Postoperative analgesic effect of dexmedetomidine combined with TPVB applied to open gastrectomy for gastric cancer

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Research Article

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Abstract

Purpose: This study is aimed to investigate the analgesic effect of combined dexmedetomidine and thoracic paravertebral nerve block (TPVB) on gastric cancer (GC) patients undergoing open gastrectomy.

Methods: From May 2019 to Nov 2020, a total of 80 GC patients preparing for open gastrectomy were enrolled in our hospital and were divided into the ropivacaine (RO) group and the ropivacaine + dexmedetomidine (RD) group ad libitum. All of the patients underwent TPVB. The characteristics, usage of patient-controlled analgesia (PCA), adverse events, visual analogue scale (VAS) scores, inflammatory cytokines, and T cell subgroups between the two groups were compared. Patients in the RD group showed the decreased occurrence rate of postoperative adverse events and VAS scores and improved anti-inflammation and immune function.

Results: These findings implied that the application of dexmedetomidine in combination with ropivacaine in TPVB has a good postoperative analgesic effect, as well as anti-inflammatory and immune-enhancing effects.

Conclusion: Thus, dexmedetomidine as an adjunct analgesic may be potentially applied in clinical practice for GC patients undergoing open gastrectomy.

Introduction

Gastric cancer (GC) is the most common malignant tumor of the digestive system in the world, and its morbidity and mortality are among the top three of all malignant tumors in our country [1]. Surgical operation is the most common and efficient strategy for GC therapy at the early stage, and the treatment outcomes are usually satisfactory [2]. It is easy to cause severe hemodynamic fluctuations during the operation and the postoperative pain of patients is obvious [3]. Postoperative adverse effects include insomnia, hypotension, and bradycardia, which may increase the risk of cardiovascular and cerebrovascular and is not conducive to the rapid recovery of patients [4]. Therefore, postoperative analgesia is a necessary application in perioperative nurse.

Currently, patient-controlled analgesia (PCA) system is a commonly used postoperative analgesia mode, which administration is more accurate and follows the principle of individualization [5]. However, the postoperative analgesic effect of PCA alone is often not satisfactory in traumatic operations such as gastrectomy [5]. Epidural analgesia is regarded as the gold standard for the analgesia of abdominal and thoracic surgeries [6]. The local anesthetics act upon the spinal nerve roots in epidural space directly, block the introduction of pain stimulation, and thus provide good analgesic effect for postoperative operation [7]. Although epidural analgesia has many advantages, some limitations such as spinal nerve injury and epidural hematoma infection are also possible [8]. In recent years, epidural analgesia has been gradually replaced by other analgesia methods [9]. Yeung et al. indicated that thoracic paravertebral nerve block (TPVB) has the same analgesic effect as epidural block, but reduced the risks of developing minor complications [10]. Additionally, compared with epidural block, TPVB has a wider scope of application...
and can maintain hemodynamic stability, which is conducive to rapid postoperative recovery [11, 12]. It has been used in some upper abdominal surgeries, such as hepatectomy [13] and nephrectomy [14]. However, there are relatively rare researches on TPVB for GC surgery.

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist recently introduced to anesthesia, which can not only inhibit the excitability of sympathetic nerves and maintain hemodynamic stability, but also plays an important role in sedation, anxiolysis, and analgesia [15–17]. Recently, dexmedetomidine in combination with local anesthetics in TPVB for postoperative analgesia has attached much attention [18–20]. Wang et al. conducted a meta-analysis on the analgesic effects of dexmedetomidine combined with local anesthetics in TPVB and revealed that this combination improved postoperative pain scores, prolonged the duration of analgesia, and reduced postoperative analgesic consumption [18]. Xu et al. believed that dexmedetomidine combined with ropivacaine prolongs the duration of postoperative analgesia and improves recovery rate of patients undergoing video-assisted thoracoscopic surgery [19]. Liu et al. demonstrated that in esophageal cancer patients received radical surgeries, dexmedetomidine combined with ropivacaine in TPVB can significantly improve the quality of anesthesia, promote the postoperative analgesic effect, and reduce the incidence of postoperative adverse events [20]. However, the postoperative analgesia effect of dexmedetomidine combined with TPVB applied to open gastrectomy in clinic is still unclear.

This study is aimed to investigate the effects of ropivacaine alone and combined with dexmedetomidine in TPVB on postoperative analgesia, inflammation, and immune function in patients undergoing gastrectomy. Our findings may deepen the understanding of the impact of dexmedetomidine combined with TPVB applied to open gastrectomy in clinic.

**Materials And Methods**

**Patients**

A total of 80 GC patients preparation for open gastrectomy were enrolled in our hospital from May 2019 to Nov 2020. The inclusion criteria were: i) body mass index (BMI) was 18–27 kg/m², ii) American Society of Anesthetists (ASA) grade I-II, iii) no obvious abnormalities of heart and lung function, iv) no communication disorders. The exclusion criteria were: i) patients with puncture contraindications such as infections, scars, and tumors at the puncture sites, ii) patients with allergic history of ropivacaine and opioids, iii) pregnant and lactating women, iv) patients with long term drinking, chronic pain and history of taking psychotropic drugs. Based on our preliminary study, we calculated the sample size with an online tool “Power and Sample Size.com”.

**Preparation before anesthesia**

Written informed consent was provided by each patient. This study was performed in line with the principles of the Declaration of Helsinki. This study obtained the approval of the ethics committee in Huizhou Municipal Central Hospital. The included patients were divided into two groups ad libitum using
a computer-generated random number table with sealed opaque envelope technique for allocation concealment: the ropivacaine (RO) group and the ropivacaine + dexmedetomidine (RD) group. All patients were fasting and not given medication 8 h before operation. The routine peripheral vein channel was established after entering the operating room and ringer lactate was instilled at a rate of 8 ml/kg/h to supplement the fluid loss caused by fasting. Meanwhile, the patients received routine electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SpO₂), blood pressure (BP), and bispectral index (BIS) monitoring.

Afterwards, ultrasound-guided TPVB was performed by an experienced anesthesiologist that was blind to the group allocation. In brief, the patient was in lateral position, and the 8–9 spinous processes of thoracic vertebrae were determined first. Before puncture, 1% lidocaine was used for local infiltration anesthesia. The puncture point was 3 cm beside the upper edge of spinous process. In-plane puncture technique was used to puncture into thoracic paravertebral space. No blood and cerebrospinal fluid were drawn back. The catheter was implanted 2.5 cm and fixed. 15 mL 0.5% ropivacaine with 2 mL dexmedetomidine (1 µg/kg) was injected paravertebrally to the patients in RD group under ultrasound guidance. Patients in the RO group received 15 mL ropivacaine (0.5%) and 2 mL normal saline. The anesthetic effect was tested to determine that nerve block was successful.

**Anesthesia induction**

After the intravenous injection of 0.2–0.4 ug/kg sufentanil, 0.2–0.3 mg/kg etomidate, and 0.2 mg/kg cisatracurium, tracheal intubation was used for mechanical ventilation. Partial pressure of end-tidal carbon dioxide (P_{ET}CO₂) was maintained at the level of 30–35 mmHg.

**Maintenance of anesthesia**

The flow of fresh oxygen during the operation was 1L/min and the inhaled oxygen concentration was 80%. Inhalation of 1.5% sevoflurane and continuous infusion of remifentanil (25 ug/ml) was used for intraoperative maintenance. Besides, the value of BIS needed to maintain at 40–50. After the operation, the endotracheal tube was pulled out when the patients were conscious.

**Postoperative analgesia**

All patients received intravenous 0.02 µg/kg/h sufentanil via a patient-controlled analgesia (PCA) pump (100 mL), with a lockout time of 15 min. The anesthetist conducted postoperative monitoring, pain assessment, and management was blinded to the patient groups. Nurses cared for patients 24 hours a day.

**Variables recorded**

The visual analogue scale (VAS) pain score (0–10) was used to evaluate the pain of patients at rest or coughing in the two groups after the operation, and 6, 12, 24, and 48 h after the operation. Score 0: no pain; score 1–3: mild pain; score 4–6: moderate pain; score 7–10: severe pain. In addition, the frequency
of PCA pressed, sufentanil consumption, and the adverse events after operation such as nausea, vomiting, cardiac arrhythmia, bradycardia, and hypotension were also recorded.

**Measurement for cytokines and T cell subgroups**

Blood samples (5 mL) were collected on the day before operation (T0) and on postoperative days 1 (T1), 3 (T2), and 7 (T3). The plasma levels of IFN-γ, IL-6, and TNF-α were measured using the corresponding commercial ELISA kits. The percentages of CD4+ and CD8+ cells in peripheral blood were measured by flow cytometric analysis.

**Statistical analysis**

SPSS 20.0 software (SPSS; Chicago, IL, USA) was used in analysis. Continuous variables conformed to normal distribution were analysed using t-test and presented as means ± SD, while chi-square test was used for categorical variables and shown as absolute number or percentage. P-value less than 0.05 indicated a statistically significant difference.

**Results**

**Analysis of patient characteristics**

We analyzed the clinicopathologic characteristics of the patients in the RO and RD groups firstly. As shown Table 1, there were no significant differences between RO patients and RD patients in age, sex, BMI, ASA, tumor stage, and operation time.

<table>
<thead>
<tr>
<th>Variable</th>
<th>RO</th>
<th>RD</th>
<th>t or χ²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>57.2 ± 11.34</td>
<td>58.6 ± 10.77</td>
<td>0.162</td>
<td>0.872</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>19/21</td>
<td>22/18</td>
<td>0.450</td>
<td>0.502</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7 ± 2.54</td>
<td>23.2 ± 1.83</td>
<td>1.01</td>
<td>0.316</td>
</tr>
<tr>
<td>ASA (I/ II)</td>
<td>15/25</td>
<td>12/28</td>
<td>0.503</td>
<td>0.478</td>
</tr>
<tr>
<td>Tumor stage (I/ II)</td>
<td>21/24</td>
<td>23/22</td>
<td>0.178</td>
<td>0.673</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>184.8 ± 40.35</td>
<td>192.5 ± 35.41</td>
<td>0.907</td>
<td>0.367</td>
</tr>
</tbody>
</table>

BMI: Body Mass Index; ASA: American Society of Anesthetists; RD: ropivacaine + dexmedetomidine; RO: ropivacaine

**Comparison for the usage of PCA in the patients**
Afterwards, the usage of PCA in the patients of these two groups was assessed. We found that PCA duration, sufentanil consumption in PCA 48 h after operation, and PCA pressing times 48 h after anesthetic recovery in RD patients were significantly reduced compared to the RO patients (4.7 ± 1.5 vs. 6.3 ± 2.4, *P* = 0.0004; 32.5 ± 5.4 vs. 45.4 ± 8.3, *P* < 0.0001; 11.4 ± 1.7 vs. 14.3 ± 2.5, *P* < 0.0001; Table 2). However, the postoperatively wake-up time of RD patients (the time from the end time point of surgery to the time when the patient fully restored mental activity) (12.8 ± 1.3) was relatively longer than that of RO patients (9.5 ± 1.1) (*P* < 0.0001).

### Table 2
Comparison of the usage of PCA between the RD and RO groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>RO</th>
<th>RD</th>
<th>t</th>
<th><em>P</em> value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperatively awake time (h)</td>
<td>9.5 ± 1.1</td>
<td>12.8 ± 1.3</td>
<td>12.26</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Duration of PCA (h)</td>
<td>6.3 ± 2.4</td>
<td>4.7 ± 1.5</td>
<td>3.68</td>
<td>0.0004</td>
</tr>
<tr>
<td>Drug dosages in PCA 48 h after operation (ml)</td>
<td>45.4 ± 8.3</td>
<td>32.5 ± 5.4</td>
<td>8.24</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PCA pressing times 48 h after operation (n)</td>
<td>14.3 ± 2.5</td>
<td>11.4 ± 1.7</td>
<td>6.07</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

PCA: patient-controlled analgesia; RD: ropivacaine + dexmedetomidine; RO: ropivacaine

**Comparison for the adverse events in the patients**

Regarding adverse events noted in the first 48 h postoperatively, on the whole, fewer adverse effects were observed in RD patients (4/40) compared to the RO patients (9/40) (Table 3). For details, 2 patients in RD group and 5 in RO group had postoperative nausea and vomiting. Respiratory depression occurred in one patient in the RO group, while no cases were found in the RD group. Meanwhile, 1 RO patient and 1 RD patient presented the bradycardia symptom, and 2 RO patients and 1 RD patient had postoperative hypotension. No cardiac arrhythmia was recorded.
Table 3
Comparison of the adverse events between the RD and RO groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>RO</th>
<th>RD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 40</td>
</tr>
<tr>
<td>Nausea and vomiting, n (%)</td>
<td>5 (12.50)</td>
<td>2 (5.00)</td>
</tr>
<tr>
<td>Cardiac arrhythmia, n (%)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Respiratory depression, n (%)</td>
<td>1 (2.50)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Bradycardia, n (%)</td>
<td>1 (2.50)</td>
<td>1 (2.50)</td>
</tr>
<tr>
<td>Hypotension, n (%)</td>
<td>2 (5.00)</td>
<td>1 (2.50)</td>
</tr>
<tr>
<td>Total occurrence rate, n (%)</td>
<td>9 (22.50)</td>
<td>4 (10.00)</td>
</tr>
</tbody>
</table>

RD: ropivacaine + dexmedetomidine; RO: ropivacaine

Comparison for VAS scores in the patients

As shown in Fig. 1A, VAS scores in RD patients were lower than those of RO patients at 12 and 24 h after anesthetic recovery when in a rest state ($P < 0.05$). Interestingly, we found that when coughing, VAS scores of RD patients were significantly decreased compared to the RO patients within one day ($P < 0.05$, Fig. 1B).

Comparison for cytokines and T cell subgroups at different time points in the patients

Before operation (T0), the levels of IFN-γ, IL-6, and TNF-α showed no significant difference between RO and RD groups (Fig. 2A-C). On postoperative day 1 (T1) and day 3 (T2), their levels in both two groups were increased compared with those at T0. On postoperative day 7, the levels of these factors were decreased to baseline except for TNF-α, whose level was higher than the baseline. Besides, IFN-γ level was significantly higher but the levels of IL-6 and TNF-α were lower in RD groups compared with those in RO group at T1 and T2. In terms of T cell subgroups, the percentage of CD8$^+$ cells in both groups showed no significant changes from T0 to T3. Both CD4$^+$ percentage and CD4$^+$/CD8$^+$ ratio was decreased in two groups at T1 and T2 compared to those of pre-operation ($P < 0.05$). Meanwhile, the percentages of CD4$^+$ cells and the ratio of CD4$^+$/CD8$^+$ cells in RD group were higher than those in RO group at T0 and T3 (Fig. 2D-F) ($P < 0.05$).

Discussion

GC is a kind of malignant tumor of the digestive system and it is currently believed that open gastrectomy-based surgical methods can improve the long-term survival rate of GC patients to a certain
extent [21]. However, postoperative pain generally leads to a series of adverse effects and increases the risk in perioperative period [4]. Therefore, effective anesthesia modes are important for improving the recovery rate of GC patients undergoing open gastrectomy. This study focused on the postoperative analgesia effect of 0.5 µg/kg dexmedetomidine combined with 0.5% ropivacaine in TPVB applied to open gastrectomy, suggesting that addition of dexmedetomidine potentiated the analgesic properties of ropivacaine, reduced requirement for postoperative sufentanil consumption, and decreased pressing frequency of PCA. In addition, adverse events, inflammation reactions, and immunosuppression in patients of anesthetics combination were also improved.

Currently, many studies have confirmed that the analgesic effect of TPVB is better than that of epidural block and the occurrence rate of complications and contraindications in TPVB such as hypotension and bradycardia are significantly less than those in epidural block [10–12, 22, 23]. We speculated that the block plane generated by epidural block is wider than that of TPVB and the inhibitory effect on sympathetic nerve is more obvious, which was consistent with the previous results [24]. On the other hand, most of the current studies on TPVB are unilateral block [25, 26] and we believed that the inhibitory effect on sympathetic nerve is slighter compared with the bilateral block in epidural block. In this study, a bilateral TPVB in patient undergoing open gastrectomy was performed. We found that there are relatively few adverse effects in patients of the RO group (9/40) and RD group (5/40), suggesting that application of TPVB in open gastrectomy may be safe and effective.

Recently, dexmedetomidine as an adjuvant has been widely used in epidural analgesia and anesthesia [27–29]. Zhang et al. found that dexmedetomidine as an adjuvant can act synergistically and provided an improved sedation and analgesic [27]. Li et al. reported that the usage of adjunct drug dexmedetomidine (> 5 µg) in epidural block makes great contributions on the decrease of post-anesthetic shivering compared to that of ≤ 5 µg [28]. A study by Cheng et al revealed that the hemodynamics are more stable and VAS scores are lower in 0.5 µg/mL dexmedetomidine + 0.08% ropivacaine group than that of the 0.5 µg/mL dexmedetomidine in combination with high concentration of ropivacaine (0.125%) group [29]. Given that the occurrence rate of complications and contraindications in TPVB are less than those in epidural block [10–12, 22, 23], we speculated that dexmedetomidine as an adjunct anesthetic in TPVB may be more efficient for analgesia. In addition, numerous studies demonstrated that the application of dexmedetomidine in patients undergoing GC surgery can improve the postoperative cognitive function [30–32]. We further speculated dexmedetomidine combined with ropivacaine in TPVB may prolong the duration of analgesia, reduce the dosages of anaesthetic, and promote the recovery of GC patients undergoing open gastrectomy. In the current study, we found that the duration of PCA, drug dosages in PCA, pressing frequency of PCA, VAS scores, and postoperative sufentanil consumption in RD group were all decreased compared to those of RO group, which confirmed our assumption.

Additionally, adjunct analgesic (such as ropivacaine) combined with epidural block is also reported to repress inflammation and improve immune functions in GC surgery [33, 34]. Interestingly, the effects of dexmedetomidine on inflammatory cytokines and T lymphocytes are confirmed in patients with kidney calculi [35] or GC surgery [36] without any block. In this study, to our knowledge, we for the first time
investigated the influences of dexmedetomidine in combination with ropivacaine in TPVB on inflammation and immune functions for GC patients undergoing open gastrectomy. Immune function during the early postoperative period was clearly reduced. We found that both in RO and RD groups, the levels of IFN-γ, IL-6, and TNF-α at T1 and T2 were significantly increased in comparison to those at T0. IFN-γ increased more in the RD group than in the RO group, while the elevated amplitudes of IL-6 and TNF-α were lower in the RD group compared to the RO group. Based on these results, we believed that dexmedetomidine combined ropivacaine in TPVB can inhibit the augmentation of inflammatory factors in post-operation. T-lymphocytes act crucial roles in anti-tumor immune activity, in which the reduced CD4+ percentage and the ratio of CD4+/CD8+ suggested the declined immune functions [37, 38]. In our study, we demonstrated that although CD4+ and CD4+/CD8+ were decreased in two groups at T1 and T2 compared with T0, the amplitudes of reduction in the RO group were significantly larger than those in the RD group. These findings revealed that dexmedetomidine administration helps relieve immunosuppression. The combination of dexmedetomidine and TPVB protected the immune function against a large decline in our study. This finding again confirms that dexmedetomidine combined with TPVB contributes to cellular immune functioning. The detailed mechanisms remain to be verified by in-depth researches.

There were also some other limitations of this study. First, the epidural block groups were not set due to the current medical environment does not allow serious complications presented. Second, the immune system is a complex system and other immune cytokines needed to be studied. We will elucidate these issues in future studies.

**Conclusions**

For GC patients undergoing open gastrectomy, combination use of dexmedetomidine and ropivacaine in TPVB not only decreases the occurrence rate of postoperative adverse events, but reduces postoperative anesthetic consumption and prolongs the duration of analgesia, but also has the functions of anti-inflammation and improving immune activity.

**Declarations**

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**Competing interests:** No potential competing interest was reported by the authors

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability:** Not applicable
Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions: WLW, ZQH, QYQ made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; WLW took part in drafting the article and revising it critically for important intellectual content; All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. This study obtained the approval of the ethics committee in Huizhou Municipal Central Hospital (Approval No. Kyll20210124).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable.

Acknowledgements: Not applicable.

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Figures

**Figure 1**

**VAS scores at rest or coughing during the 48 h after operation.** (A) VAS scores at rest during the 48 h after anesthetic recovery. (B) VAS scores at coughing during the 48 h after anesthetic recovery. *P < 0.05, **P < 0.01 vs. the RO group.
Comparison for cytokines and T cell subgroups at different time points in the patients. (A-C) The levels of IFN-γ, IL-6, and TNF-α at different time points in the patients. *$P < 0.05$ vs. the T0 stage. #$P < 0.05$ vs. the RO group. (D-F) The CD4+ percentage, CD8+ percentage, and CD4+/CD8+ ratio at different time points in the patients. *$P < 0.05$ vs. the T0 stage. #$P < 0.05$ vs. the RO group. T0: before operation, T1: postoperative 1 day, T2: postoperative 3 days, T3: postoperative 7 days.