Effect of ultra-low-dose naloxone with ultrasound-guided transversus abdominis plane block on postoperative pain relief in patients undergoing laparoscopic cholecystectomy

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Introduction Transversus abdominis plane (TAP) blocks have been described as an effective component of multimodal postoperative analgesia for a wide variety of abdominal procedures such as bowel resection, open/laparoscopic appendectomy, cesarean delivery, hysterectomy, laparoscopic cholecystectomy, open prostatectomy, renal transplant surgery, and abdominoplasty. Various adjuvants have been added to augment the effect and prolong the duration of action of analgesia in TAP block. The mechanism of action of ultra-low-dose naloxone includes selective inhibition of the impulses from excitatory opioid receptors and release of encephalin.

Aim This study investigated the effect of ultra-low-dose naloxone on intensity and duration of analgesia of transversus abdominis plane block (TAP block). The primary outcome of the work is to assess the quality of TAB block with addition of ultra-low-dose naloxone in terms of time to first analgesic request (rescue analgesia) and visual analogue score (VAS) score. The secondary outcome is to assess opioid consumption and occurrence of complications (nausea and vomiting).

Patients and methods A total of 100 elective laparoscopic cholecystectomy patients were included in our study who were divided randomly into two groups: in the naloxone group (N) (50 patients), bilateral ultrasound-guided subcostal TAP block was done with injection of bupivacaine 0.25% in the plane +100 ng naloxone with total volume of 20 ml in each side, and in the control group (C) (50 patients), bilateral ultrasound-guided subcostal TAP block was done with injection of bupivacaine 0.25% in the plane with total volume 20 ml in each side. Then, the patients were assessed for postoperative pain after full recovery as baseline and then every 4 h for 24 h by VAS. Time to first analgesic request (rescue analgesia), postoperative opioid consumption for the first 24 h, and any adverse effects (nausea and vomiting) were noted.

Results We found, a highly significant decrease in VAS scores at 12, 16, 20, and 24 h in naloxone group compared with the control group ($P<0.01$). There was a nonsignificant difference regarding VAS scores at PACU, 4, and 8 h ($P>0.05$). Moreover, there was a highly significant increase in time to first analgesic request in naloxone group compared with the control group ($P<0.01$). Regarding secondary outcomes, there was a highly significant decrease in postoperative opioid consumption in naloxone group compared with the control group ($P<0.01$), and nonsignificant difference regarding nausea and vomiting ($P>0.05$).

Conclusion Ultra-low-dose naloxone usage in TAP block helps in reducing postoperative pain scores and postoperative opioid consumption in patients who underwent laparoscopic cholecystectomy.

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Introduction

Postoperative pain is associated with a variety of unwanted consequences, including patient suffering, distress, confusion, chest and heart problems, and prolonged hospital stays. Traditionally, postoperative pain relief is provided by medications injected intravenously such as meperidine or paracetamol, administering local anesthetic into the skin around the surgical wound, nerve block, or providing epidural injection [1].

Pain after abdominal surgeries is related mainly to somatic pain signals derived from the nerve endings in the anterior abdominal wall that originate from the skin, muscles, or parietal peritoneum. The anterior abdominal wall is supplied by sensory neurons derived from the anterior rami of spinal nerves T6–L1, which include the intercostal nerves (T6 to T11), the subcostal nerve (T12), and the ilioinguinal and iliohypogastric nerves (L1). These neurons travel through the neurofascial plane between the internal oblique and the transversus abdominis muscles [2].

The transversus abdominis plane (TAP) block is a field block used to provide analgesia to the anterior and lateral abdominal wall; it was first introduced by Rafi [3] in 2001 as a landmark-guided technique via the triangle of Petit to achieve a field block. It involves the injection of a local anesthetic solution into a plane between the internal oblique muscle and transversus

abdominis muscle. As the thoracolumbar nerves originating from the T6 to L1 spinal roots run into this plane and supply sensory nerves to the anterolateral abdominal wall, the local anesthetic spread in this plane can block the neural afferents and provide analgesia to the anterolateral abdominal wall [4].

Rafi [3] and McDonnell *et al*. [5] were the first to describe this novel abdominal field block. They described an anatomical landmark technique and provided evidence of blockade to the mid/lower thoracic and upper lumbar spinal nerves as they travelled in the fascial plane between the transversus abdominis and internal oblique muscles. With the advancement of ultrasound technology, transversus abdominis plane block (TAP block) has become technically more easier and safer to perform. The ultrasound-guided approach was first introduced in 2007 by Hebbard [6]. In 2008, Hebbard [7] described another ultrasound-guided TAP block technique designed for upper abdominal surgery referred to as the oblique subcostal approach, which is an effective method of blocking the sensory afferents supplying the anterior abdominal wall above the level of the umbilicus.

TAP blocks have been described as an effective component of multimodal postoperative analgesia for a wide variety of abdominal procedures such as bowel resection, open/laparoscopic appendectomy, cesarean delivery, hysterectomy, laparoscopic cholecystectomy, open prostatectomy, renal transplant surgery, and abdominoplasty [8]. Various adjuvants have been added to augment the effect and prolong the duration of action of analgesia in TAP block. This study investigated the effect of ultra-low-dose naloxone on intensity and duration of analgesia of TAP block [8]. Naloxone has proved to have paradoxical effects as it antagonize the opioid analgesia if given in high doses (micrograms) and produces antinociceptive effect if given in ultra-low-dose (nanogram) [9]. Different mechanisms have explained the effect of ultra-low-dose naloxone including selective inhibition of the impulses from excitatory opioid receptors and release of enkephalin [10,11]. It has been used safely via the epidural and intrathecal routes for reducing opioid adverse effects or enhancing analgesia [12]. Moreover, it was added to fentanyl and lidocaine for peribulbar anesthesia and prolonged the duration of postoperative analgesia without adverse effects [13].

Aim

The primary outcome of the work is to assess quality of block in terms of time to first analgesic request (rescue analgesia) and visual analogue score (VAS) score. The secondary outcome is to assess opioid consumption and occurrence of complications (nausea and vomiting).

Patients and methods

Patients

This is a prospective randomized controlled blind study carried out in Al Azhar University Hospital (Al-Hussein) from May 2018 to November 2018. A total of 100 patients with ASA status I and II, age between 21 and 55 years, of both sexes, undergoing elective laparoscopic cholecystectomy were included. They were divided randomly into two equal groups, control (n=50) and naloxone (n=50) groups, using a simple randomization method using sealed opaque envelops after the approval from the institutional ethics committee.

Exclusion criteria were as follows:

(1) Patient refusal.
(2) Any allergy to the drugs used.
(3) Chronic pain.
(4) Diabetes mellitus with complications.
(5) Uncontrolled hypertension.
(6) Ischemic heart disease.
(7) Severe liver or renal impairment.
(8) Pre-existing coagulation disorder.
(9) Local infection at the site of the block.
(10) Hemodynamically unstable patients.
(11) Administration of opioid 24 h before operation.

Methods

On admission, all patients fasted for 8 h according to the fasting guidelines, and were informed about the study design, objectives, as well as tools and techniques. They provided written informed consent to participate in the study after being aware about the maneuvers of this study.

Patients were informed about the analgesic techniques on the day of surgery and were instructed on how to express pain intensity with use of the VAS (0=no pain and 10=the worst imaginable pain).

After preoperative assessment by clinical examination and laboratory investigations and on arrival to operating room, a peripheral intravenous cannula (20-G) was inserted in the nondominant hand; premedications were given in the form of ondansetron 4 mg, midazolam 0.04 mg/kg, and fentanyl 2 μg/kg. After preoxygenation for 3 min, general anesthesia was induced with propofol 2 mg/kg, tracheal intubation

was performed after 3 min following administration of a nondepolarizing neuromuscular blocking drug atracurium 0.5 mg/kg, and general anesthesia was maintained with 1.2% isoflurane in oxygen and atracurium 0.1 mg/kg/h infusion.

Volume-controlled ventilation was used to maintain O_2 saturation more than 98% and end tidal CO_2 35–40 mmHg. Overall, 50 μg of fentanyl was given when heart rate or blood pressure increased by 20% from the baseline reading, and ephedrine 10 mg if blood pressure decreased by 20%. Continuous monitoring was done during the procedures using GE Datex-Ohmeda (GE Healthcare, Chicago, Illinois), which involved 5-lead ECG, noninvasive blood pressure, pulse oximetry, and end tidal CO_2.

At the end of the surgery and before emergence from general anesthesia, patients were divided into two groups:

(1) The naloxone group (N) (50 patients): bilateral ultrasound-guided subcostal TAP block was done with injection of bupivacaine 0.25% in the plane with 100 ng naloxone with total volume 20 ml in each side.
(2) The control group (C) (50 patients): bilateral ultrasound-guided subcostal TAP block was done with injection of bupivacaine 0.25% in the plane with total volume 20 ml in each side. In all patients, ultrasound was used (sonosite m turbo Fujifilm, Bothell washington, USA) with high-frequency probe, and a 22-G spinal needle [BD Quincke (BD Company, Haryana, India) spinal needle] was used for local anesthetic injection (control group).

Patients were assessed by VAS for postoperative pain after full recovery of patients as baseline and then every 4 h for 24 h. If VAS score is at least 3 or on patient request, mepridine 50 mg intravenous was given as rescue analgesia, which was recorded. Time to first analgesic request (min) and postoperative opioid consumption (mg) for the first 24 h were assessed. Any adverse effects (nausea and vomiting) were also recorded and treated by metoclopramide 10 mg intravenous.

Statistical analysis

Data entry, processing, and statistical analysis was carried out using MedCalc version 18.2.1 (MedCalc, Ostend, Belgium). Tests of significance (Mann–Whitney *U*, Student's *t*, and χ^2-tests) were used. Data were presented, and suitable analysis was done according to the type of data (parametric and nonparametric) obtained for each variable. *P* values less than 0.05 (5%) was considered to be statistically significant.

Results

Regarding primary outcome (VAS score and time to first analgesic request), follow-up period revealed the following:

(1) There was a highly significant decrease in VAS scores at 12, 16, 20, and 24 h in naloxone group compared with the control group, with highly significant statistical difference ($P<0.01$). The median values of VAS scores in naloxone group were 2, 2, 2, and 2 and in control group were 3, 3, 4, and 4, at 12, 16, 20, and 24 h, respectively, with highly significant statistical difference ($P<0.01$), as shown in Table 1.
(2) There was a nonsignificant difference regarding VAS scores on arrival to PACU, 4, and 8 h ($P>0.05$), as shown in Table 1.
(3) There was a highly significant increase in time to first analgesic request in naloxone group (mean value: 150 min) compared with the control group (mean value 108 min), with highly significant statistical difference ($P<0.01$; Table 2).

Regarding secondary outcomes (postoperative opioid consumption and complications), follow-up period revealed the following:

(1) There was a highly significant decrease in postoperative opioid consumption in naloxone

Table 1 Comparison between the two groups as regards visual analogue scale

Variables	Naloxone group (50) [median (IQR)]	Control group (50) [median (IQR)]	Mann–Whitney *U* (*P* value)
VAS (PACU)	2 (1–7)	2 (1–8)	>0.05
VAS (4 h)	2 (1–4)	2 (1–4)	>0.05
VAS (8 h)	2 (1–3)	2 (1–5)	>0.05
VAS (12 h)	2 (1–4)	3 (2–4)	<0.001**
VAS (16 h)	2 (1–3)	3 (3–5)	<0.001**
VAS (20 h)	2 (1–3)	4 (2–5)	<0.001**
VAS (24 h)	2 (1–3)	4 (3–6)	<0.001**

IQR, interquartile range; VAS, visual analogue scale. **means highly significant.

Table 2 Comparison between the two groups as regards time to first analgesic request

Variable	Naloxone group (50) (mean ±SD)	Control group (50) (mean ±SD)	Student's *t* (*P* value)
Time to first analgesic request (min)	150±94.4	108.4±90.3	<0.001**

**means highly significant.

group (mean value: 70 mg) compared with control group (mean value: 138 mg), with highly significant statistical difference ($P<0.01$; Table 3).

(2) There was a nonsignificant difference regarding nausea and vomiting ($P>0.05$), as shown in Table 3.

Discussion

In this study, a total of 100 cholecystectomy patients between 21 and 55 years of age were included in the study.

Regarding primary outcomes, VAS score and time to first analgesic request, follow-up period revealed the following:

There was a highly significant decrease in VAS scores at 12, 16, 20, and 24 h in naloxone group compared with control, with highly significant statistical difference ($P<0.01$ respectively). The median values of VAS scores in naloxone group were 2, 2, 2, and 2 and in control group were 3, 3, 4, and 4 at 12, 16, 20, and 24 h, respectively, with highly significant statistical difference ($P<0.01$). These results are in agreement with Movafegh *et al.* [14], who studied the effect of addition of ultra-low-dose naloxone to lidocaine with or without fentanyl in axillary brachial plexus block, which prolonged the time of first postoperative pain and motor blockade.

There was also a highly significant increase in time to 1st analgesic request in naloxone group (mean value 150 min) compared with control group (mean value 108 min), with highly significant statistical difference ($P<0.01$). These results are in agreement with Ezz and Elkala [15], who studied the effect of ultra-low-dose naloxone added to fentanyl and lidocaine for peribulbar anesthesia and found an increase in time of first rescue analgesic in naloxone group than the other group.

Regarding secondary outcomes, postoperative opioid consumption and complications, follow-up period revealed the following:

There was a highly significant decrease in postoperative opioid consumption in naloxone group (mean value

Table 3 Comparison between the two groups as regards postoperative opioid consumption and complications data

Variables	Naloxone group (50)	Control group (50)	χ^2 *P* value
Nausea	8 (16)	7 (14)	>0.05
Vomiting	2 (4)	3 (6)	>0.05
Postoperative opioid consumption (mg)	70±20.7	138±19.1	<0.001

70 mg) compared with the control group (mean value 138 mg), with highly significant statistical difference ($P<0.01$). These results are in agreement with Gan *et al.* [16], who reported that ultra-low-dose naloxone infusion increased morphine analgesia and decreases postoperative narcotics consumption after hysterectomy.

On the contrary, Urman [17] reported that patients taking buprenorphine/naloxone require higher than usual doses of opioid to control severe acute pain.

Abdallah *et al.* [18] in a meta-analysis of 12 randomized controlled trials studied the duration of analgesia associated with posterior and lateral TAP blocks in lower abdominal surgery and found reduced postoperative morphine consumption by 9.1 mg and lowered pain scores at 24, 36, and 48 h.

Conclusion

Ultra-low-dose naloxone with TAP block is a good alternative adjuvant that reduces postoperative pain scores and postoperative opioid consumption in patients who underwent laparoscopic cholecystectomy.

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Conflicts of interest

There are no conflicts of interest.

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