ORIGINAL ARTICLE

Effect of Parecoxib and transversus abdominis plane block on postoperative anxiety and cognition: A randomised controlled-trial

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Abstract

Objective: To investigate the impact of parecoxib and transversus abdominis plane block on postoperative anxiety and early cognitive function in patients undergoing laparoscopic intestinal surgery.

Method: The multicentre, randomised controlled trial was conducted at three tertiary hospitals in China from September 1, 2020, to September 30, 2022, and comprised individuals aged 60-85 years scheduled for elective laparoscopic intestinal surgery They were randomised into 4 groups. Patients in group C received normal saline. Patients in group P were given parecoxib 40mg intravenously 30 minutes before the start of surgery and 10 minutes after the end of surgery. In group T, a bilateral transversus abdominis plane block was performed 30 minutes before the start of surgery. Patients in group PT received a combination of interventions used in groups P and T. Serum samples of all the patients were obtained one day before surgery, 30 minutes after surgery and 24 hours after surgery. Anxiety levels were assessed one day before surgery, 24 hours after surgery, and 7 days after surgery. Data was analysed using SPSS 25.

Results: Of the 205 patients, 115(56%) were males and 90(44%) were females. There were 51(24.9%) patients in group C with mean age 67.61±5.46 years, 51(24.9%) in group P with mean age 66.53±4.30 years, 52(25.3%) in group T with mean age 67.23±5.36 years and 51(24.9%) in group PT with mean age 66.49±4.62 years. Compared to group C, anxiety scores in groups P and PT were significantly lower at 24 hours post-surgery ($p<0.05$). Compared to group C, the concentration of tumour necrosis factor-alpha in the serum samples of groups P and group PT was significantly lower at 30 minutes after surgery ($p< 0.05$).

Conclusion: A single transversus abdominis plane block did not have a significant effect on postoperative anxiety and cognition, while parecoxib could alleviate postoperative anxiety in elderly patients undergoing laparoscopic intestinal surgery.

RCT Reg No: ChiCTR1900024953.

Key Words: Anti-inflammatory agents, Non-steroidal, Anxiety, Cognition.

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Introduction

The surgical procedure and accompanying anaesthesia have been reported to have a negative impact on cognitive function, particularly in older patients.[1] Postoperative cognitive dysfunction (POCD) and anxiety are common outcomes in elderly patients undergoing intestinal surgery, posing significant challenges for clinicians, and adversely affecting patient outcomes.[2] Given the increasing life expectancy worldwide, the growing proportion of elderly patients undergoing intestinal surgery requires particular attention to the management of POCD and anxiety, which can hinder recovery, and lead to prolonged hospitalisation and reduced quality of life (QOL).[3,4] However, current strategies to address these challenges remain limited and lack consistent efficacy, and the pathophysiology remains incomplete. Furthermore, there is a lack of well-designed, prospective studies investigating effective interventions to reduce postoperative anxiety and cognitive dysfunction in this population.

Parecoxib, as a selective cyclooxygenase-2 inhibitor, has fewer side-effects than traditional non-steroidal anti-inflammatory drugs (NSAIDs). For example, parecoxib has minimal effects on gastric mucosa and platelet function, and does not increase the risk of perioperative bleeding or thromboembolism.[5,6] Parecoxib is safe and effective for multimodal analgesia.[7] Pain is a common trigger of postoperative anxiety, and inflammation is also associated with anxiety disorders.[8] Therefore, it is hypothesised that parecoxib may alleviate anxiety by relieving pain and reducing the inflammatory response

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after surgery. Although related research is limited, neuroinflammation is considered one of the mechanisms of neurocognitive dysfunction.[9,10] Studies have shown that parecoxib may decrease the incidence of POCD, although the findings are inconsistent.[11] Additionally, research results may vary depending on the diagnostic criteria of POCD and the statistical methods used. Further research is needed to investigate the impact of parecoxib on POCD.

The transversus abdominis plane (TAP) block is a regional anaesthesia technique that is safe and effective for surgical analgesia and reducing opioid requirements.[12] The TAP block has been increasingly utilised in abdominal surgeries. It is hypothesised that TAP block may alleviate postoperative anxiety by relieving pain and minimise the negative impact of general anaesthetics on cognitive function by reducing the intraoperative use of general anaesthetics. However, there is a lack of related research, and the precise effect of TAP block on postoperative anxiety and cognitive function remains to be explored.

The current study was planned to fill th gap in literature by investigating the impact of parecoxib and TAP block on postoperative anxiety and early cognitive function in patients undergoing laparoscopic intestinal surgery, and provide a reference for perioperative management. It was also planned to delve into the biochemical underpinnings of the phenomenon by monitoring changes in multiple serum biomarkers after surgery.

Patients and Methods

The multicentre, randomised controlled trial (RCT) was conducted from September 1, 2020, to September 30, 2022 at three tertiary hospitals in China; the Second Hospital of Hebei Medical University, the Zhangjiakou First Hospital, and the Tangshan People's Hospital. The RCT followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines, and was registered with the clinical trial registry (Registration No: ChiCTR1900024953).[13] Prior to the commencement of the study, approval was obtained from the ethics review committee of the Second Hospital of Hebei Medical University, and all the participants furnished written informed consent. The patients were randomised into 4 groups. Patients in group C received normal saline. Patients in group P were given parecoxib 40mg intravenously 30 minutes before the start of surgery and 10 minutes after the end of surgery. In group T, a ultrasound-guided bilateral TAP block was performed 30 minutes before the start of surgery. Patients in group PT received a combination of interventions used in groups P and T. The TAP block was performed by physicians having >2 years of experience in TAP block.

The sample size was calculated using PASS 2015.0.5 with mean State-Trait Anxiety Inventory (STAI) score 72±11, 75±9, 81±12, and 76±10, in the 4 groups, respectively, with 10% dropout rate, and a two-sided 5% significance level.[14] The value of confidence was 0.9, and power was 0.9.

Those included were patients aged 60-85 years who had been scheduled for elective laparoscopic intestinal surgery, had an American Society of Anaesthesiologists (ASA) physical status classification of II-III, body mass index (BMI) 18-30kg/m^2, weight >50kg, and education level of primary school or above.[15]

Those excluded were patients with existing cognitive dysfunction or trend of cognitive change within the preceding year, those allergic or hypersensitive to lidocaine, ropivacaine, injectable parecoxib or other NSAIDs and sulfonamide drugs, those with active gastrointestinal ulcers or gastrointestinal bleeding, those with congestive heart failure, confirmed ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, those with severe liver damage (serum albumin <25g/L or Child-Pugh score ≥10), those with severe mental illness, using sedatives or antidepressants, those with history of drug or alcohol abuse, those who used any NSAID a day before surgery, those having comprehension and sensory communication disorders, and those with local infections or any other reason making TAP impossible.

To ensure unbiased group allocation, a random number table-generated sequence was used to assign the participants to one of the 4 groups. The sequence was kept in opaque, sealed envelopes, and both the researchers responsible for follow-ups and the participants were blinded to the group allocation. The information of nerve block was given to all the patients whether receiving or not receiving the block.

Professional preoperative education was provided by ward nurses, ensuring that each patient received the same preoperative counselling.

Anaesthesia was induced with a combination of intravenous midazolam 0.05mg/kg, propofol 1.5mg/kg, cisatracurium 0.15mg/kg, and sufentanil 0.3μg/kg. Following this, the patients were endotracheally intubated and mechanically ventilated. During anaesthesia maintenance, a continuous pump injection of propofol 3-6mg/(kg·h) and remifentanil 0.1-0.3μg/(kg·min) was administered until the end of the operation. In addition, intermittent intravenous injection

of cisatracurium was given. During the operation, blood pressure was maintained at ±20% of the basic value, heart rate was held at 60-100 beats/min, the pressure of end-tidal carbon dioxide was maintained at 35-45mmHg, and the value of electroencephalogram bispectral index was maintained in the range of 40-60.

Following the operation, patient-controlled intravenous analgesia (PCIA) was used for all patients for 2 days. The medication was a 100mL mixture consisting of sufentanil 1μg/kg, dexmedetomidine 2μg/kg, dezocine 0.4mg/kg and saline. The patients were able to self-administer 0.5mL boluses, with a lockout time of 15 minutes and an infusion rate of 2ml/h. In instances where the pain was unbearable, opioids or tramadol were given intravenously as rescue analgesia.

The serum samples of patients were obtained one day before surgery (t1), 30 minutes after surgery (t2), and 24 hours after surgery (t3). The primary outcomes were postoperative anxiety levels, and cognitive function. The cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) tool, excluding the drawing part.[16] The anxiety levels were assessed using STAI one day before surgery (t1), 24 hours after surgery (t3), and 7 days after surgery (t4). To test the learning effect of repeated testing, 30 patients aged 60-85 years using the MoCA with the same time interval. These patients had intestinal diseases and were waiting for surgery. The changes in MoCA scores were compared in patients waiting for surgery from baseline to 2 days and 8 days after the first testing. The mean changes were considered to be representing learning effects. The final MoCA scores postoperatively were obtained by subtracting the corresponding learning effect from the MoCA score at t2 or t3. The International Study of Post-Operative Cognitive Dysfunction (ISPOCD) recommended the "Z-score method" to evaluate the presence of POCD.[17] The Z-value was calculated using the formula Z = (postoperative change of the patient from before - mean of the change in the control group) / standard deviation of the change in the control group. A patient was considered to have POCD if the Z-score was >1.96.[17]

The secondary outcomes included the postoperative visual analogue scale (VAS) score ranging 0-10, and the concentration of brain-derived neurotrophic factor (BDNF), high-mobility group box 1 (HMGB1) protein, interleukin-10 (IL-10), and tumour necrosis factor-a;pha (TNF-α) in the serum. These outcomes were detected using enzyme-linked immunosorbent assay (ELISA).

Data was analysed using SPSS 25. Continuous data was presented as means +/- standard deviation (SD) for normally distributed data, and as medians with interquartile range (IQR) for non-normally distributed data. Frequencies and percentages were used to summarise categorical variables. Student's t-test or Mann–Whitney U test was used to analyse continuous variables, while categorical variables were compared using chi-square or Fisher's exact test. All tests were two-sided. P<0.05 was considered statistically significant.

Results

Of the 222 patients initially enrolled, 121(54.5%) were from the Second Hospital of Hebei Medical University, 52(23.4%) from the Zhangjiakou First Hospital, and 49(22.1%) from the Tangshan People's Hospital. One (0.45%) patient was removed for undergoing an emergency operation due to intestinal anastomotic fistula on the 4th day after surgery, 4(1.8%) patients were removed due to the use of additional NSAIDs after surgery, and 12(5.4%) were removed for refusing to cooperate with the evaluation post-operation. The study was completed by 205(92.3%) patients; 115(56%) males and 90(44%) females. There were 51(24.9%) patients in group C with mean age 67.61±5.46 years, 51(24.9%) in group P with mean age 66.53±4.30 years, 52(25.3%) in group T with mean age 67.23±5.36 years and 51(24.9%) in group PT with mean age 66.49±4.62 years. Baseline demographic and clinical variables were not significantly different among the groups (p>0.05) ((Table 1-2).

There were no significant differences in STAI scores among the groups at t1 and t4 (p>0.05), but the scores in

Table-1: Baseline demographic variables

Group	n (%)	Age(years) Mean±SD	Gender (M/F)	BMI (kg/m^2) Mean±SD	ASA (II/III)	Complication (yes/no)
Group C	51 (24.9)	67.61±5.46	28/23	24.50±3.70	38/13	35/16
Group P	51 (24.9)	66.53±4.30	29/22	24.55±3.42	41/10	26/25
Group T	52 (25.4)	67.23±5.36	31/21	23.96±3.39	38/14	30/22
Group PT	51 (24.9)	66.49±4.62	27/24	23.66±2.86	40/11	24/27
F/χ2		0.623	0.509	0.843	0.984	5.539
P		0.601	0.917	0.472	0.805	0.136

SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anaesthesiologists.

Table-2: Mean distribution of baseline clinical variables.

Group	n (%)	Duration of operation (min)	Blood loss(ml)
Group C	51 (24.9)	208.61±74.48	78.33±116.00
Group P	51 (24.9)	217.67±93.86	41.96±30.73
Group T	52 (25.4)	206.42±75.97	70.02±76.84
Group PT	51 (24.9)	227.75±101.79	65.59±49.93
F		0.637	2.179
P		0.592	0.092)

Table-3: Comparison of State-Trait Anxiety Inventory (STAI) score among the groups.

Group	n (%)	T1 Mean±SD	T3 Mean±SD	T4 Mean±SD
Group C	51 (24.9)	76.33±12.10	80.22±11.73	74.18±12.29
Group P	51 (24.9)	76.76±12.45	75.55±11.84*	71.61±11.40
Group T	52 (25.4)	78.38±13.26	78.21±12.43	75.35±12.69
Group PT	51 (24.9)	79.00±10.46	75.61±10.20#	74.41±11.49
F		0.566	1.930	0.915
P		0.638	0.126	0.435

SD: Standard deviation.
* Compared with group C, P=0.043
# Compared with group C, P=0.046

Table-4: Comparison of median values with interquartile range (IQR) of Visual Analogue Scale (VAS) among the groups.

Group	n (%)	T1	T3	T4
Group C	51 (24.9)	0 (0,3)	4 (0,6)	2 (0,4)
Group P	51 (24.9)	0 (0,4)	2(0,4)*	1 (0,4)*
Group T	52 (25.4)	0 (0,3)	2 (0,5)*	1 (0,4)*
Group PT	51 (24.9)	0 (0,1)	2 (0,5)*	1 (0,3)*
H		2.420	40.669	23.955
P		0.490	<0.001	<0.001

* Compared with group C, P<0.05

Table-5: Mean distribution of the concentration of tumour necrosis factor-alpha (TNF-α) in serum samples.

Group	n (%)	T1 Mean±SD	T3 Mean±SD	T4 Mean±SD
Group C	51 (24.9)	3.36±2.72	4.46±4.42	4.87±5.80
Group P	51 (24.9)	3.64±2.87	2.79±1.44*	3.63±2.47
Group T	52 (25.4)	3.36±2.16	3.97±2.86	3.58±3.62
Group PT	51 (24.9)	3.30±3.32	3.28±2.21#	3.35±3.41
F		0.15	3.21	1.50
P		0.929	0.024	0.217

SD: Standard deviation.
* Compared with group C, P=0.005
# Compared with group C, P=0.044

groups P and PT were significantly lower than in group C at t3 (p<0.05) (Table 3).

The learning effects at days 2 and 8 after the first testing were 2.03±1.33 and 1.40±1.45, respectively. There were 3(5.9%) POCD patients in group C and 3(5.7%) in group T at t3, and 1(1.96%) POCD patient in group C at t4. Although the incidence of POCD was lower in groups P and PT compared to group C, the difference was not significant (p>0.05).

Compared to group C, the VAS scores in the other groups were significantly lower at t2 and t4 (p<0.05) (Table 4), and the concentration of TNF-α in the serum samples from groups P and PT was significantly lower at t2 (p< 0.05) (Table 5). There was no significant difference in the

Table-6: Mean distribution of the concentration of interleukin-10 (IL-10) in serum..

Group	n (%)	T1 Mean±SD	T3 Mean±SD	T4 Mean±SD
Group C	51 (24.9)	3.12±2.04	4.26±3.42	4.53±4.29
Group P	51 (24.9)	3.56±2.07	3.88±2.30	4.25±2.58
Group T	52 (25.4)	4.01±3.10	5.10±4.46	5.07±3.35
Group PT	51 (24.9)	3.36±2.22	6.05±7.68	4.71±4.32
F		1.27	1.98	0.44
P		0.288	0.119	0.728

SD: Standard deviation.

Table-7: Mean distribution of the concentration of BDNF in serum.

Group	n (%)	T1 Mean±SD	T3 Mean±SD	T4 Mean±SD
Group C	51 (24.9)	29.20±9.69	30.81±9.56	29.80±9.36
Group P	51 (24.9)	29.01±10.34	26.35±10.45	25.26±9.93
Group T	52 (25.4)	31.57±9.40	29.84±9.52	28.81±10.17
Group PT	51 (24.9)	32.00±8.05	28.54±9.89	26.69±9.60
F		1.41	1.96	2.24
P		0.241	0.122	0.084

BDNF: Brain-derived neurotrophic factor, SD: Standard deviation.

Table-8: Mean distribution of the concentration of HMGB1 in serum

Group	n (%)	T1 Mean±SD	T3 Mean±SD	T4 Mean±SD
Group C	51 (24.9)	3.86±1.77	3.20±1.82	4.25±2.33
Group P	51 (24.9)	3.62±2.62	2.92±1.75	3.95±2.82
Group T	52 (25.4)	3.61±2.00	3.59±2.20	3.64±2.28
Group PT	51 (24.9)	4.10±2.14	3.88±1.99	4.44±2.78
F		0.59	2.39	0.95
P		0.623	0.070	0.418

HMGB1: High-mobility group box 1, SD: Standard deviation.

serum concentrations of IL-10, BDNF and HMGB1 among the groups (p>0.05) (Tables 6-8).

Discussion

The study's hypothesis was that TAP block might alleviate postoperative anxiety by relieving pain, and minimise the negative impact of general anaesthetics on cognitive function by reducing the intraoperative use of general anaesthetics. However, the study did not find any impact of TAP block on postoperative anxiety and cognitive function. Nonetheless, there is enough reason to continue investigating the impact of TAP block on postoperative anxiety and cognitive function in elderly patients because there is still no clarity about whether continuous TAP block can alleviate postoperative anxiety through analgesia.

The current results revealed that parecoxib may alleviate postoperative anxiety in elderly patients undergoing

laparoscopic intestinal surgery. Another study also showed that parecoxib could reduce postoperative anxiety levels in patients undergoing total knee arthroplasty.[18] However, the mechanisms of parecoxib to relieve anxiety were not investigated in the other study.

The VAS scores of current groups P and PT were significantly lower compared to group C. Hence, the analgesic effect may be one of the mechanisms of parecoxib to alleviate postoperative anxiety.

Increased inflammatory biomarkers have been found to be associated with anxiety, depression and bipolar disorder.[19-22] It has been observed that trauma, stress and pain associated with surgery can lead to an increase in inflammatory factors. The current study analysed the concentrations of TNF-α, IL-10, BDNF and HMGB1 in serum to observe the effect of parecoxib on these factors. TNF-α is a pro-inflammatory factor, and IL-10 is an anti-inflammatory factor. The concentration of BDNF in serum may be used to assess the anxiety level of generalised anxiety disorder.[23] The neuroinflammatory initiating effect of HMGB1 is involved in stress-induced depression. The current study found that the concentration of TNF-α in serum samples from groups P and PT were significantly lower at t2 compared to group C. However, there was no significant difference in the serum concentration of IL-10, BDNF and HMGB1 among the 4 groups. This indicates that the mechanism of parecoxib to alleviate postoperative anxiety may also involve inhibiting TNF-α rather than changing IL-10, BDNF or HMGB1.

A meta-analysis suggested that perioperative administration of parecoxib can improve the mini-mental state examination (MMSE) score.[11] In addition, a study on elderly patients undergoing total hip or knee replacement surgery showed that multidose parecoxib decreased the incidence of postoperative delirium.[24] The current study observed that the incidence of POCD was lower in groups P and PT compared to group C, but there was no significant difference. It is possible that the administration frequency of parecoxib was low and, hence, the effect of parecoxib was non-significant. There is no literature available on the effect of postoperative daily administration of parecoxib for a few days.

It is important to note that the study population, disease types, surgical methods, cognitive assessment scales, follow-up time, and diagnostic criteria for POCD vary among studies. Therefore, the incidence of POCD also varies. The current study observed that the incidence of POCD was relatively low, which could be attributed to several factors. Firstly, it is worth noting that parecoxib is prohibited in patients with ischaemic heart disease, cerebrovascular disease, and severe liver dysfunction. Therefore, patients with these conditions were excluded, which made the general situation of the patients included in this study relatively good. Secondly, the current study only used partial MoCA, and did not include the painting part. Using full-scale MoCA to evaluate postoperative cognitive function in patients is a common practice. Elderly patients often refuse to cooperate to complete the drawing part of MoCA due to postoperative pain, weakness, or poor vision rather than cognitive impairment. Therefore, using complete MoCA to assess cognitive function within one week after surgery would have likely resulted in lower scores. Also, the learning effect of repeated testing with the MoCA eliminated in the current study.

he current study has limitations. Firstly, there was no long-term postoperative cognitive assessment because evaluating MoCA after discharge was difficult. Secondly, the results could only demonstrate that 80mg parecoxib did not improve the early postoperative cognitive function of the elderly patients in the sample. Therefore, more research is needed on the effect of multidose parecoxib.

Despite the limitations, however, the findings suggest that parecoxib could be a promising option to alleviate postoperative anxiety in elderly patients undergoing laparoscopic intestinal surgery. This could lead to improved postoperative recovery and QOL for patients, making it a valuable treatment option for physicians to consider. Additionally, analysing the levels of BDNF, HMGB1, IL-10 and TNF-α in serum could provide a better understanding of the underlying mechanisms, which could be useful for future research in this area.

Conclusion

A single TAP block did not have an effect on postoperative anxiety and cognition. However, it parecoxib might be useful in alleviating postoperative anxiety in elderly patients undergoing laparoscopic intestinal surgery. This could be due to its analgesic properties and the inhibition of TNF-α.

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