Doi: 10.5152/TJAR.2019.60251

Review

Regional Anaesthesia

Turkish Journal of Anaesthesiology & Reanimation

The Effect of Transversus Abdominis Plane Block for Analgesia in Patients Undergoing Liver Transplantation: A Systematic Review and Meta-Analysis

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Cite this article as: Sharma A, Goel AD, Sharma PP, Vyas V, Agrawal SP. The Effect of Transversus Abdominis Plane Block for Analgesia in Patients Undergoing Liver Transplantation: A Systematic Review and Meta-Analysis. Turk J Anaesthesiol Reanim 2019; 47(5): 359-66.

Abstract

Objective: Ultrasound-guided regional anaesthesia using transversus abdominis plane (TAP) block is a newer and safer method that can be used in patients undergoing liver transplant surgeries. This systematic review and meta-analysis was done to quantify the analgesic potential and opioid-sparing capability of TAP block in these patients.

Methods: The studies comparing TAP-block to conventional analgesic regimens for liver transplant were searched. The studies evaluating the comparative 24-h morphine consumption during postoperative period in patients undergoing liver transplant surgeries were searched and included as the primary outcome in the analysis.

Results: We found two randomised controlled trials and two retrospective studies that on meta-analysis showed that TAP block group had significantly lower requirement of morphine (WMD=27.59 mg; 95% CI: 33.47–21.70) at 24 h for pain mitigation. Also, postoperative nausea and vomiting was lower (RR=0.76; 95% CI: 0.47–1.22) but not statistically significant.

Conclusion: Ultrasound-guided TAP block provides postoperative analgesic efficacy in patients undergoing liver transplant surgeries. This study was registered in International prospective register of systematic reviews [PROSPERO: CRD42018094595].

Keywords: 24-h morphine, transversus abdominis plane (TAP) block, postoperative nausea and vomiting

Introduction

For patients undergoing liver transplant surgeries, adequate analgesia can often be challenging for the transplant teams. Prescriptions of analgesic drugs need consideration for deranged pharmacokinetics of drugs and higher chances of associated adverse effects (1). Perioperative care teams rely on opioids or different forms of regional analgesia. The use of epidural analgesia is considered as a gold standard for major abdominal surgeries, but it also has limitations in this population because of altered coagulation profile (2). Evidence suggests against the use of central neuraxial block in patients with chronic liver failure due to associated coagulation disorders (3).

Many trials have studied different regimens that can have opioid-sparing effect for patients undergoing organ transplantation (4). Recently, ultrasound-guided peripheral nerve blockade has been used for management of acute postoperative pain. These blocks can be executed with low risk of complications (5). Transversus abdominis plane (TAP) block is one of them. It requires anaesthesia to the sensory nerve supply of the anterior abdominal wall. Blockade of

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Received: 02.09.2018 Accepted: 04.01.2019
Available Online Date: 24.04.2019

sensory nerves is achieved in the neurofascial plane between the internal oblique and transversus abdominis muscles either through landmarks technique or by use of ultrasound (6).

Ultrasound-guided regional anaesthesia using TAP block is a relatively newer and safer method in patients undergoing open abdominal surgeries like liver transplant donors and recipients for perioperative analgesia and opioid-sparing potential (7). This systematic review and meta-analysis was done to review the existing evidence and quantify the analgesic potential and opioid-sparing capability of TAP block in patients undergoing liver transplant surgeries.

Methods

This study was registered in International prospective register of systematic reviews [PROSPERO: CRD42018094595]. For the present analysis, Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. A population, intervention, control, and outcome study (PICOS) format was used to identify the potential trials that could be included in the present meta-analysis. After literature search, trials were abstracted into a standardised PICOS format (Table 1), and two independent reviewers assessed relevance to our research question. The studies evaluating the comparative 24-h morphine consumption during postoperative period in patients undergoing liver transplant surgeries were included as the primary outcome in the analysis. The salient features of trials included in the final analysis are shown in Table 2.

Search strategy

Two independent researchers performed the preliminary data search in Cochrane Central Register of Controlled Trials, Clinical trial registry, PubMed, Scopus and Google Scholar. Comparative trials published until April 2018 were included in the analysis. The following keywords were searched for in the above said databases – ("transversus abdominis plane block" OR "TAP Block") AND ("Liver Transplantation"[Mesh] OR "Liver transplantation" OR "Liver transplant" OR "Hepatic transplantation" OR "OLT" OR "Liver donor" OR "Liver recipient"). In this analysis, comparative trials of both prospective and retrospective nature were included.

We also manually searched the references for relevant studies in grey literature and peer-reviewed abstracts published in the proceedings of meetings. Once the abstracts were analysed by the authors and found appropriate, the full text of the articles were further studied. The decision to include a trial into final analysis was based on the independent assessment of the two authors. Any disagreements between the two were harmonised by consensus and arbitration by a third neutral author. Another independent researcher assessed for quality of evidence and possible methodological bias.

Data extraction

Data were abstracted into a standardised format for characteristics like study design, country of publication, year, sample size, primary and secondary outcomes, drug doses used in TAP block, use of ultrasound, catheter for continuous block, opioids needed in perioperative period, pain scores at various time intervals, incidence of postoperative nausea vomiting (PONV), and specific adverse effects (Table 2). Authors who had reported outcomes as median and interquartile range were contacted to provide values in mean and standard deviation. If authors did not reply, we estimated the mean using the validated formula: mean=(2m + a + b)/4 where m is the median and a and b are first and third quartiles, respectively (8). The SD was estimated by the formula given by the Higgins et al: interquartile range=1.35 SD (9, 10).

Table 1. Data extraction framework based on PICOS format

Population	- Adults (≥18 years)
	- Healthy donors for liver transplantation
	- Patients with chronic liver failure for liver transplantation (recipients)
Interventions	Patients receiving local-anaesthetic-based transverse abdominis plane (TAP) block during the preoperative or immediately after the surgery.
	The TAP block could be single shot or catheter-guided continuous block.
	TAP block could be ultrasound-guided, tactile-pop-based or surgeon-assisted catheter insertion during closure.
Controls	Donor and recipients undergoing liver transplant surgery and receiving perioperative multimodal intravenous analgesia not based on TAP block.
Outcomes	**Primary outcome**
	Comparison of first postoperative day opioids (in morphine equivalents) consumption in both the groups
	Secondary outcome
	Postoperative nausea vomiting incidence comparison
Study design	Comparative trials evaluating use of TAP block against conventional intravenous analgesics – including prospective, retrospective cohort and case series.

Table 2. Data extraction sheet

Author/Year	County	Study Design	Participant Profile	Intervention Group Characteristics (USG-guided TAP + IV Opioid) Timing/ USG-guided TAP	Control Group Characteristics (Only IV opioid used)	Measured Outcomes
Kitlik et al. (13) (2017)	Turkey	RCT- double blinded	18–65 Yr, Living Liver Donors TAP (n=25) IV (n=25)	Inj. 0.5% bupivacaine at the conclusion of surgery Single injection bilateral subcostal mL each side; total 40 mL)	Intraoperative: - Remifentanil - Morphine Postoperative: - Morphine PCA - Acetaminophen	- Postoperative Opioid (24-h morphine consumption) - Pain Intensity (VAS) at rest and movement - PONV
Erdogan et al. (14) (2017)	Turkey	RCT- double blinded	18–65 Yr, Living Liver Donors TAP (n=22) IV (n=22)	Inj. 0.5% bupivacaine before surgical incision Single injection bilateral subcostal (20 mL each side; total 40 mL)	Intraoperative: - Fentanyl - Remifentanil - Morphine PCA - IV acetaminophen	- Postoperative Opioid (24-h morphine consumption) - Perioperative remifentanil consumption - Mean BP - HR - Mean desflurane requirement - Anaesthesia recovery time, - Frequency of emergency vasopressor use - Length of hospital stay
Maeda et al. (15) (2015)	Japan	Retrospective	Adult (>16 Yr) Living Live donors TAP (n=16) IV (n=16)	(>16 Yr) X levobupivacaine at the conclusion of surgery Single injection bilateral subcostal (10 mL each side; total 20 mL) AND Continuous subcostal infusion of 0.125% levobupivacaine for 48 h	Intraoperative: - Fentanyl - Remifentanil - Flurbiprofen Postoperative (either of following): - Fentanyl - Flurbiprofen - Acetaminophen or - Oral loxoprofen	- Cumulative postop fentanyl consumption for 48 h - Time to first supplemental analgesia - Total number of requests for supplemental analgesia - VRS scores at 3, 6, 12, 24 and 48 h postop - PONV in the first and second 24 h - PT-INR value - Number of meals missed postop - Duration of postop hospital stay
Milan et al. (16) (2011)	United Kingdom	Retrospective pilot study	Adult Liver Transplant Recipients TAP (n=17) IV (n=17)	Inj. 0.5% levobupivacaine before surgical incision Single injection bilateral subcostal (20 ml each side; total 40 ml)	Intraoperative: - Remifentanil Postoperative: - Morphine PCA - IV acetaminophen	- Postoperative Opioid (24-h morphine consumption) - Pain scores - Time to extubation

Statistical analysis

Data were pooled for meta-analysis using MetaXL plugin for Microsoft Excel (11). Fixed effect model and random effect model were used based on the absence or presence of significant heterogeneity, which was in turn assessed using the I^2 statistic. I^2 values of >90% were considered as high heterogeneity between studies; 40%–90% was considered as moderate heterogeneity and <40% as low heterogeneity (12). Continuous variables like 24-h morphine consumption between intervention and control groups were expressed as pooled mean differences. Dichotomous variables like presence of postoperative nausea and vomiting (PONV) were expressed as pooled relative risks. Sensitivity analysis was done for studies having extreme effect estimates. P value <0.05 was considered significant. Publication bias was assessed using Egger's test and funnel plot.

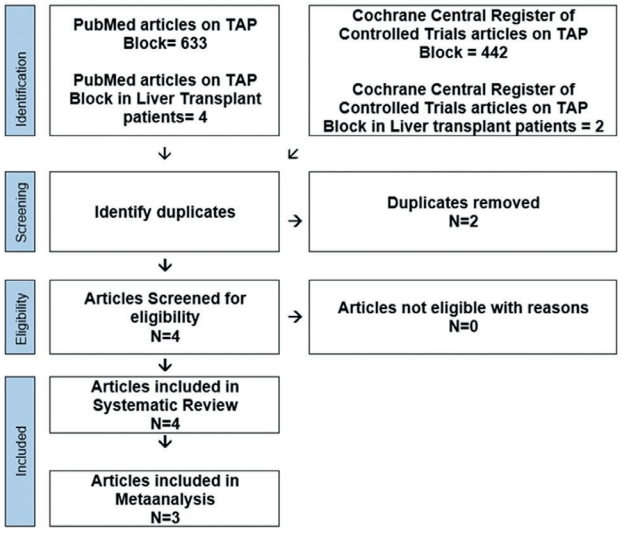

Figure 1. PRISMA flowchart

Results

We searched Cochrane Central Register of Controlled Trials, Clinical trial registry, PubMed, Scopus and Google Scholar for eligible articles. Cross-references and manual searching was also performed. There were 627 articles regarding TAP Block in PubMed and 405 in Cochrane database of which 6 articles were about comparative assessment in patients with liver transplant. Two articles were in duplicate thus giving four eligible articles whose full texts were read for inclusion in systematic review. Of these, two were prospective randomised trials by Kitlik et al. (13) and Erdogan et al. (14). Other two by Maeda et al. (15) and Milan et al. (16) have performed retrospective comparisons between patients receiving TAP block and otherwise. Out of these four articles, three studies [Kitlik et al. (13), Erdogan al. (14) and Maeda et al. (15)] were on living liver donors, and one study [Milan et al. (16)] included liver transplant recipients. All the four studies were included for systematic review (Figure 1).

Kitlik et al. (13) in Turkey have compared 25 liver transplant donors receiving ultrasound-guided TAP block with another 25 donors who did not receive TAP block. The mean total morphine consumption values after 24 h were 40 mg and 65 mg, respectively. They found that the TAP block significantly reduced 24-h postoperative morphine consumption and postoperative visual analogue pain scores (VAS) both at rest and during movement till 24 hours.

Erdogan et al. (14) also compared 22 living liver donors who received subcostal TAP block in combination with 22 who received general anaesthesia alone. They concluded that combining subcostal TAP blocks with general anaesthesia significantly decreased opioid consumption and provided shorter anaesthesia recovery time and length of hospital stay in living liver donors. In this study, pain intensity was not compared between the two groups.

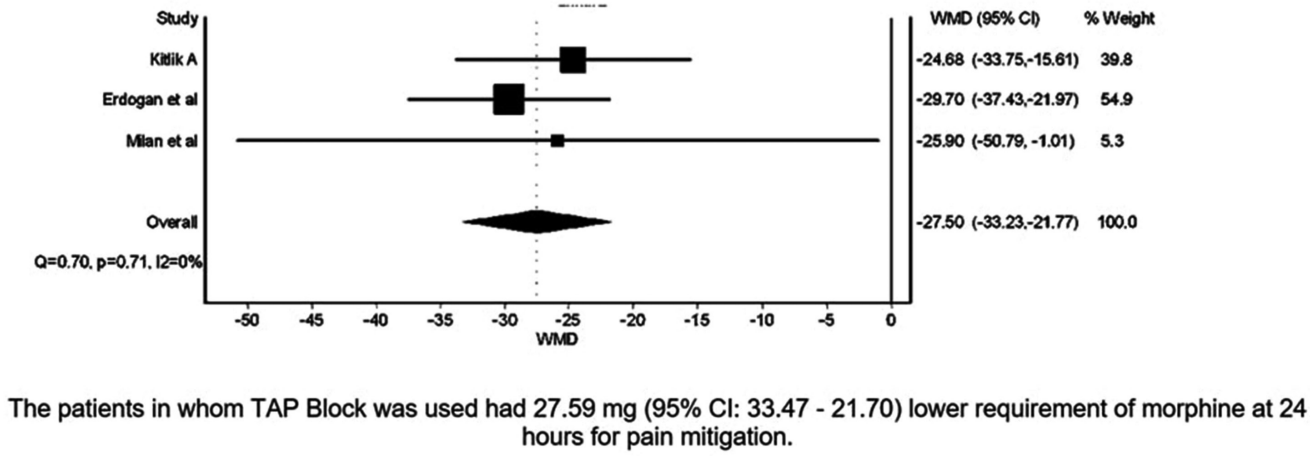

Figure 2. Forest plot showing effect of TAP block on 24-h morphine use

Maeda et al. (15) in their retrospective analysis compared 16 living liver donors receiving continuous subcostal TAP block with 16 donors who received only IV fentanyl-based analgesia. The result of this study showed that continuous subcostal TAP block provided an effective opioid-sparing analgesia, lower incidence of nausea and vomiting during 24–48 h postoperatively and fewer delays in the initiation of oral intake. In this study, pain intensity was assessed on a four-level verbal rating scale (VRS) scores, which were lower in the TAP group than in the control group at 3 h and 6 h.

Milan et al. (16) retrospectively compared 17 liver transplant recipients receiving TAP block with 17 patients who received only IV analgesia. The total amount of morphine consumption over 24 h was 45.9±33.9 mg in the TAP group and 71.8 ± 39.9 mg in the control group ($p<0.005$). Their study showed significant reduction in postoperative morphine consumption in recipients who received TAP block. In this study, pain scores (0 – no pain and 3 – worst pain imaginable) were lower in the TAP group, but there was no significant difference compared with the control group.

The pooled effect size by random effects model showed that TAP group had 27.59 mg (95% CI: 33.47–21.70) lower requirement of morphine at 24 h for pain mitigation (Figure 2 and Table 3). However, this measure is only from two studies from a single centre and are highly homogenous as shown by $I^2=0\%$. This may reduce the generalisability of findings. The patients in whom TAP block was used had 0.76 (0.47–1.22) times lower risk for PONV than in controls, but this was not statistically significant (Figure 3).

As per established guidelines of Cochrane collaboration, the quality assessment for bias in the included studies was performed as shown in Figure 4. Publication bias was examined for the primary outcome. There is a chance of publication bias in the included studies to report lesser morphine consumption with TAP block. Funnel plot distribution was skewed with studies results falling beyond expected neutral funnel boundary (towards positive side) (Figure 5). Egger's regression test also confirmed the above finding.

Table 3. Steps in calculation of pooled estimate

Study	Intervention group n	Mean (X_i)	SD	Control group n	Mean (X_j)	SD	Mean difference ($X_i - X_j$)	Variance of mean difference	Weights =1/Var(D)	WiDi	Pooled estimate	S.E. of pooled estimate
	a	b	c	d	e	f	g (=b-e)	h	i (=1/h)	j (=i x g)	k	l
Kitlik et al. (13)*	25	40.96	14.80	25	65.64	17.79	−24.68	21.42	0.047	−1.152		
Erdogan et al. (14)*	22	40.75	13.44	22	70.45	12.72	−29.70	15.57	0.064	−1.908	$\sum$ WiDi /$\sum$ Wi	$\sqrt{(1/\sum wi)}$
Milan et al. (16)	17	45.90	33.9	17	71.80	39.90	−25.90	161.25	0.006	−0.161		
									0.117	-3.221	−27.50	2.922

*Data were reported as median in published article. Their mean and standard deviation were provided by authors

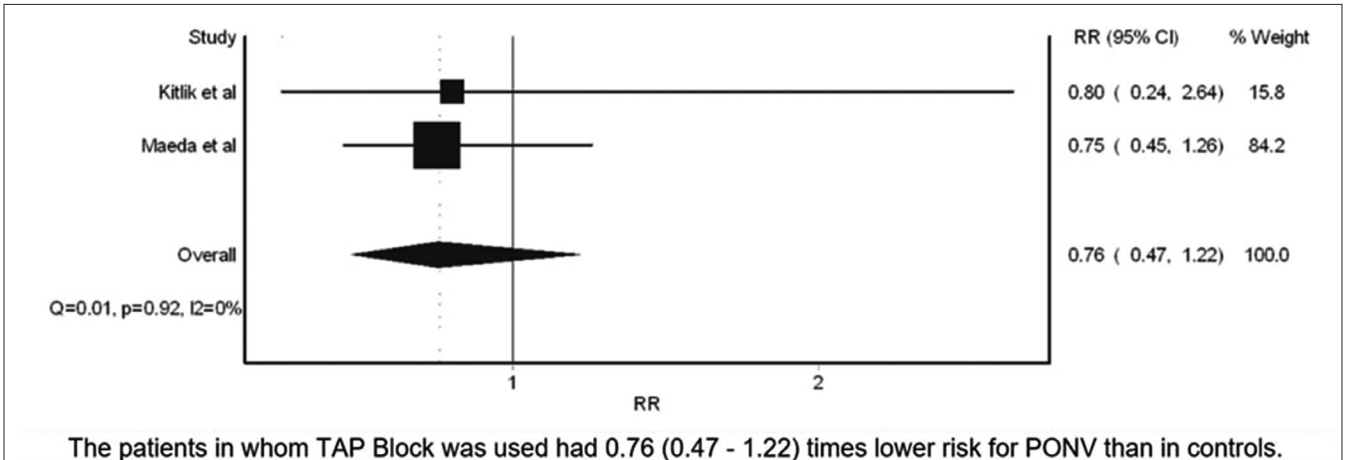

Figure 3. Forest plot showing effect of TAP block on risk of PONV

Discussion

This meta-analysis and systematic review of the literature is the first to evaluate the postoperative analgesic efficacy of ultrasound-guided TAP block in liver transplant surgery recipients and donors. Here, we have reviewed two randomised controlled trials and two retrospective studies having 160 participants. Although the sample size is small, it reiterates the benefit of TAP block as shown by many other studies in other abdominal surgeries like renal transplantation (17), caesarean section (18), hernia surgery (19), laparoscopic cholecystectomy (20), laparoscopic gastric sleeve resection (21), radical cystectomy (22), abdominoplasty (23), colorectal surgery (24), and meta-analysis in various other surgeries (25-29). In this study, the patients in whom TAP block was used had 27.59 mg (95% CI: 33.47–21.70) lower morphine requirement at 24 h for pain mitigation. The patients in whom TAP block was used had 0.76 (0.47–1.22) times lower risk for PONV than in controls.

Epidural blockade is used most commonly for intraoperative and postoperative analgesia in living donor liver transplantation (LDLT) donors (30). These living liver donors are at risk of deranged coagulation profile after donor hepatectomy (31). Maeda et al. (15) in their study incidentally found two donors who had higher PT-INR than 1.5 even after two days after operation, which might have caused a delay in epidural catheter removal or a serious haematoma if they had received epidural analgesia. They emphasised that an alternative method that ensures safety against potential risk is desirable. TAP block is one of the options available in these patients as it can be administered in patients with coagulopathies. It will help in change of practice of putting the epidural in LDLT donors and then waiting for stopping of heparin dose to remove epidural catheters as we usually do at our centres.

Our meta-analysis shows a significant morphine-sparing effect of the TAP block in patients undergoing liver transplant surgery. Any reduction in intraoperative opioid analgesics that

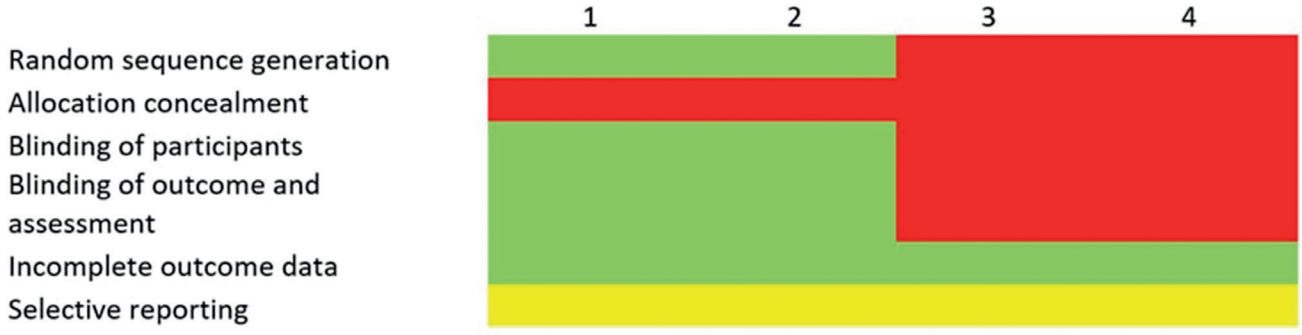

Figure 4. Assessment of risk of bias summary of all analysed studies as per Cochrane collaboration recommendations

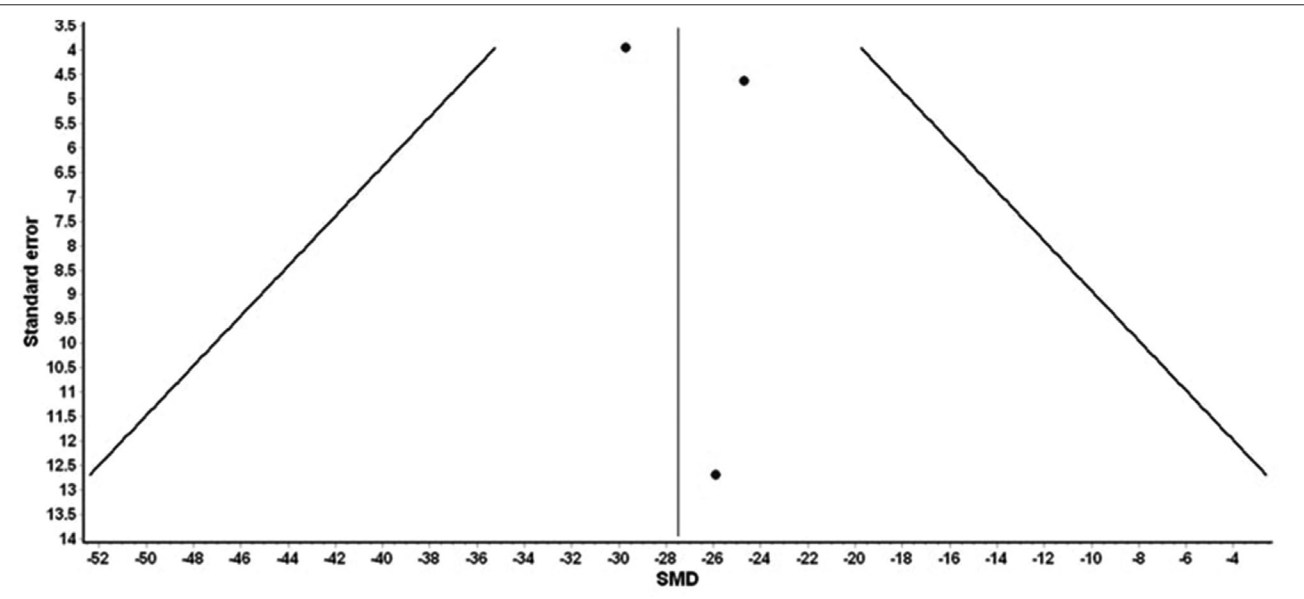

Figure 5. Funnel plot evaluating publication bias length of stay showing asymmetrical distribution of trials

may also cause sedation would also improve recovery profile and eventually lower the sedation-related complications (32).

TAP block provides analgesia by blocking somatic component of pain sparing the visceral component. This limitation can be overcome by supplementing with NSAIDs, paracetamol, tramadol, gabapentin, N methyl D- aspartic acid antagonist and so on. TAP block can be included as a part of multimodal analgesia for open or laparoscopic abdominal surgeries. It can be used for the postoperative analgesia depending on the choice and skills of the anaesthesiologist supplementing intravenous (IV)/intramuscular (IM) analgesics for these surgeries (33). Various studies in the literature have established that additional analgesic requirements and related adverse effects can be reduced by supplementing a multimodal analgesic regimen with a TAP block (17, 18). Compared with the standard regimen alone, it also increases the duration of first analgesic request and provides better satisfaction with pain relief (33).

Opioids act on presynaptic receptors in the myenteric nerve plexuses that leads to more non-propulsive contraction of the bowel, by that decreasing forward peristalsis (34). In this way, TAP block can also reduce incidence of postoperative ileus caused by opioids and thus shortens the hospital stay.

There are massive fluids shifts after functioning of graft during immediate transplant period. If it does not function properly, it is difficult to predict fluid dynamics and the pharmacokinetics of systemically administered drugs (17). TAP block reduces opioid requirements and has a positive clinical impact by lowering the need for systemic analgesic drugs.

Patient satisfaction towards surgery is influenced by many intra and postoperative factors. Pain and PONV are the most common causes of dissatisfaction. Our analysis shows that not only analgesic requirements in TAP block are lower but the PONV incidence tends to be smaller. Meta-analyses of TAP block in renal transplant recipients by Singh et al. (17) revealed a decrease in the 24-h opioid consumption by 14.61±4.34 mg that was in accordance with the results of the present study. Similar to our study, the two larger meta-analyses using TAP block for analgesia showed a decrease of IV morphine consumption of 9.1 and 5.7 mg within the first 24 h postoperatively (35, 36).

The results of our meta-analysis have several limitations. Not many centres seem to have started using TAP block for liver transplantation. We could find only four studies of which only two were randomised control trials. More RCTs at different centres and setups will be required for more robust evidence in favour of TAP block in liver transplantation. None of the included studies specifically sought to assess the sensory blockade after the ultrasound-guided TAP block. Thus, the success rate of the technique is unknown and may therefore have affected our analysis. We could not compare pain scores as various studies used different pain scales. Finally, we could not pool time to discharge, because only one prospective trial and one retrospective study sought to capture this outcome. Consequently, the impact of the ultrasonography-guided TAP block on functional outcomes during postoperative recovery remains undetermined.

Conclusion

Ultrasonography-guided TAP block provides postoperative analgesic efficacy in patients undergoing liver transplant surgeries.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.S.; Design – A.S., A.D.G.; Supervision – V.V.; Resources – A.S., A.D.G.; Materials – A.S.; Data Collection and/or Processing – A.S., A.D.G.; Analysis and/or Interpretation – A.D.G., P.P.S., V.V.; Literature Search – S.P.A., V.V., A.S.; Writing Manuscript – A.S., A.D.G.; Critical Review – V.V., S.P.A.; Other – P.P.S., V.V.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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