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Ain-Shams Journal of Anesthesiology (2022) 14:85
https://doi.org/10.1186/s42077-022-00286-3

Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

"Preoperative oral duloxetine: does it affect duration of spinal anesthesia and early postoperative pain after arthroscopic ACL repair?" A prospective, randomized, double-blind controlled trial

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Abstract

Background: Postoperative pain is one of the problems in which a lack of adequate controls can cause many complications. Duloxetine is a potent serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed for the treatment of depression, chronic pain, neuropathy, and recently early postoperative pain.

Results: The results showed that the effect of duloxetine on the onset and duration of the spinal anesthesia was statistically non-significant ($P = 0.067$ and $P = 0.21$) respectively; also, duloxetine delayed the time to the first dose of rescue analgesia request (479.71 ± 50.32 vs 218.29 ± 12.48) ($P < 0.001$) and maintained VAS score in the lower range in comparison to control group ($P = 0.001$) with less frequency and total morphine consumption (4.2 ± 2.08 vs 10.37 ± 1.52) ($P < 0.001$) up to 24 h. No significant differences in adverse effects.

Conclusions: A single dose of 60mg duloxetine orally 2 h before arthroscopic ACL repair provided better postoperative pain control and decreased total morphine consumption without affecting the duration of spinal anesthesia.

Keywords: Duloxetine, Serotonin and norepinephrine reuptake inhibitors, Postoperative pain, Morphine, Arthroscopic ACL repair, Spinal anesthesia

Background

Arthroscopic knee surgeries are very common procedures as ambulatory day case surgeries and are preferred by most patients (Weale et al., 1998). Many patients complain of moderate to severe pain 24 h after surgery (McGrath et al., 2004; Pavlin et al., 2004), and pain affects the patient's activity level and satisfaction (Pavlin et al., 2004).

Activation of a specialized nerve ending "nociceptor" initiates pain in response to various stimuli (mechanical, chemical, or thermal) directly through trauma or indirect via biochemical mediators from tissue damage; Arachidonic acid, histamine, prostaglandins, serotonin, and bradykinins are the common mediators that stimulate and upregulate nociceptors and augment pain process, so long duration of the stimulus leads to more mediators release, more receptors stimulation, and more pain sensation (Carr & Leonidas, 1999; Cohen & Schecter, 2005).

The fast myelinated A-delta fibers transmit the signals of initial sharp pain, whereas the slow unmyelinated C fibers transmit the signals of later deep aching or throbbing pain.

The pain fibers transmit signal from the periphery to the dorsal horn of the spinal cord, stimulate the

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adjacent spinal segments, and elicit spinal reflexes. Pain fibers cross the midline and stimulate ascending spinothalamic tract which terminates in the thalamus, limbus, and brain stem; the pain signal is transmitted to higher cortical areas for localization and pain perception. Substance P is considered the main transmitter in ascending pain pathway.

Central feedback occurs by activation of descending fibers from the cerebral cortex to the spinal cord and periphery to reduce the severity of pain via serotonin, norepinephrine, encephalin, and gamma-aminobutyric acid (GABA) neurotransmitters.

Pain activates the release of stress hormones (cortisol, catecholamines, and vasopressin) which elevate blood glucose levels, impair immune functions, and break down fat and muscle. Also, pain activates the autonomic nervous system mainly at the level of the dorsal horn which is manifested by nausea, sweating, and changes in heart rate and blood pressure (Carr & Leonidas, 1999; Cohen & Schecter, 2005).

Preemptive analgesia is defined as the administration of analgesics before the nociceptive stimuli, with better pain control after surgery. The afferent input processing is modified by anti-nociceptive drugs to prevent magnification and perception of pain signals (Kissin, 2000). Preemptive analgesia is used to decrease acute postoperative pain and enhance analgesic effects (Bromley, 2006).

Multimodal analgesia uses the synergistic effects of different pain-relieving drugs to decrease postoperative pain with fewer narcotic requirements and fewer adverse effects (Kaya et al., 2010; Zhang et al., 2016). Different adjuvants are utilized to extend the duration of spinal anesthesia, reduce postoperative pain, and decrease analgesic needs after surgery (Ota et al., 1994; Ben-Menachem, 2004). Duloxetine is a potent serotonin and norepinephrine reuptake inhibitor (SNRI) prescribed for the treatment of depression, chronic pain, neuropathy, and recently early postoperative pain. Opioid requirements were decreased following total knee replacement during the early 48 h (Ho et al., 2010; Quilici et al., 2009). Also, after lumbar laminectomy, duloxetine reduced morphine requirements and pain scores (Attia & Mansour, 2017).

Statement of clinical relevance

Although many researchers evaluated the effects of duloxetine on postoperative pain control and opioid consumption, limited research assessed its effects on the duration of spinal anesthesia as a standard technique for lower limbs surgeries where it allows early mobilization and better pain control.

Hypothesis

Preoperative oral duloxetine will allow early mobilization and better pain control after spinal anesthesia for arthroscopic anterior cruciate ligament (ACL).

Methods

Study design and ethics

A parallel-group, prospective, randomized, nonfunded, and single-institute study was conducted after obtaining approval from Ethics committee and registration at ClinicalTrials.gov according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was signed by all participants.

Study setting, patients' recruitment, randomization, and control of potential bias

- Study settings:
- Recruitment between *March 2021* and *July 2021*.
- A computer-generated codes placed in opaque sealed envelopes with a 1:1 allocation ratio by an anesthesiologist not directly involved in the trial or patient care.
- Follow-up was done by a researcher unaware of the group allocation. So, the patient, anesthesiologist, and follow-up researcher were blinded to group allocation.

Study population

Seventy patients (ASA-PS class I and II, both sexes, 18 to 50 years old, 60–80 kg weight, 155–180cm height) undergoing arthroscopic ACL repair under spinal anesthesia were included in the study.

Patients who declined to sign written informed consent; patients with a history of allergy to duloxetine, patients on sedatives or opioid drugs, patients with alcohol or drug addiction, patients with an inability to communicate to evaluate the postoperative pain, patients with a need for postoperative ICU hospitalization, patients with a history of taking duloxetine or any SSRIs, patients with contraindications for spinal anesthesia, and patients with psychiatric illness (tricyclic or MAOIs) or hepatic or renal failure were excluded.

Study groups

Patients undergoing arthroscopic ACL repair under spinal anesthesia were randomly assigned into one of the following groups:

- *Group D (duloxetine group)*: Two hours before the operation, duloxetine patients received 60mg of duloxetine tablets orally in the ward and then trans-

ferred to OR to receive spinal anesthesia before surgery.

- *Group C (control group)*: The patients received placebo tablets in the ward and then transferred to OR to receive spinal anesthesia before surgery.

Anesthesia

All patients were clinically assessed, and routine preoperative investigations were done, including CBC, coagulation profile, liver function tests, kidney function tests, fasting blood sugar, and ECG.

Intraoperative setting

Standard monitoring (ECG, pulse oximetry, and NIBP) were connected to all patients in the operating room, and baseline vital data (HR, SpO2, systolic, diastolic, and mean arterial blood pressure) were recorded, and subsequently, every 5 min, an intravenous (IV) line was inserted.

For both groups, after administration of 6 mL/kg intravenous crystalloid, and under complete aseptic conditions, Tuffier's (intercristal) line as L4–L5 level was defined, 5ml of 2% lidocaine infiltrated at L3–L4 midline level as local anesthesia in the sitting position, through 25 Gauge Quincke spinal needle 3.5 mL of 0.5% hyperbaric bupivacaine intrathecally injected, then patients positioned supine for 20 min. Patients were operated on by the same team and techniques. When systolic blood pressure decreased more than 30% or mean arterial blood pressure below 60 mmHg, intravenous 3mg incremental ephedrine was given, whereas intravenous 0.5mg atropine was given when HR was below 50bpm.

Pinprick test was used to assess sensory block every 1 min till peak sensory level, then every 5 min for the next 30 min after that assessments were performed by the surgeon every 15 min intraoperatively, and a trained nurse continued the assessment during the postoperative period till regression to the L2 segment level, with recording the time to T10 sensory level as the onset of sensory block, time to peak sensory level.

Two-dermatome regression from the peak sensory level defined the sensory recovery time.

The motor block was assessed by a modified Bromage scale (grade 3 no movement, grade 2 unable to flex knees, can flex ankle, grade 1 unable to raise an extended leg but able to move the knees and ankles, grade 0 no paralysis) (Bromage et al., 1964), time to Bromage 1 defined as the onset of motor block whereas return to Bromage 2 defined motor recovery and motor block duration.

Patients were taught before the surgery to scale their pain by visual analog scale (VAS score) where 0 = no pain and 10 = worst possible pain every 4 h for the first 24 h after the operation.

Regular intravenous paracetamol, 1 g every 8 h, and ondansetron 4mg (at the end of surgery) were given (Hetta et al., 2020) to all patients, where postoperative rescue analgesics were given by hospital nursing staff to VAS score of $\geq$ 4 in the form of intravenous 3mg morphine and not repeated within 4 h limited to 12 mg morphine per 24 h after operation (Hetta et al., 2020; Stanley et al., 1996); the first rescue analgesic need, frequency, and total morphine consumption timing were recorded. Adverse effects were recorded as HR less than 50 bpm (intravenous 0.5mg atropine was given), arrhythmia, systolic blood pressure less than 90 mmHg (20ml/kg ringer was infused), dry mouth, PONV (ondansetron 4mg), and seizures.

Outcome measurements

- *Primary outcome*:

  Our primary outcome is to assess the onset of spinal anesthesia.
- *Secondary outcome*:
- Duration of spinal anesthesia (two-dermatome regression for sensory recovery and return to Bromage 2 for motor recovery).
- Visual analog scale (VAS score) where 0= no pain and 10= worst possible pain every 4 h for the first 24 h after the operation.
- Time for first postoperative rescue analgesia request, frequency, and total morphine consumption.

Sample size calculation

Using G power software for sample size calculation, setting power at 90% and alpha error at 0.05, and assuming a large effect size difference between study groups regarding the time of spinal anesthesia (D=0.8), a sample size of 35 patients per group will be needed (total 70 patients).

Data management and analysis

The statistical analysis was performed using a standard SPSS software package version 23 (Chicago, IL). Normally distributed numerical data are presented as mean ± SD and differences between groups were compared using the independent Student's *t*-test; data not normally distributed were compared using the Mann-Whitney test and are presented as median (IQR) and categorical variables were analyzed using the χ^2 test or Fisher's exact test and are presented as number (%). All *P* values are two-sided. $P < 0.05$ is considered statistically significant.

Results

Seventy-five patients were screened for eligibility and five patients were excluded (2 refused to participate and 3 were not meeting the inclusion criteria). The 70 included patients were randomized into either the duloxetine group ($n = 35$) or the control group ($n = 35$) and all were available for final analysis (Fig. 1).

There were no significant differences in terms of demographic or surgical data between the two groups (Table 1). All surgical procedures were completed without complications.

There are no statistically significant differences between the two groups as regards the onset of anesthesia in the form of time to T10 sensory block (P =0. 067) and time to Bromage 1 motor block (P =0.158) in addition to peak sensory level and time to reach peak sensory level; also, there is no statistically significant difference between groups as regards the duration of spinal anesthesia in the form of time to two-dermatome regression ($P = 0.21$) and time to L2 regression ($P = 0.076$) sensory recovery and time to Bromage 2 return ($P = 0.126$) motor recovery (Table 2).

There were statistically significant differences between the two groups according to VAS scores at 4, 8, 12, 16, 20, and 24 h as shown in Table 3 and Fig. 2.

Table 4 shows highly statistically significant differences between the two groups as regards frequency of morphine (P<0.001), total morphine consumption (4.2 ± 2.08 vs 10.37 ± 1.52) ($P < 0.001$) up to 24 h, and the time to first dose of rescue analgesia request (479.71 ± 50.32 vs 218.29 ± 12.48) ($P < 0.001$).

Table 1 Demographic and surgical data

	Group C (n=35)	Group D (n= 35)	p-value
Age (years)	36.77 ± 10.66	36.86± 9.5	**0.97**
Sex (M/F)	19/16	15/20	**0.473**
Height (cm)	169.34 ± 4.18	168.9 ± 4.8	**0.713**
Weight (kg)	71.7± 5.04	71.34± 4.5	**0.748**
Operative duration (min)	83.43± 16.9	80.4± 16.64	**0.458**

Data are presented as mean ± SD, ratio of patients

p-value > 0.05 is considered statistically non-significant

As regards adverse effects (hypotension, vomiting, and dry mouth), there were no statistically significant differences between the two groups (Table 5).

Discussion

This prospective randomized controlled trial was designed to investigate the effects of 60 mg oral duloxetine 2 h preoperatively on the onset and the duration of the spinal anesthesia in an arthroscopic anterior cruciate ligament (ACL) repair and 24 h postoperative pain control.

Our results showed that the effect of duloxetine on the onset (as primary outcome) and duration of the spinal blockade were statistically non-significant; also, duloxetine delayed the time to the first dose of rescue analgesia request about double the time and maintained VAS score in the lower range in comparison to control group; frequency and total morphine consumption (half the dose) were less in duloxetine group when compared to

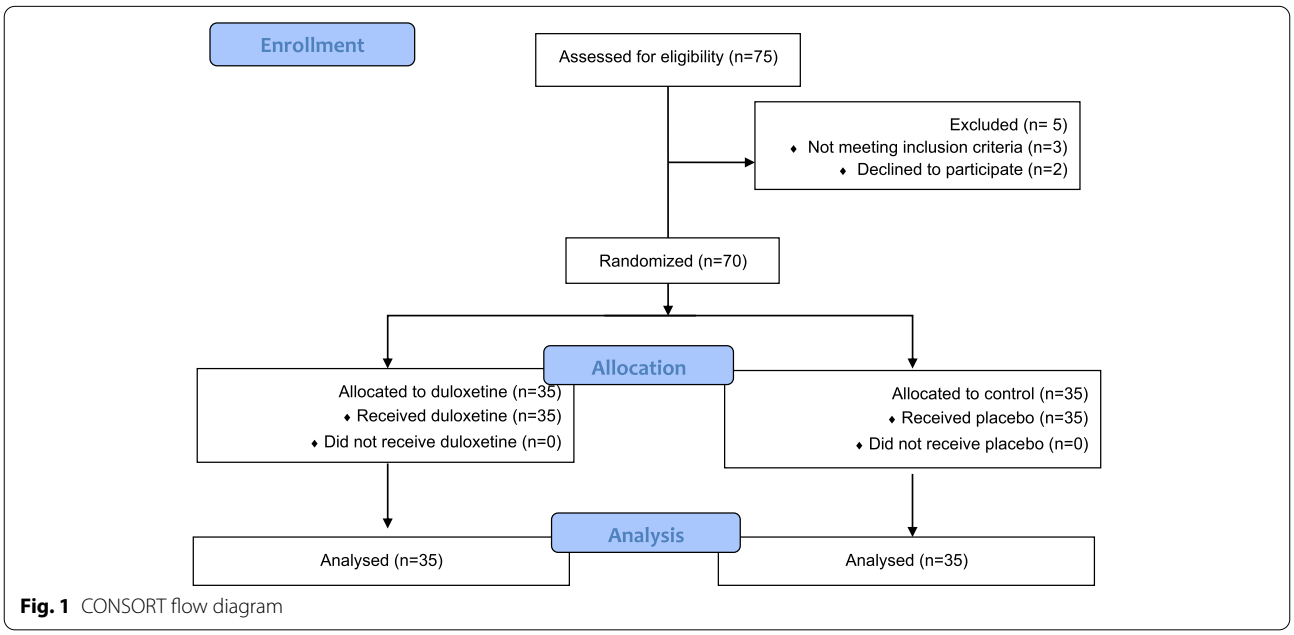

Fig. 1 CONSORT flow diagram

Table 2 Onset and duration of spinal anesthesia

	Group C (*n*=35)	Group D (*n*= 35)	*p*-value
Sensory level	7 (5–7)	7(5–7)	**0.973**
Time to T10	3.58 ±0.91	3.2 ± 0.74	**0. 067**
Time to Bromage 1	8.4 ±0.86	8.2± 0.7	**0.158**
Time to peak sensory level	14.9 ± 0.9	15 ± 1.2	**0.063**
Time to 2 dermatomes regression	79.3 ± 5.7	81.4 ± 7.9	**0.21**
Time for Regression to L2	129.1 ± 7.7	133.6 ± 12.7	**0.076**
Time to Bromage 2	180 ± 10.7	184.1± 14	**0.126**

Data are presented as mean ± SD, median (IQR)

P value < 0.05 is considered statistically significant

P value > 0.05 is considered statistically non-significant

Table 3 Visual analog scale (VAS)

	Group C (*n*=35)	Group D (*n*= 35)	*p*-value
4h	4 (3–4)	2 (2–2)	<0.001
8h	4 (3–4)	2 (2–3)	<0.001
12h	3 (3–4)	2 (2–3)	<0.001
16h	4 (3–5)	3 (2–4)	**0.001**
20h	4 (3–4)	3 (2–3)	<0.001
24h	3 (3–4)	2 (1–2)	<0.001

Data are presented as median (IQR)

P value < 0.05 is considered statistically significant

placebo up to 24 h as a secondary outcome. No significant differences in adverse effects were observed between the duloxetine group and placebo with consideration of prophylactic ondansetron for postoperative nausea and vomiting (PONV).

There was a great conflict about when should we start the drug preoperative. This is because few studies were done to evaluate duloxetine for acute postoperative pain with different regimens.

Duloxetine 60mg dosage depended on a review of the previous publications, Hetta et al., who compared different doses of oral duloxetine 30, 60, and 90mg 2 h before modified radical mastectomy and concluded that 60 and 90mg duloxetine reduced analgesic requirements with less adverse effects in 60 mg group (Hetta et al., 2020); also Ho and his colleagues found that morphine consumption decreased in total knee arthroplasty (TKA) after two doses of 60 mg duloxetine (Ho et al., 2010).

The standard duloxetine dose was 60mg per day for treatment of chronic and neuropathic pain, in comparison to 20mg ineffective dose and 120mg non-superior dose (Lunn et al., 2014).

After tissue injury, central and peripheral sensitizations occur with neuroplastic changes which may lead to hyperalgesia or allodynia after surgery (Wilder-Smith & Arendt-Nielsen, 2006).

Duloxetine is a selective SNRI prescribed for depression, anxiety, and chronic pain like diabetic neuropathy and fibromyalgia; it acts through central and peripheral pain modulation as it increases dorsal horn serotonin and norepinephrine level and potentiates inhibitory descending pain pathways in the spinal cord, also cognitive modulation of pain through activation of the prefrontal cortex (Onuțu, 2015).

Duloxetine decreases neuronal firing after peripheral tissue trauma through its local anesthetic effect mediated by sodium channel blockade (Onuțu, 2015; Nakajima et al., 2012).

Sun et al. injected intrathecal duloxetine in rats to confirm the site of action as they used in vivo microdialysis and found elevated serotonin and norepinephrine in the dorsal horn. The antagonist was used to partially decrease the anti-hyperalgesia effects of duloxetine (Sun et al., 2014).

In agreement with our study, Hetta et al. 2021, evaluated 62 patients undergoing major abdominal cancer surgery divided into 2 equal groups, who received 2 h preoperatively oral duloxetine 60 mg or placebo, and reported that a single preoperative dose (2 h) of oral duloxetine 60 mg reduced postoperative pain in the form of VAS score, decreased 48 h opioid consumption, and improved the quality of recovery (Hetta et al., 2021).

In agreement with our study, Elbehairy et al. evaluated the efficacy of administration of 30 mg of oral duloxetine every 12 h for 3 days before surgery and 2 h before and 12 h after surgery on the duration of spinal block and postoperative pain control in hip operations and found no statistically significant difference on the spinal block duration (complete regression of sensory and motor block), also lowered postoperative pain (VAS score), total narcotic requirements, and improved patients' mode with decreased adverse effects, those agree with ours although different doses and administration (Elbehairy et al., 2019).

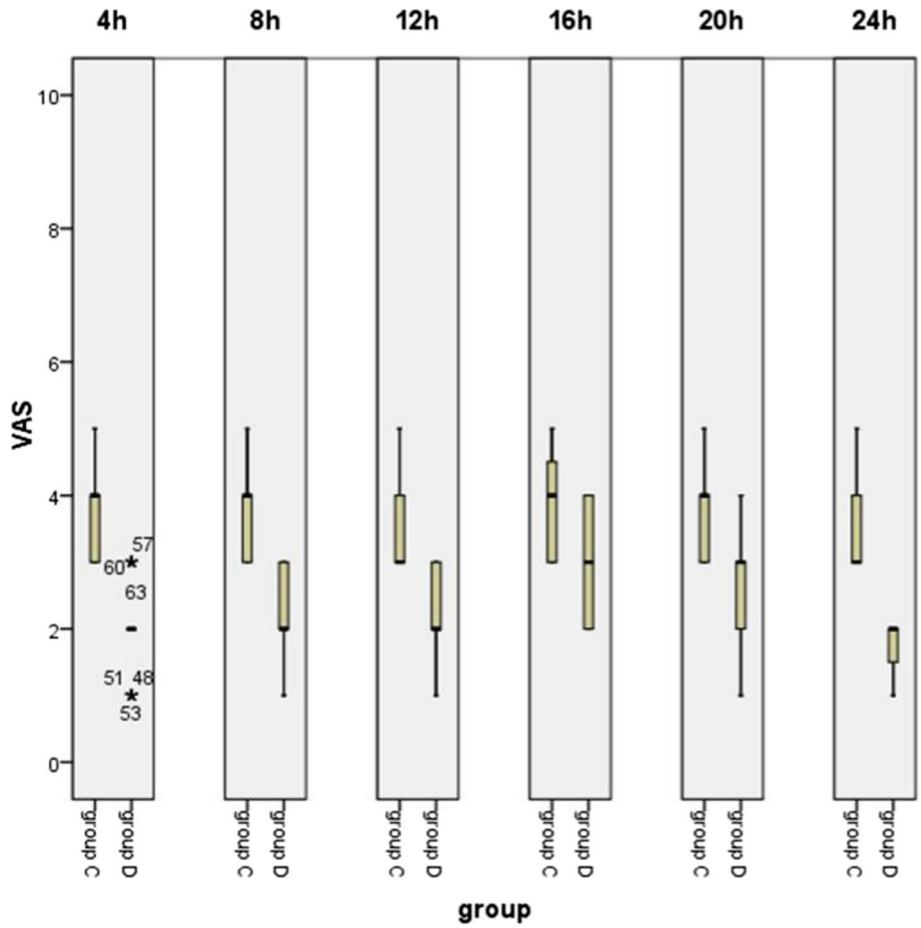

Fig. 2 Visual analog scale (VAS). The middle black solid line represents the median; the upper and lower margins of each box represent the IQR. Asterisk is maximum and minimum values; asterisk represents the number of patients with outlier data

Table 4 Analgesic requirements

	Group C (*n*=35)	Group D (*n*= 35)	*p*-value
Frequency of morphine (number of doses)	3 (3–4)	2 (1–2)	**<0.001**
Total morphine consumption (mg)	10.37 ± 1.52	4.2 ± 2.08	**<0.001**
First analgesic requirements (minutes)	218.29 ± 12.48	479.71 ± 50.32	**<0.001**

Data are presented as mean± SD, median (IQR)

P value < 0.05 is considered statistically significant

Table 5 Adverse effects

	Group C (*n*=35)	Group D (*n*= 35)	*p*-value
Hypotension	6	7	1
Vomiting	5	8	0.54
Dry mouth	0	4	0.114

Data are presented as number of patients

p-value> 0.05 is considered statistically non-significant

Also, in agreement with our study, Nasr (Nasr, 2014), Castro et al. (Castro-Alves et al., 2016), Bedin et al. (Bedin et al., 2017), and Attia and Mansour (Attia & Mansour, 2017) all showed a significant decrease in post-operative opioid requirements and pain scores (VAS scores) with duloxetine group in comparison to placebo.

Saoud and his colleague evaluated perioperative oral 60 mg duloxetine daily for 2 weeks in anterior cervical

microdiscectomy and fusion and concluded that duloxetine prolonged the time to first rescue of analgesia request and decreased total analgesic requirements in 48 h with early ambulation and less adverse effects; as regards VAS score, his study showed no statistically significant difference between two groups; he explained this by higher opioids consumption in the control than in the duloxetine group (Saoud & Elkabarity, 2013).

Ho et al. noted that VAS was non-statistically significantly higher in the early postoperative period in the duloxetine group and not clinically important as it remained less than 3 in both groups mostly as the time to achieve duloxetine peak plasma concentration is about 6 h after oral intake (Ho et al., 2010).

Bastanhagh et al. studied preoperative 60mg oral duloxetine 2 h before elective abdominal hysterectomy and concluded that no significant differences in opioid consumption after surgery with a higher frequency of PONV. This disagreement is mostly due to different anesthesia techniques general versus spinal and different surgeries (Bastanhagh et al., 2020).

Limitations

Future studies should extend the duration of observation to more than 24 h and follow up patients for 3 to 6 months for the development of chronic pain, use different techniques of anesthesia (general, regional, and nerve block), and optimize the dose for each operation.

Conclusions

A single dose of 60mg duloxetine orally 2 h before arthroscopic ACL repair provided better postoperative pain control and decreased total morphine consumption without affecting the duration of spinal anesthesia.

Abbreviations

ACL: Arthroscopic anterior cruciate ligament; ASA-PS: American society of anesthesiologists- Physical status; ICU: Intensive care unit; MAOIs: Monoamine oxidase inhibitors; OR: Operating room; PONV: Postoperative nausea and vomiting; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor; TKA: Total knee arthroplasty; VAS: Visual analog scale.

Acknowledgements

Not applicable.

Statement of clinical relevance

Although many researches evaluated the effects of duloxetine on postoperative pain control and opioids consumption, limited researches assessed its effects on the duration of spinal anesthesia as a standard technique for lower limbs surgeries where it allows early mobilization and better pain control.

Authors' contributions

The authors confirm contribution to the paper as follows: study conception and design: TA and IM; data collection: TA and IM; analysis and interpretation of results: TA; discussion writing: TA; manuscript preparation: TA and IM; journal submission: TA. All authors reviewed the results and read and approved the final manuscript.

Funding

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

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Registered and approved by the Ethics committee of Ain Shams University Hospital (FMASU R 63/ 2021) on 7/3/2021. Written informed consent to participate was obtained from all participants.

Consent for publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/parent/guardian/ relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

Received: 7 March 2022 Accepted: 11 November 2022
Published online: 26 November 2022

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