The

190 analyses were performed with JMP Pro 13.0 for Mac (SAS Institute Inc., Cary, NC, USA).

Results

Seventy-five consecutive patients were included in both study groups (CTRL and DEX) (Supplemental Fig 1.). There were no statistically significant differences in patient characteristics and demographic data which are shown in Table 1. The mean (SD) weight adjusted dose of IN dexmedetomidine was 1.30 (0.19) µg/kg in the DEX group.

The cumulative 48 h postoperative opioid requirement was significantly reduced in the DEX group compared to the control group (- 28.5 mg, 95% CI 12-47 mg $P < 0.001$). The cumulative dose was significantly different between the groups at all measured (2, 12, 24 and 36 h) postoperative timepoints ($p < 0.001$) (Figure 1; Table 2). Median (IQR) LOS was lower in the DEX group (49 h (49-51)) compared to the CTRL group (51 h (50-70)) ($p < 0.001$). In the DEX group 64 patients (85 %) and in the CTRL group 56 patients (75 %) were discharged within 2 days of surgery (p=0.10).

Patients in the DEX group had lower postoperative MAP and HR compared to CTRL group ($p < 0.001$) (Figure 2, Table 3). In the DEX group weight adjusted dexmedetomidine dose (µg/kg) was negatively associated with MAP change ($r = -0.25$; $p = 0.03$), but not with change of HR ($r = 0.01$; $p = 0.98$). There was no difference in PACU stay ($p = 0.51$) or in the incidence of PONV between two groups ($p = 0.64$). However, patients in DEX group did receive less antiemetics than the control group. Intraoperative target concentrations of propofol and remifentanil were lower in the DEX group ($p < 0.001$; $p = 0.002$) (Figure 3). Intraoperative response entropy levels were similar (Figure 4) and blood loss was minimal in both groups (p=0.86).

All patients in the study were discharged to home. There was no difference in the amount of 30 day or 90-day readmissions between the groups ($p = 0.60$).

Discussion

Our analysis indicates that single dose of intraoperative IN dexmedetomidine reduces postoperative opioid consumption in patients undergoing TKA under general anesthesia. This finding is consistent with previous studies after hip surgery [12]. Clinically important opioid-sparing effect after TKA has been suggested to be > 20 % or 20-30 mg decrease in postoperative morphine consumption over 48 postoperative hours [15]. Our results show that opioid consumption decreased over 20% at all postoperative timepoints after dexmedetomidine and 48 h opioid consumption decreased 32 mg compared to CTRL group, suggesting that our findings are clinically important.

Despite the lack of official approval, use of IN dexmedetomidine is considered to be safe and effective [12,18–20]. IN dexmedetomidine has been used perioperatively for adult population with doses of 1-2 µg/kg [21-24]. The most popular dose of IN dexmedetomidine in adult population appears to be 1.5 µg/kg [21-22]. In our study patients received a mean (SD; range) dose of 1.30 µg/kg (0.19; 1.00-1.67) of dexmedetomidine, which was well tolerated. Although low-dose dexmedetomidine (0.65 µg/kg) has been shown to have opioid sparing effect in patients undergoing total hip arthroplasty [25], we wanted to study higher dose in patients undergoing TKA, which may be associated with stronger pain compared to total hip arthroplasty [1,26]. IN dexmedetomidine has several benefits over intravenous administration, for example less adverse hemodynamic effects are encountered and single dose administration is more convenient. Moreover IN dexmedetomidine has good bioavailability [18,20]. Some studies indicate that IN administration might also bypass blood-cerebrospinal fluid barrier via the olfactory and trigeminal nerves, leading to increased local concentrations compared to other systemic administration routes [27,28], but direct absorption of dexmedetomidine from nasal mucosa to central nervous system has not been studied in humans.

Rehabilitation after surgery is considerably influenced by adequacy of perioperative analgesia. Poorly controlled postoperative pain may slow rehabilitation and lengthen recovery [29]. Other adverse outcomes include prolonged hospital stay, increased health care costs and prolonged opioid use with increased risk for chronic pain [3]. Risk for chronic opioid use is increased after many surgical operations, but it has been suggested that patients undergoing TKA are at highest risk [30]. In our study postoperative LOS was lower in the DEX group. It has been previously demonstrated that poorly controlled postoperative pain predicts readmissions [31]. There were no difference in readmissions between the two groups in our study.

Opioids are effective for TKA pain management but their adverse effects, such as such as respiratory depression, PONV, constipation, opioid tolerance and opioid-induced hyperalgesia produce problems [32,33]. Besides adverse effects, potential risk of misuse is worrisome. Opioid misuse poses a global threat, referred often as “opioid crisis” or even “opioid epidemic” [7,34]. This international problem is forcing us to limit opioid use and utilize new opioid-sparing techniques instead [7]. Multimodal pain management, which aims to minimize side-effects and maximize benefits by combining several drugs with different mechanisms of action, is an efficient way to reduce opioid consumption in orthopedic patients [7,35]. All patients in our study received multimodal analgesia consisting of paracetamol as premedication, intraoperative betamethasone and NSAID at the end of the surgery, as well as opioids. Local infiltration anesthesia (LIA) has become a common practice in TKA and all patients in our study received intra- and periarticular LIA-block. Despite extensive multimodal analgesia, considerable amount of patients still experience disturbing pain after TKA [36]. All patients in our study received identical medications, apart from dexmedetomidine, suggesting that dexmedetomidine caused the difference in postoperative opioid consumption between the two groups and appears to be efficient as part of multimodal pain management strategy.

All study patients were operated under general anesthesia. Despite a recurring debate on which anesthetic method should be chosen, both spinal and general anesthesia are widely accepted and applicable for patients undergoing TKA. Large international meta-analysis (ICAROS-study) suggests that spinal anesthesia might be better option, as neuraxial anesthesia is associated with less postoperative complications [4]. However, a recent study comparing spinal and general anesthesia on patients undergoing TKA found that both anesthesia methods were equal in terms of postoperative pain, incidence of postoperative complications and length of hospital stay [5]. Spinal anesthesia is not always applicable and some studies suggest that many patients prefer general anesthesia over spinal anesthesia [37].

There was no difference in intraoperative response entropy levels between the groups, suggesting that depth of anesthesia was similar in both groups. Optimal depth of anesthesia was achieved with significantly smaller amount of propofol in the DEX group. The anesthetic-sparing effect of IN dexmedetomidine is consistent with previous studies [34] and it has been previously demonstrated that dexmedetomidine lowers entropy levels similarly to propofol [32].

Dexmedetomidine has biphasic effect on hemodynamics, depending on plasma concentration and rate of infusion. IN administration has more gradual onset of action and hence causes less adverse hemodynamic effects than intravenous administration [38]. Results of our study were similar, and the need for vasoactive medications did not differ between DEX group and CTRL group. Patients

in the DEX group had lower HR and MAP in PACU. However, there was no difference in the PACU time between the two groups, hemodynamic parameters remained clinically acceptable, and no treatments were needed. Increased MAP in DEX group in the end of surgery was probably related to vasoconstrictive effect of dexmedetomidine, since there was no difference in the depth of anesthesia or vasoactive requirement between the groups.

Limitations

Retrospective design is an obvious limitation of this study, followed by inherent biases. Only consecutive patients were included to avoid any selection bias. There might be some potential confounding factors that we did not take into account, such as smoking. Another limitation was imperfection in the recording of pain scores, which is why we were not able to analyze postoperative VAS. However, anesthesia reports are well documented and especially opioid use is strictly under surveillance, which is why we can be certain that data has been documented meticulously.

Future prospects

A prospective study is needed to confirm these findings. A case-crossover design should be considered to reduce impact of interindividual variation on pain perception. It would be also reasonable to study use of IN dexmedetomidine in TKA patients treated under spinal anesthesia.

Conclusion

Intraoperatively administered IN dexmedetomidine reduces postoperative opioid consumption and may be associated with shorter hospital stay in patients undergoing TKA under general anesthesia.

Ethics

This was a retrospective register-based study that did not require Ethics Committee approval.

Disclosures

This was a non-commercial, investigator-initiated study, and it has not received any funding from the industry.

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444 **Figure legends**

445 **Figure 1.** Cumulative postoperative opioid requirement of dexmedetomidine (DEX) and control
446 (CTRL) groups in morphine equivalent doses (MED) within 2, 12, 24, 36 and 48 h of surgery.

447 **Figure 2.** Perioperative heart rate (1/min) in dexmedetomidine (DEX) and control (CTRL) groups
448 preoperatively, at incision, 1 h after anesthesia induction, at the end of surgery and before
449 admission from post anesthesia care unit (PACU).

450 **Figure 3.** Perioperative mean arterial pressure (mmHg) in dexmedetomidine (DEX) and control
451 (CTRL) groups preoperatively, at incision, 1 h after anesthesia induction, at the end of surgery and
452 before admission from post anesthesia care unit (PACU).

453 **Figure 4.** Intraoperative Entropy levels in dexmedetomidine (DEX) and control (CTRL) groups at
454 incision, 1 h after anesthesia induction and during wound closure.

455 **Supplemental Figure 1.** Flow diagram of the study

456

TABLE 1. Patient characteristics. Data are shown as mean ± SD.

	CTRL (n=75)	DEX (n=75)	p-value
Age (yr)	68 (8)	66 (8)	0.14
Weight (kg)	81 (11)	78 (11)	0.18
BMI (kg/m2)	28.9 (4.1)	27.9 (3.3)	0.14
Male/Female (n)	23/52	23/52	1.00
Intraoperative time (min)	62 (6)	61 (5)	0.23

CTRL = control group, DEX = dexmedetomidine group, BMI = body mass index

TABLE 2. Postoperative opioid requirement in morphine equivalents during five different time intervals. Data are shown as median and interquartile range

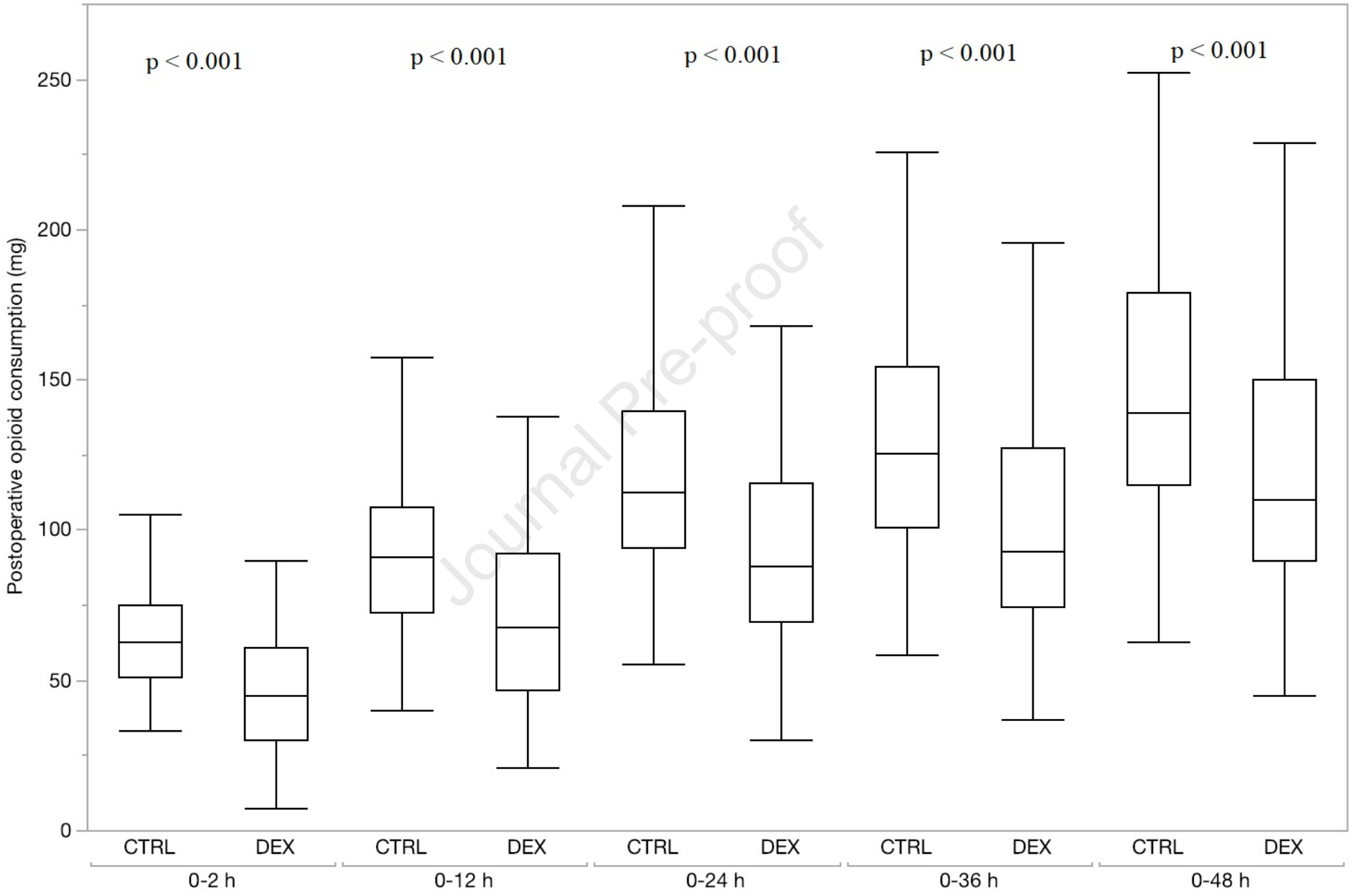
	CTRL (n=75)	DEX (n=75)	p-value
Opioid requirement 0-2 h (mg)	63 (51-75)	45 (30-60)	< 0.001
Opioid requirement 0-12 h (mg)	91 (72-107)	67 (48-92)	< 0.001
Opioid requirement 0-24 h (mg)	113 (94-140)	87 (70-115)	< 0.001
Opioid requirement 0-36 h (mg)	125 (101-155)	92 (74-127)	< 0.001
Opioid requirement 0-48 h (mg)	140 (116-180)	108 (89-149)	< 0.001

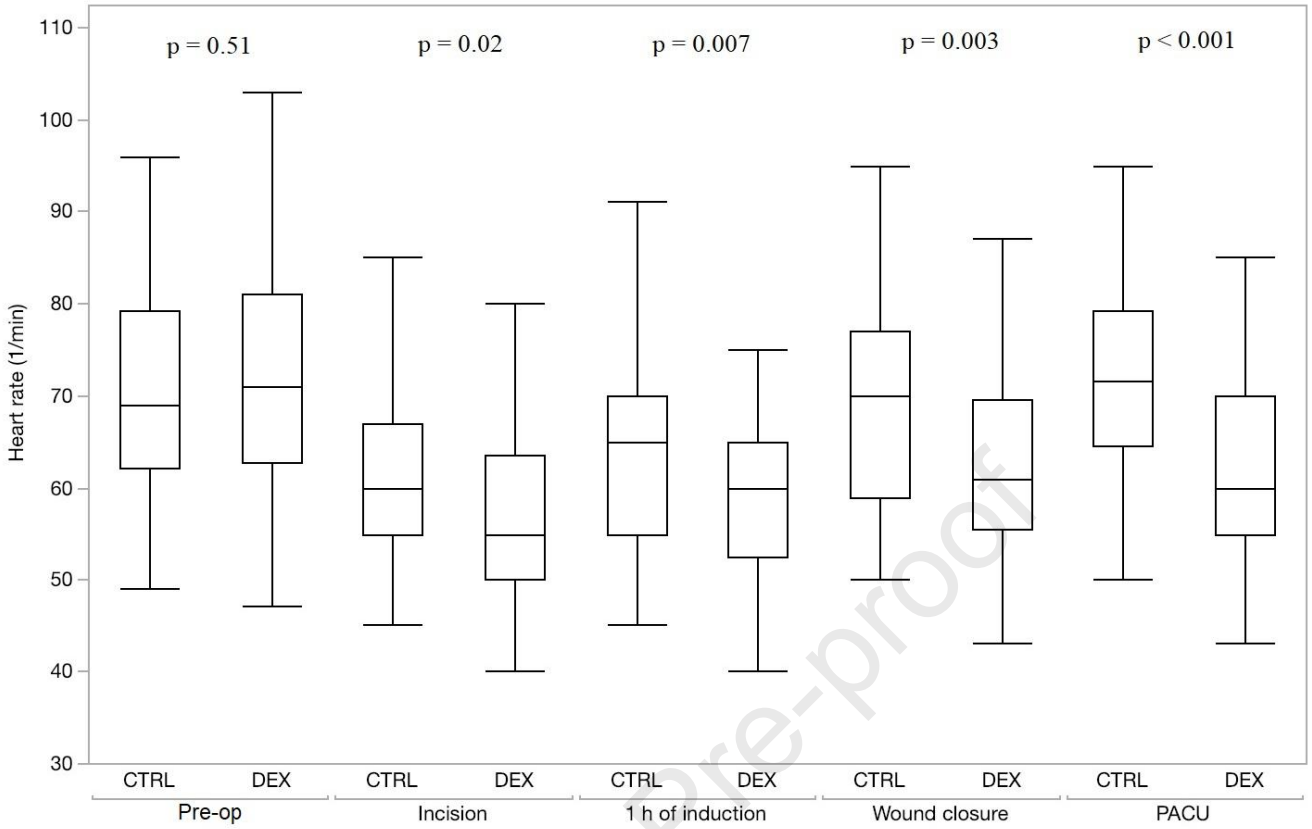
CTRL = control group, DEX = dexmedetomidine group

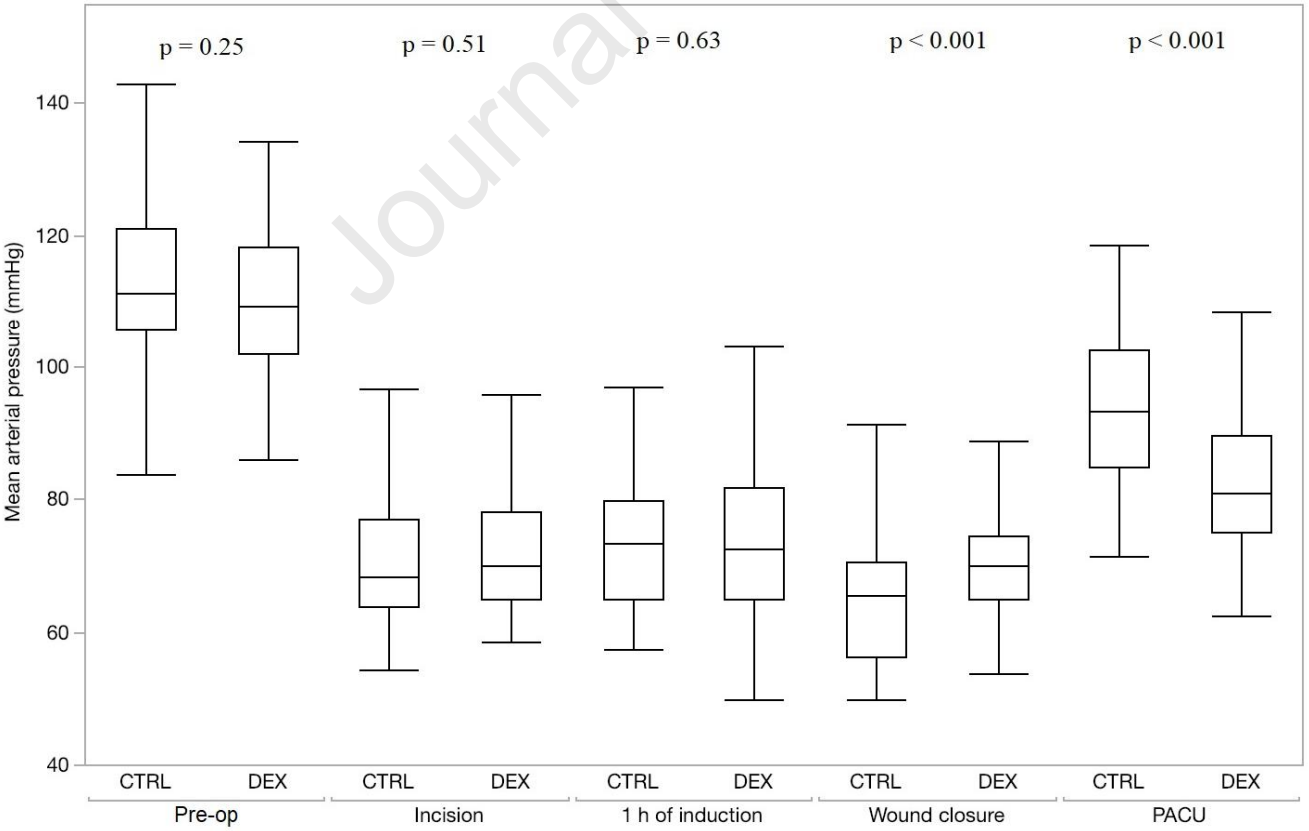
TABLE 3. Perioperative heart rate, mean arterial pressure and estimated intraoperative blood loss. Data are shown as median and interquartile range.

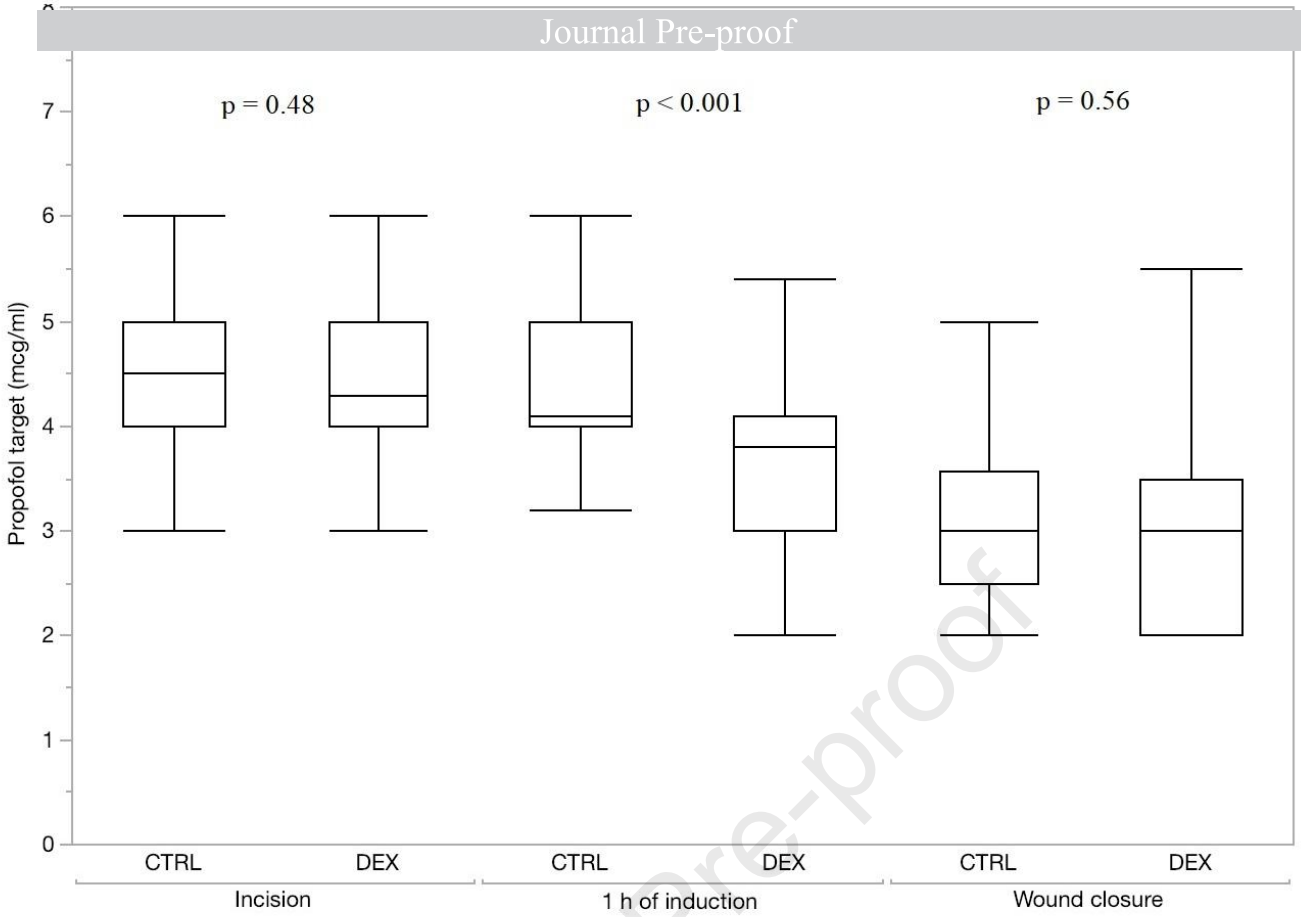
Parameter	Timepoint	CTRL (n=60)	DEX (n=60)	p-value
HR (bpm)	Pre-op	69 (63-79)	71 (62-81)	0.51
	Incision	60 (55-67)	55 (50-64)	0.02
	1 h of induction	65 (55-70)	60 (53-65)	0.007
	Wound closure	70 (59-77)	61 (56-70)	0.003
	PACU	72 (65-79)	60 (55-70)	< 0.001
MAP (mmHg)	Pre-op	111 (106-121)	109 (102-118)	0.25
	Incision	68 (64-77)	70 (65-78)	0.51
	1 h of induction	73 (65-80)	73 (65-82)	0.63
	Wound closure	66 (56-70)	70 (65-75)	< 0.001
	PACU	93 (85-103)	81 (75-90)	< 0.001
Blood loss (ml)		100 (50-200)	100 (50-250)	0.86

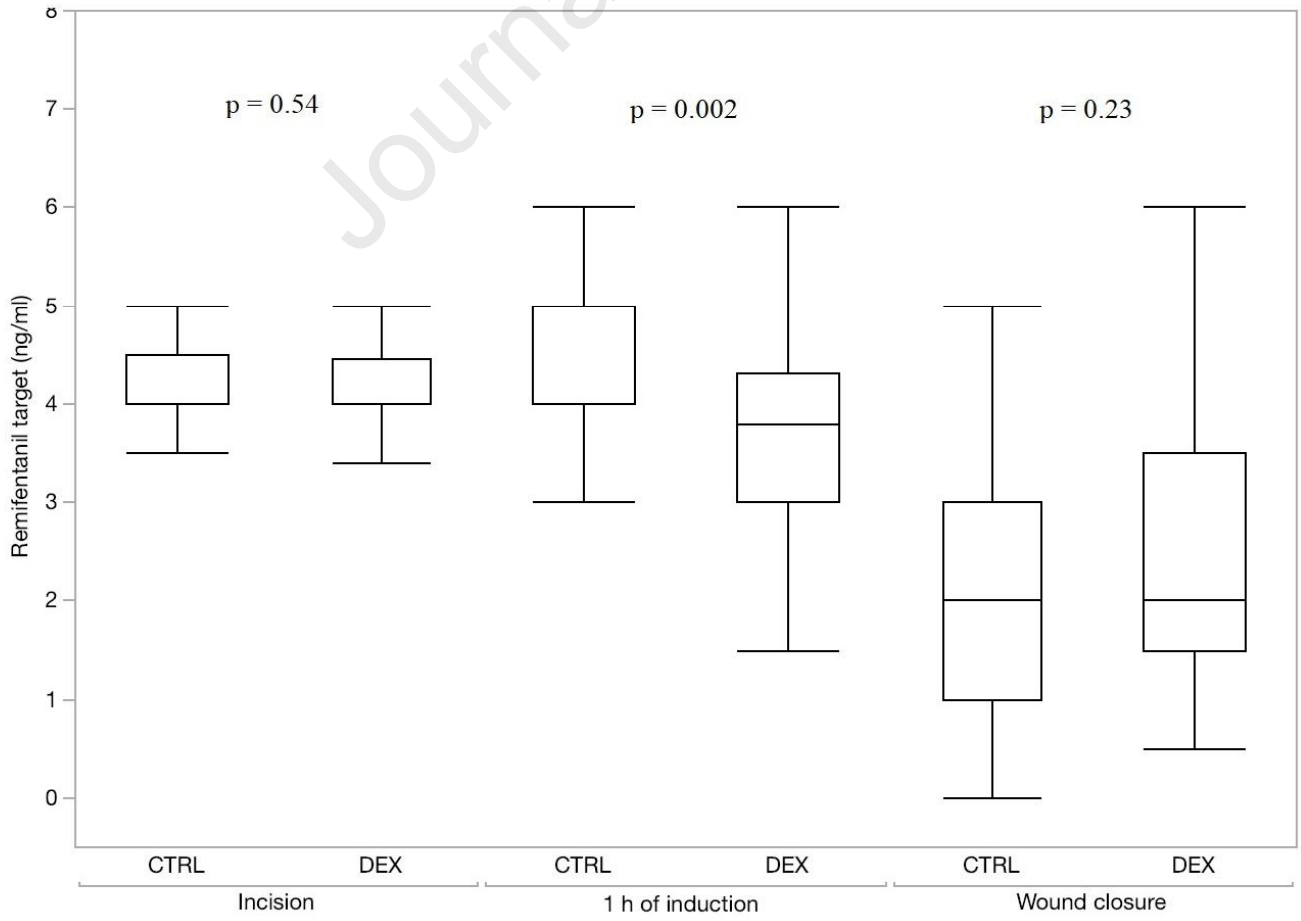
CTRL = control group, DEX = dexmedetomidine group, HR, heart rate; bpm = beats per minute; MAP, mean arterial pressure; Pre-op = preoperative, PACU = post anesthesia care unit











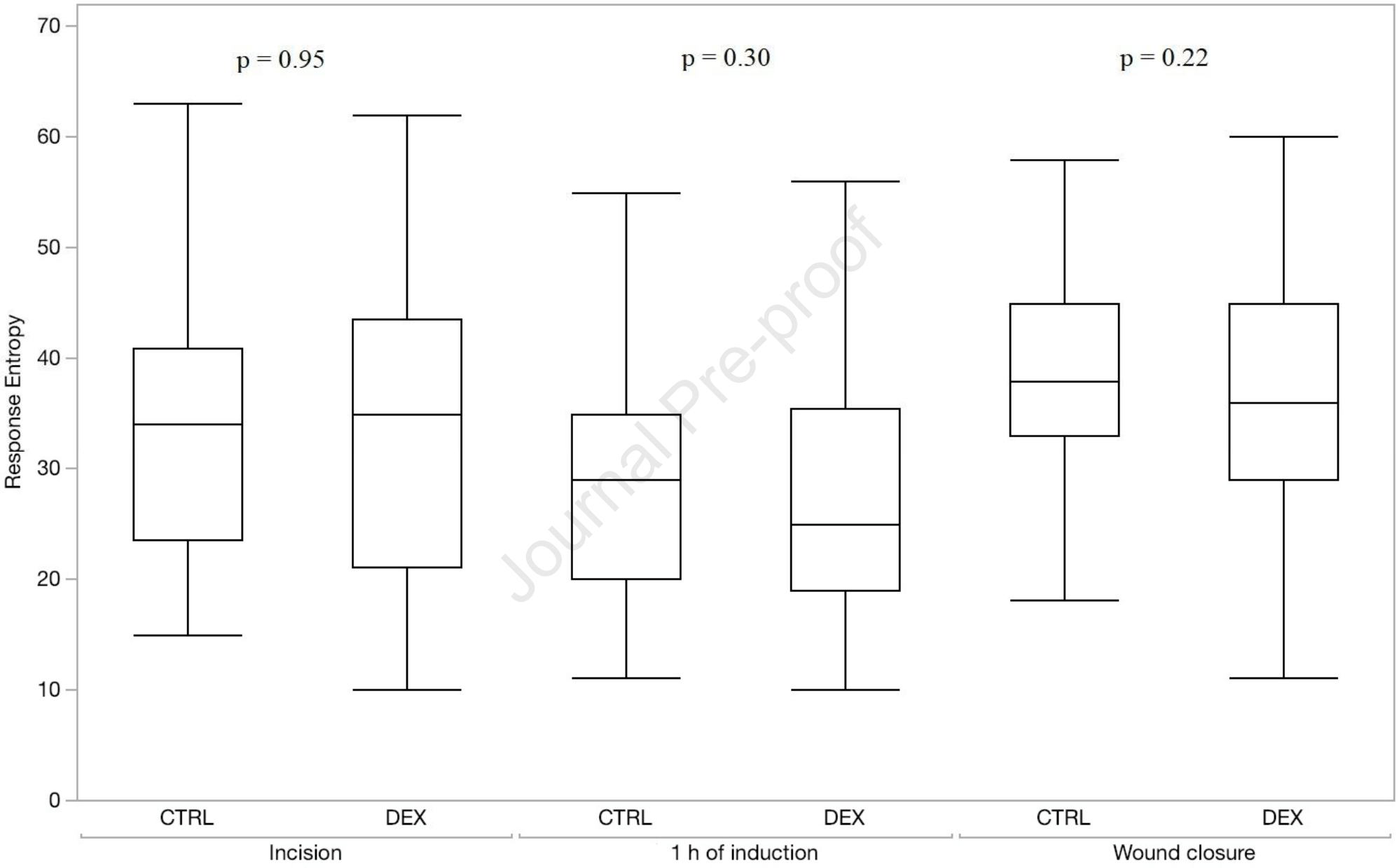


Figure legends

Figure 1. Cumulative postoperative opioid requirement of dexmedetomidine (DEX) and control (CTRL) groups in morphine equivalent doses within 2, 12, 24, 36 and 48 h of surgery.

Figure 2. Perioperative heart rate (1/min) and mean arterial pressure (mmHg) in dexmedetomidine (DEX) and control (CTRL) groups preoperatively, at incision, intraoperatively (1 h after anesthesia induction), at the end of surgery and before admission from post anesthesia care unit (PACU).

Figure 3. Intraoperative propofol and remifentanil target plasma levels in dexmedetomidine (DEX) and control (CTRL) groups at incision, intraoperatively (1 h after anesthesia induction), at the end of surgery and before admission from post anesthesia care unit (PACU).

Figure 4. Intraoperative Entropy levels in dexmedetomidine (DEX) and control (CTRL) groups at incision, intraoperatively (1 h after anesthesia induction) and during wound closure.

Supplemental Figure 1. Flow diagram of the study