

## Postoperative Analgesia after Laparoscopic Cholecystectomy - Prospective, Randomized, Double Blind, Control Trial

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### Rezumat

#### *Analgezia postoperatorie în colecistectomia laparoscopică - studiu prospectiv, randomizat*

Scopul acestui studiu prospectiv, randomizat, dublu orb, a fost de a evalua cea mai eficientă modalitate de analgezie postoperatorie în colecistectomia laparoscopică.

*Material și metodă:* 81 de pacienți incluși în studiu, au fost randomizați în 3 grupuri. Grupul A a inclus pacienți cu analgezie multimodală clasică cu opioid, grupul B a inclus pacienți cu analgezie prin tehnica de bloc de plan transvers abdominal (TAP) cu abord subcostal și grupul C a inclus pacienți cu analgezie prin tehnica infiltrației cu anestezic local a locului de inserție a trocarelor. Obiectivul principal a fost evaluarea eficienței analgeziei realizate, în primele 24 ore postoperator, utilizând ca instrument de evaluare a durerii, scala analogă vizuală de durere (VAS). Obiectivul secundar a fost consumul de opioide, intraoperator și în primele 24 ore postoperator.

*Rezultate:* 75 pacienți au fost incluși în analiza finală a datelor. Scorul VAS evaluat în condiții de repaus, în primele 24 ore postoperator, a fost semnificativ mai mic în grupul pacienților cu bloc TAP comparativ cu grupurile A și C ( $p < 0.001$ ). Consumul intraoperator de fentanil și de petidină postoperator au fost semnificativ mai reduse în grupul pacienților cu bloc TAP comparativ cu celelalte 2 grupuri de studiu ( $p < 0.001$ ).

*Concluzii:* În colecistectomia laparoscopică, tehnica de analgezie utilizând blocul de plan transvers abdominal a fost mult mai eficientă comparativ cu tehnica clasică de analgezie cu opioide sau tehnica de infiltrație cu anestezic local a locului de inserție a trocarelor.

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Cuvinte cheie: colecistectomia laparoscopică, analgezie postoperatorie, bloc de plan transvers abdominal, infiltrație cu anestezic local

## Abstract

In this prospective, randomized, double blind control trial we aim to investigate which of the most used analgesic techniques after laparoscopic cholecystectomy is the most efficient.

*Methods:* This study included 81 patients that were randomly distributed into 3 groups using a computer-generated random number which was enclosed in a sealed envelope: group A (control) received classic multimodal iv opioid analgesia, group B received Tap block in oblique subcostal approach (OSTAP) and group C received local anesthetic infiltration of the trocar insertion sites (LAI). The primary outcome of this trial was to evaluate the efficacy of each analgetic technique by measuring VAS pain scores. Secondary outcome included intraoperative opioid requirement and the opioid consumption in the first 24h postoperatively. Intraoperative parameters and outcome data were recorded by an anesthesiologist who was blinded to the study groups.

*Results:* We analyzed a total of 75 patients. For the primary outcome variable, VAS pain scores at rest were significantly reduced in OSTAP group at each time point assessed in the first 24 hours after surgery compared with LAI group and IV opioid analgesia group ( $p < 0.001$ ). Intraoperative fentanyl consumption and 24h pethidine consumption were also significantly reduced in TAP block group compared with LAI group and IV opioid analgesia group ( $p < 0.001$ ).

*Conclusions:* Our study showed that OSTAP block is a more efficient analgesia technique compared with IV opioid analgesia and with local anesthetic infiltration of trocar sites after laparoscopic cholecystectomy surgery. This trial was registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT02707250).

Key words: laparoscopic cholecystectomy, postoperative analgesia, Tap-block, local anesthetic infiltration

## Introduction

Laparoscopic cholecystectomy (LC) is the mainstay surgical treatment of gallstone disease. Despite the minimally invasive nature of this procedure, the postoperative pain may be moderate or severe in the first 24 hours post-surgery and can contribute to patient discomfort, prolonged immobilization, and delayed discharge.

Pain after laparoscopic cholecystectomy is more complex and involves 3 components: somatic (incisional) pain, visceral (deep intra-abdominal) pain, shoulder pain and carries a high interindividual variability in intensity and duration. Visceral pain due to the trauma of gallbladder resection and to the diaphragmatic irritation by the CO<sub>2</sub> pneumoperitoneum seems to be more prominent in the first 24 hours after

surgery and is increased by coughing and not affected by mobilization (1,2). Due to these complexities of pain after laparoscopic cholecystectomy, the analgesic approach should be multimodal.

The routine multimodal analgesia approach includes paracetamol, conventional NSAID/COX2 selective inhibitor and opioid as a rescue analgesia (3), but this conventional pain management with opioids can increase the incidence of adverse effects, such as excessive sedation and postoperative nausea and vomiting (PONV). As these side effects may increase hospital stay durations, proper pain control and management are therefore critical for improving clinical outcomes (1).

The administration of local anesthetic via a transversus abdominal plane (TAP) block, or as infiltration of the trocar sites have been

used as a part of a multimodal strategy to optimize postoperative pain control in laparoscopic cholecystectomy (3-6).

Ultrasound-guided (USG) transversus abdominis plane (TAP) block, and in particular the oblique subcostal approach (OSTAP), is an effective strategy for pain relief in patients undergoing laparoscopic cholecystectomy, reducing pain intensity, opioid consumption, and opioid-related side effects (4-10).

Local anesthetic infiltration (LAI) of trocar insertion sites has been shown to decrease postoperative pain (11,12). It remains uncertain whether one of these techniques is superior to the other.

The aim of this study was to compare the ultrasound-guided bilateral oblique transversus abdominis plane block with local anesthetic infiltration of trocar sites and conventional multimodal analgesia in terms of intra- and postoperative analgesia efficiency in laparoscopic cholecystectomy surgeries. The primary outcome was to evaluate the pain scores in the first 24 hours. The secondary outcomes were the intraoperative opioid need, postoperative opioid consumption in the first 24 hours and time to give the first dose of opioid postsurgery. The duration of surgery and local and systemic complications due to local anesthetic were also registered.

## Materials and Methods

This prospective, double-blind, randomized control trial was approved by the Institutional Ethics Committee of the Regional Institute of Gastroenterology and Hepatology „Prof. Dr. Octavian Fodor” Cluj-Napoca (2063/25.II.2017). Signed informed consent was obtained voluntarily from all patients included in the study. This study was performed at Regional Institute of Gastroenterology and Hepatology „Prof. Dr. Octavian Fodor” Cluj-Napoca, Romania and complied with the Declaration of Helsinki and adhered to the applicable CONSORT guidelines.

Adult patients over 18 years, with American Society of Anesthesiologists (ASA) physical status class I–II, scheduled for

elective laparoscopic cholecystectomy were included in the study. Patients were randomly assigned into three groups using a computer-generated random number which was enclosed in a sealed envelope and was opened by an anesthesiologist who was not involved in the study.

Patients in group A (IV opioid group) received a standard multimodal IV analgesia that included opioid and non-opioid analgesics; patients in group B (TAP block group) received bilateral subcostal USG TAP block with bupivacaine 0.25%. Group C (LAI group) included patients that received preincisional local infiltration of trocar sites with bupivacaine 0.25%.

Exclusion criteria were as follows: patient's refusal, patients with local anesthetic and pethidine allergy, morbidly obese patients with a BMI > 35 kg/m<sup>2</sup>, patients with ASA class III; acute cholecystitis, daily pain medication for chronic pain, patients who were converted to open surgery.

All patients received a standardized anesthetic regimen. Anesthesia was induced with intravenously (IV) administered propofol 2 mg/kg (propofol 1%, Fresenius Kabi, Romania), fentanyl 2 mcg/kg (500 mcg / 10 ml Kalcelex), and atracurium (50 mg / 5 ml Kalcelex) 0.5 mg/kg or 0.6 mg/kg rocuronium bromide (Esmeron 100 mg/10 ml; MSD) to facilitate endotracheal intubation. Anesthesia was maintained with oxygen, air (in a mixture of 50% oxygen, 50% air) and 2 MAC (minimum alveolar concentration) sevoflurane (Sevoanesteran 250 ml Rompharm) using pressure-controlled ventilation.

The following parameters were recorded intraoperatively every 5 min: HR, ECG, SpO<sub>2</sub>, NIBP, and end-tidal carbon dioxide. The neuromuscular block was assessed using train of four stimulation (TOF).

At the end of the surgery, the neuromuscular block was reversed with neostigmine 0.04 mg/kg and atropine 0.01 mg/kg. Patients were extubated when awake and TOF ≥ 90%.

After the induction of anesthesia, patients received their analgesic intervention according to group allocation.

The IV analgesics group (group A) received standard intraoperative analgesia with opioid (fentanyl). For patients undergoing TAP block (group B), all block procedures were performed by the same experienced anesthesiologists. A US-guided OSTAP block with 20 ml bupivacaine 0.25% each side was performed bilaterally before surgical incision. A high frequency linear ultrasound probe (6-10 MHz, Mindray DC-3 Biomedical Electronics, Shenzhen, China) was placed subcostally in the epigastric area, then moved along the subcostal edge to identify the rectus abdominis and transverse abdominis (TA) muscles. Then, a 22-gauge, 150-mm needle (SonoTap cannula, PAJUNK, Medizintechnologie, Germany) was inserted in the plane of the US probe, and on entering the TAP. The patient included in group C (LAI group), received preincisional infiltration of the port insertion site with 5 ml of 0.25% bupivacaine at each port insertion site performed by the surgeon.

For an increase in HR or mean blood pressure of more than 20% of baseline intraoperatively, supplemental analgesia was provided with 0.5-1 mcg/kg IV fentanyl in all study groups.

A standardized postoperative analgesic regimen was used consisting of IV acetaminophen 1000 mg every 6 hours (the first dose initiated intraoperatively, 30 minutes before end of surgery) and pethidine 25-50 mg bolus on request. Before surgery, all patients were instructed how to quantify the pain intensity using an ungraded 10-cm visual analogue scale (VAS) which displays a line indicating a pain score (0.no pain at one end, 10. intolerable pain at the other end).

Patient were admitted to the postanesthetic care unit (PACU) room and were assessed for pain using VAS score. When the pain intensity was moderate (VAS > 4) or severe (VAS > 7), patients received pethidine 25-50 mg bolus until the VAS < 4 was achieved. The criteria for discharge from the PACU were pain control (VAS < 3), absence of nausea and vomiting, hemodynamic stability, and alert or appropriately responsive to voice. On discharge, all patients had achieved a modified Aldrete score of  $\geq 9$ .

In the ward, analgesia requirement was checked at 30 minutes and moderate to severe pain was treated. For nausea and vomiting, ondansetron 4 mg IV was given.

The primary outcome measure of the study was VAS pain scores at 0, 6, 12, and 24 hours postoperatively. The secondary outcome measures of the study were intraoperative fentanyl consumption and postoperative pethidine consumption in the first 24 hours, time to first dose of pethidine postoperatively.

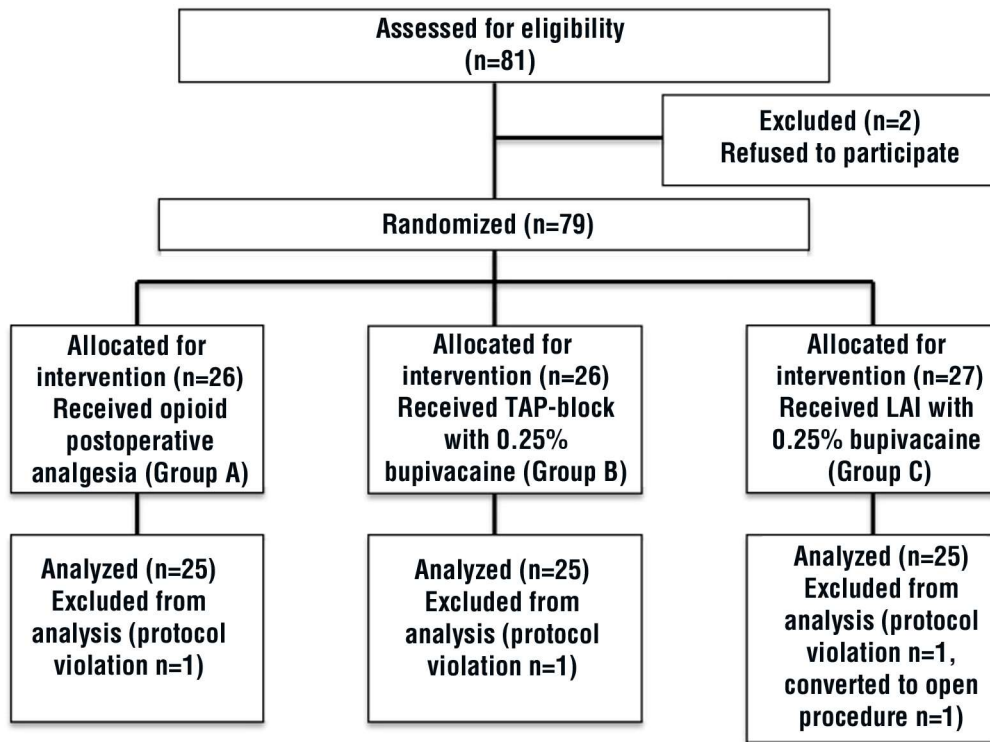
Intraoperative parameters were recorded by an anesthesiologist who was blinded to the study groups. Outcome data were collected either by anesthesiologist or by nursing staff who were blinded to the study groups.

### *Statistical Analysis*

Sample size calculation. For the main outcome measurement, we looked for a minimum difference between two VAS measurements of 2, assuming a standard deviation of 2 per group (a study found a 1.3 standard deviation for TAP) (13), respectively an interquartile range of 2 to 3 (14). With a power of 80% (using a t-test for independent samples, with a two-sided p-value) and a level of confidence of 0.017 (since in our study we used three comparisons for the three arms, a Bonferroni correction would reduce three times the 0.05 level of confidence), a total sample size of 69 subjects (i.e., 23 subjects per each group) was obtained. We set the final sample size of 81 to allow for possible loss to follow-up.

R- Environment for Statistical Computing ver.3.2.1 was used for statistical analysis. The Shapiro-Wilk test was employed to determine whether data sets differed from a normal distribution. Quantitative data were described as means and standard deviation for those with normal distribution or as a median and interquartile for those who are not normally distributed.

Evaluation of the association between qualitative variables was tested by  $\chi^2$  test. To assess whether there are differences between three or more independent groups of quantitative data, Kruskal - Wallis test was used (for



**Figure 1.** Flow diagram of patient distribution. TAP- transversus abdominis plane. LAI-Local anesthetic infiltration

data without a normal distribution) or ANOVA test (for data with normal distribution). The Tukey-Kramer HSD (honestly significant difference) test was used post hoc to determine if there are differences between the study groups. The threshold for statistical significance was set at 0.017, considering the Bonferroni correction for the three comparisons.

## Results

Eighty-one patients were eligible to be enrolled in the study. Seventy-nine patients were recruited and randomly assigned to their treatment group. However, 4 patients were later excluded resulting in 75 patients in the final analyses (*Fig. 1*).

All US-guided OSTAP blocks were performed without any complications.

**Table 1.** Demographic and perioperative data

| Group                         | Group A<br>(n=25) | Group B<br>(n=25) | Group C<br>(n=25) | P<br>value |
|-------------------------------|-------------------|-------------------|-------------------|------------|
| Age (year)                    | 52.6 ± 13.4       | 52.5 ± 15.8       | 49.9 ± 12.4       | 0.75       |
| Weight (kg)                   | 74.4 ± 17.8       | 74.2 ± 12.2       | 76.8 ± 11.4       | 0.77       |
| ASA psychical status (n) I/II | 10 /15            | 16 /9             | 14 /11            | 0.22       |
| Sex F/M                       | 17/8              | 15/10             | 14/11             | 0.67       |
| Surgery time (min)            | 45 (35, 55)       | 40 (35, 50)       | 40 (35, 60)       | 0.69       |

Group A- IV-opioid analgesia, group B - OSTAP block, Group C (LAI) -local anesthetic infiltration

Data are expressed as mean ± standard deviation, median (interquartile range) or number

Data were analysed using Kruskal - Wallis test, ANOVA for comparison between all 3 groups and post-hoc Tukey-Kramer method for pairwise comparisons.

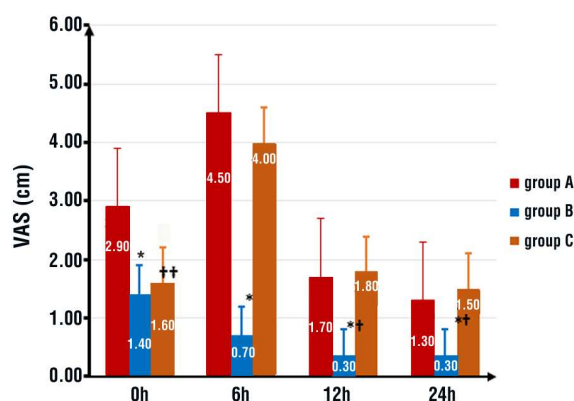
Patients' characteristics and perioperative data are depicted in *Table 1*; there were no significant differences between groups.

In terms of postoperative analgesia quality, there were statistically significant differences between the three groups (*Fig. 2*).

The primary outcome variable, VAS pain scores at rest were significantly reduced in TAP block group at each time point assessed in the first 24 hours after surgery compared with LAI group and IV opioid analgesia group ( $p < 0.001$ ). TAP block group had a statistically significant lower VAS pain score ( $0.7 \pm 0.4$ ) at 6 hours post-surgery compared with VAS pain score in LAI group ( $4.0 \pm 0.9$ ) and in IV opioid analgesia group ( $4.5 \pm 1.1$ ) ( $p < 0.001$ ) (*Fig. 2*). The VAS pain scores in TAP block group were significantly reduced at 6, 12, 24 hour after surgery vs local anesthetic infiltration group ( $p < 0.001$ ) (*Fig. 2*). TAP block and trocar infiltration site with local anesthetic demonstrated similar analgetic efficiency in the first hour after surgery. The secondary outcomes, intraoperative fentanyl consumption and postoperative pethidine consumption in the first 24 hours, time to first dose of pethidine postoperatively, were presented in *Table 2*.

Intraoperative fentanyl consumption was significantly lower in OSTAP group ( $168.4 \pm 47.5$  mcg) than in groups receiving local anesthetic infiltration (group C) or IV opioid analgesia group (group A) ( $297.6 \pm 83.8$  mcg;  $379.2 \pm 73.2$  mcg) ( $p < 0.001$ ).

Median pethidine consumption (0-24 hours postoperatively) was 30 mg (IQR 0-60 mg) in the OSTAP block group (group B) compared to 60 mg (IQR 60-60) in the LAI group (group C) ( $p < 0.006$ ). Also, median pethidine consump-



**Figure 2.** Visual Analog Scale (VAS) Pain Scores (mean and SD) at rest

Group A - IV opioid analgesia; Group B (OSTAP-block), Group C (LAI) - local anesthetic infiltration. Data were analyzed using Kruskal - Wallis test for comparison between all 3 groups and post- hoc Tukey-Kramer method for pairwise comparisons. VAS pain scores were significantly lower in OSTAP block group vs IV opioid analgesia and LAI groups at 0 to 24 hours ( $p < 0.001$ ).

\* $p < .001$ - VAS pain scores were significantly lower in OSTAP group vs IV opioid group at 0 to 24 hours;

† $p < .001$ - VAS pain scores were significantly lower in OSTAP group vs LAI group at 12 and 24 hours after surgery;

†† $p < .001$ - VAS pain scores were significantly lower in LAI group vs IV opioid analgesia group at 0 hour postoperatively.

tion (0-24 hours postoperatively) was significantly lower in OSTAP block group than in IV opioid analgesic group, (30 mg IQR 0-60 vs 90 mg IQR 60-90) ( $p < 0.001$ ).

## Discussion

In this study, we have demonstrated that the application of bilateral OSTAP or LAI with bupivacaine 0.25% in patients undergoing laparoscopic cholecystectomy was more effective in reducing overall pain score at rest compared with IV multimodal analgesia in the first 24 hours postoperatively. OSTAP block was more effective in reducing VAS pain scores at 6, 12, and 24 hours as compared to

**Table 2.** Opioid consumption, time to first dose of pethidine

| Group                                     | Group A<br>(n=25) | Group B<br>(n=25) | Group C<br>(n=25) | P <sup>a</sup><br>value |
|-------------------------------------------|-------------------|-------------------|-------------------|-------------------------|
| Intraoperative Fentanyl consumption (mcg) | 379.2 ± 73.2      | 168.4 ± 47.5      | 297.6 ± 83.8      | < 0.001                 |
| Pethidine consumption /24h (mg)           | 90 (60, 90)       | 30 (0, 60)        | 60 (0, 60)        | < 0.001                 |
| Time to first dose of pethidine (min)     | 10.8 ± 8.0        | 17.8 ± 8.1        | 12.4 ± 10.7       | 0.11                    |

Group A - IV-opioid analgesia, group B - OSTAP block, group C (LAI) - local anesthetic infiltration

Data are expressed as mean ± standard deviation, median (interquartile range).

Data were analysed using Kruskal - Wallis test for comparison between all 3 groups<sup>a</sup> and post- hoc Tukey-Kramer method for pairwise comparisons<sup>b</sup>

patients receiving local anesthetic infiltration of port insertion. Furthermore, a significantly lower postoperative opioid consumption (pethidine) in the first 24 hours postoperatively, was noted in patients receiving bilateral OSTAP or LAI compared to those who received IV multimodal analgesia.

In a retrospective study of 515 patients who had undergone laparoscopic cholecystectomy, Tekeli et al. (10) demonstrated that bilateral TAP block performed after anesthesia induction, significantly reduced pain scores in the first 6 hours postoperatively and the need for additional analgesic. Furthermore, TAP block reduced the rate of adverse effect such as nausea and vomiting. In our study, we performed a USG guide bilateral OSTAP block after anesthesia induction, and we found a VAS pain scores significantly lower than with IV analgesics at each time point assessed (6, 12, 24 hours postoperatively).

Similar results were reported by Peng K (4) Wang W et al. (6) and in two meta-analyses which showed a significant reduction in pain intensity as well as reduced opioid consumption up to 24 hours in patients undergoing LC who received USG-guided TAP block, relative to group patients receiving a conventional analgesia. These results were reported when the TAP block was performed preincisional, after anesthesia induction or at the end of surgery, and the technical approaches of the block were subcostal or posterior. Some other studies showed no difference in pain scores of TAP blocks compared to conventional analgesia with opioids (15,16).

Local anesthetic infiltration of trocar insertion sites, a common practice for LC, does not require additional equipment and has been shown to decrease postoperative pain and the analgesic requirement in the first 24 hours; but the clinical importance of this reduction in pain seems to be small compared to conventional analgesia techniques (12-17).

Laparoscopic cholecystectomy is the type of surgery that can be performed not only electively, but also as a day surgery, so postoperative analgesia has become a challenge for the anesthetist, knowing the fact that post-

operative pain can be severe and can require high doses of opioid. Multimodal IV analgesia with opioids, sometimes in high doses, leads to a delayed discharge because of undesirable side effects as PONV, sedation, respiratory depression.

In an attempt to reduce the use of postoperative opioids, various regional analgesia techniques have been described, the most intensively studied being TAP and LAI.

The subcostal transversus abdominis (STA) block, is a recently described variation on the TAP block which produces unilateral supra-umbilical analgesia, and has been studied in laparoscopic cholecystectomy showing the reduction of postoperative pain and opioid use (5,7,9,13,18). The same results we demonstrated in our study using OSTAP as a component of perioperative analgesia. There are also studies that have not demonstrated the superiority of OSTAP block compared with IV morphine in providing effective analgesia during laparoscopic cholecystectomy (19,20), one of the possible explanations being that OSTAP is carried out by ultrasound guidance, which requires a learning curve with the acquisition of some skills to achieve this technique correctly.

In our study, we found that OSTAP block was more effective in reducing VAS pain scores at rest at 6, 12, and 24 hours as compared to patients receiving local anesthetic infiltration of port insertion. Furthermore, the opioid consumption up to 24 hour was significantly reduced in OSTAP block compared to IV conventional multimodal analgesia and local anesthetic infiltration. The efficiency of local anesthetic infiltration technique was short, comparable with OSTAP block only in first postoperative hour, so at 6, 12, 24 hours postoperatively, the VAS pain scores were higher than in OSTAP block group. Similar results were demonstrated by other studies. Thus, a recent meta-analysis of Grape S et al. (21) showed a significant difference in pain score during rest at 2, 12, 24-hour postoperative hours in favor of TAP block when compared to wound infiltration despite the heterogeneity regarding timing in the block (preincisional vs

end of surgery), the impact of volume on spread within the TAP plane vs administration into the wound directly. Postoperative morphine consumption at 12 and 24 hours was significantly lower in patients who received a TAP block compared to wound infiltration (20). Some other studies demonstrated the superiority of ultrasound-guided bilateral subcostal TAP block in providing postoperative analgesia after laparoscopic cholecystectomy compared to port-site infiltration (22,23).

In our study, the lower VAS pain scores in OSTAP block group of patients vs LAI group at 12-24h can also be explained by the differences in the volume of local anesthetic used between the two methods. For OSTAP block group, a total of 40 ml of bupivacaine 0.25% was infiltrated, while for LAI group, a total of 20 ml of bupivacaine 0.25% was infiltrated. This increased volume of local anesthetic could have influenced the quality and duration of postoperative analgesia between the two groups.

Another study compared TAP block with LA infiltration into the wounds showed no difference in providing postoperative analgesia after laparoscopic cholecystectomy (6,24, 25). Furthermore, a meta-analysis compared transversus abdominis-plane block with local anesthetic wound infiltration in lower abdominal surgery, showed comparable short-term postoperative analgesia, but TAP block has better long-lasting effect (26).

In our study, the intraoperative opioid consumption was reduced by the OSTAP block and LAI block which were performed before the application of the painful stimulus. Also, the reduction in intraoperative opioid use after preoperative TAP block has been shown in various surgeries (27,28).

There are several limitations to this study. The success of sensory block in the target area could not be assessed. The Pain score was not evaluated with patient's movement. We have no assessment points from 0 to 6 hours or after 24 hours postoperatively. The volume of local anesthetic infiltrated at all four-trocar port

site was lower than total volume of anesthetic infiltrated at bilateral transversus abdominis plane and can influence pain scores at different time point assessed in the first 24 hours after surgery.

## Conclusions

In conclusion, our study showed that OSTAP block in addition to basic analgesic regimen with acetaminophen after laparoscopic cholecystectomy had reduced pain scores as well as opioid consumption more than local anesthetic infiltration of trocar insertion sites in the first 24 postoperative hours.

## Ethical Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of IRGH Cluj (2063/25.II.2017).

## Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

## Data Availability Statement

All data supporting those findings are available for review at "O. Fodor" Regional Institute of Gastroenterology and Hepatology Cluj-Napoca Romania

## Conflicts of Interest

The authors declare no conflict of interest.

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