Effects of Systemic Lidocaine Versus Dexmedetomidine on the Recovery Quality and Analgesia After Thyroid Cancer Surgery: A Randomized Controlled Trial

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ABSTRACT

Introduction: Surgical management is commonly used for thyroid cancer. We evaluated the effects of systemic lidocaine versus dexmedetomidine on the recovery quality and analgesia after thyroid cancer surgery.

Methods: A total of 120 patients with thyroid cancer were randomly allocated to group L (received lidocaine 1.5 mg/kg loading, continuously infused 1.5 mg/kg per hour), group D (received dexmedetomidine 0.5 μg/kg loading, continuously infused 0.5 μg/kg per hour) and group C (received normal saline), with 40 cases in each group. Anaesthesia induction and maintenance were performed using target-controlled infusions (TCIs) of propofol and remifentanil. The primary outcome of the quality of recovery-15 (QoR-15) score was recorded on the day before surgery and postoperative day 1 (POD1). Secondary outcomes included the consumption of remifentanil during surgery, time to first required rescue analgesia, number of patients requiring rescue analgesia, postoperative cumulative consumption of tramadol, visual analogue scale (VAS) pain score, incidence of postoperative nausea or vomiting (PONV) and side effects.

Results: The total score of the QoR-15 at POD1 (median, IQR) was higher in group L (128.0, 122.0–132.8) and group D (127.5, 122.5–132.5) compared to group C (118.5, 113.0–123.5) (P = 0.000). Compared to group C, systemic lidocaine and dexmedetomidine reduced cumulative consumption of remifentanil and VAS pain score (P = 0.000). The time to first required rescue analgesia (mean, SD) was longer in group L (8.1 h, 1.2 h) and group D (8.5 h, 1.9 h) than group C (5.9 h, 0.9 h) (P = 0.000). The number of patients requiring rescue analgesia was lower in group L (8/40, 20%) and group D (6/40, 15%) than group C (16/40, 40%) (P = 0.029), and cumulative consumption of tramadol (mean, SD) was lower in group L (44.0 mg, 17.1 mg) and group D (51.7 mg, 14.1 mg) than group C (73.9 mg, 18.4 mg) (P = 0.000). The incidence of PONV in group L (7/40, 17.5%) and group D (9/40, 22.5%) was lower than group C (18/40, 45.0%) (P = 0.016). Bradycardia (heart rate less than 50 beats/min or lower) was noted in 25 patients (25/40, 62.5%), which was reversed by intravenous administration of atropine 0.5 mg.

Conclusion: Systemic lidocaine and dexmedetomidine had similar effects on enhancing the quality of recovery, alleviating the intensity of
pain and reducing the incidence of PONV after thyroid cancer surgery. However, dexmedetomidine may result in bradycardia. Therefore, lidocaine was superior to dexmedetomidine. **Trial registration**: ChiCTR.org.cn (ChiCTR2000038442). Registered on September 22, 2020.

**Keywords**: Lidocaine; Dexmedetomidine; Quality of recovery; Analgesia; Thyroid cancer

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### Key Summary Points

#### Why carry out this study?

Patients undergoing total thyroidectomy experience mild-to-moderate postoperative pain for up to 48 h. Poorly controlled early postoperative pain and incidence of postoperative nausea or vomiting may contribute to delaying recovery.

Lidocaine and dexmedetomidine are anaesthetic adjuvant during surgery for the analgesic and sedative properties. And both are effective in alleviating postoperative pain. However, there are currently only few studies reporting the efficacy of two anaesthetic adjuvants on the quality of recovery (QoR). In particular, the effects of both medicines on QoR in thyroid cancer surgery were limited reported.

#### What was learned from the study?

This study revealed that systemic lidocaine and dexmedetomidine had similar effects on enhancing the quality of recovery, alleviating the intensity of pain and reducing the incidence of postoperative nausea or vomiting after thyroid cancer surgery. But intravenous infusion of dexmedetomidine may result in bradycardia.

Therefore, intravenous infusion of lidocaine was superior to dexmedetomidine in patients following total thyroidectomy.

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### INTRODUCTION

Thyroid cancer is the most common malignant tumour in the endocrine system [1]. Total thyroidectomy is recommended in the management for thyroid cancer in many cases [2]. Nevertheless, many patients undergoing total thyroidectomy experience mild-to-moderate postoperative pain for up to 48 h [3]. Opioid and non-steroidal analgesics can effectively relieve postoperative acute pain. But opioid agent is frequently associated with dose-related substantial side effects such as nausea and vomiting [4]. Additionally, secretions and painful stimulation of the throat could cause postoperative nausea and vomiting (PONV) after thyroidectomy [5]. Poorly controlled postoperative pain and incidence of PONV may contribute to delaying recovery.

Lidocaine can antagonize the N-methyl-D-aspartate (NMDA) receptor to provide analgesic effects and reduce opioid consumption with lesser concern for side effects than opioids [6]. Systemic administration of low-dose lidocaine has been increasingly used to reduce perioperative pain in many type surgeries [7, 8]. And continuous infusion of lidocaine during operation could reduce the severity of postoperative pain and the consumption of narcotics [7]. Dexmedetomidine is a highly selective α₂-adrenergic receptor agonist with well-known sedative, analgesic, sympatholytic and anxiolytic properties. Systemic infusion of dexmedetomidine can reduce the use of other anaesthetics and the severity of postoperative pain with lower concern for side effects [9]. Given the aforementioned factors, low-dose lidocaine or dexmedetomidine might be a reliable option for relieving postoperative pain.

Commonly, lidocaine and dexmedetomidine are anaesthetic adjuvant during surgery for the analgesic and sedative properties. Besides, previous studies have shown that both are effective in alleviating postoperative pain [7, 10]. However, there are currently only few studies reporting the efficacy of two anaesthetic adjuvants on the quality of recovery (QoR). In particular, the effects of both medicines on QoR in thyroid cancer surgery were limited reported.
Therefore, the present study identified the effects of systemic lidocaine and dexmedetomidine on QoR and analgesia in patients undergoing total thyroidectomy. We hypothesised that systemic lidocaine and dexmedetomidine would improve the QoR and analgesia in patients undergoing total thyroidectomy.

METHODS

Study Design and Settings

This double-blind randomized controlled clinical trial was performed at Anqing Medical Center of Anhui Medical University from October 1, 2020 to November 30, 2021. The Ethics Committee of Anqing Medical Center of Anhui Medical University approved the study protocol, which was prospectively registered at www.chictr.org.cn (No. ChiCTR2000038442, registration date September 22, 2020). Each participant signed an informed consent form before surgery. Our study followed the Consolidated Standards and Regulations.

Participants

A total of 120 patients aged 18–65 years with American Society of Anesthesiologists (ASA) physical status I–II scheduled for elective thyroid cancer surgery (conventional open total thyroidectomy with therapeutic central compartment neck dissection) were enrolled in the study. Patients were excluded if they had known lateral neck node metastases, distant metastasis, bilateral central neck node metastases, recurrent laryngeal nerve invasion, local anaesthetic allergy, depression, anxiety, posttraumatic stress disorder, illicit drug use, severe pain, general poor health, bradycardia (heart rate less than 50 beats/min), second- or third-degree heart block, severe hepatic, renal or respiratory dysfunction, or refusal to participate in the study.

Eligible participants were randomized at a 1:1:1 ratio to receive lidocaine, dexmedetomidine or normal saline placebo using a computer-generated random table. The randomization sequence was kept in opaque envelopes, and a research nurse who was responsible for preparing the anaesthetics opened the corresponding envelopes. Blinding of all eligible participants, data collectors, medical care personnel and researcher staff was maintained during the entire trial period. Details of scales of QoR-15, visual analogue scale (VAS) and postoperative nausea or vomiting (PONV) intensity were explained to each patient 1 day before surgery.

Protocol

Standard monitoring, including heart rate, mean arterial pressure, peripheral pulse oximeter value and electrocardiogram, was performed throughout the procedure. According to the study design, patients in group L received a loading dose of lidocaine (1.5 mg/kg) over 10 min before induction of anaesthesia followed by continuous infusion at a rate of 1.5 mg/kg per hour until 30 min before the end of surgery. Patients in group D received a loading of dexmedetomidine (0.5 µg/kg) over 10 min before induction of anaesthesia followed by continuous infusion at a rate of 0.5 µg/kg per hour until 30 min before the end of surgery. To attain double-blinding, 50-ml syringes containing lidocaine (12 mg/ml), dexmedetomidine (4 µg/ml) or saline were prefilled. Before anaesthesia induction, each patient received an intravenous infusion at a rate of 0.75 ml/kg per hour over 10 min. This rate corresponded to 1.5 mg/kg lidocaine or 0.5 µg/kg dexmedetomidine. Each patient received continuous infusions at a rate of 0.125 ml/kg per hour until 30 min before the end of surgery, and this rate corresponded to 1.5 mg/kg per hour of lidocaine and 0.5 µg/kg per hour of dexmedetomidine.

Anaesthesia induction was performed using target-controlled infusions (TCIs) of propofol and remifentanil. The initial TCI levels of plasma propofol and remifentanil were set as 3.0 µg/ml and 5.0 ng/ml, respectively. Vecuronium (0.08–0.1 mg/kg) was administered when the bispectral index (BIS) value decreased to less than 60. A continuous intraoperative
neuromonitoring of recurrent laryngeal nerves (internal diameter 7.5 mm or 7.0 mm) was inserted after adequate muscle relaxation using a portable video laryngoscope, as described previously. Volume-controlled ventilation was performed to maintain an end-tidal carbon dioxide concentration between 35 and 45 mmHg using an anaesthetic machine (Aespire 7100, Datex-Ohmeda, Madison, WI), and the inspired oxygen fraction (FiO₂) was 0.5 (balanced with air) during the anaesthesia period. No neuromuscular blocking agent was administered after anaesthetic induction. The BIS value was maintained between 45 and 60 by adjusting the TCI of the plasma propofol concentration during surgery. As reported previously, remifentanil infusions were administered manually or switched to manual infusion to maintain the fluctuation of mean arterial pressure and heart rate within 20% of the preoperative baseline value during surgery. If hypotension was not effectively treated with fluid replacement therapy and adjustment of the TCI of plasma remifentanil concentration, ephedrine 6 mg was administered. Atropine 0.5 mg was injected intravenously when the heart rate was less than 50 beats/min during the perioperative period. To alleviate the intensity of postoperative pain, sufentanil (0.2 μg/kg) was given intravenously at 30 min before the end of surgery. The surgeon tried to avoid recurrent laryngeal nerve injury via proactive exposure and neuromonitoring during total thyroidectomy.

To prevent PONV, ondansetron (4 mg) was administered intravenously at 10 min prior to the end of surgery. Parecoxib (40 mg) was provided every 12 h for 24 h. If VAS pain score exceeded 3, tramadol (50 mg) was administered intravenously for breakthrough rescue pain not alleviated by parecoxib.

Outcome Measures

The QoR-15 score on day 1 after surgery (POD1) was the primary endpoint. The QoR-15 questionnaire was used to evaluate the quality of recovery in five dimensions, namely physical comfort (five items), emotional state (four items), pain (two items), psychological support (two items) and physical independence (two items). The total score of the QoR-15 ranged from 0 (extremely poor recovery) to 150 (excellent recovery) [11]. Time to awareness, length of PACU (post-anaesthesia care unit) stay, cumulative consumption of remifentanil, time to first rescue analgesia, postoperative tramadol consumption, VAS pain score and incidence of PONV were the secondary outcomes. The incidence of PONV was assessed by the PONV intensity scale. A 10-cm VAS scale (0 = no pain, 10 = the most pain imaginable) was used to rate the VAS pain score at 2, 4, 8, 12 and 24 h after surgery. Side effects, such as arrhythmia (bradycardia of 50 beats/min or slower, A-V block, bundle branch block), hypotension (systolic blood pressure less than 90 mmHg), need for vasopressors, and prolonged respiratory support were recorded.

Sample Size Calculation

On the basis of our pilot study, the QoR-15 score was 10.2 points lower in group C than groups L and D on POD1. The standard deviation was 8 points on the QoR-15 [11]. The allowable error was 0.05, and each group needed 36 patients (assuming a power of 80%). Forty patients were included per group, allowing for a 10% dropout rate.

Statistical Analysis

SPSS 16.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. The Kolmogorov–Smirnov test was used to determine whether continuous data obeyed a normal distribution. Normally distributed data are presented as means (standard deviation, SD). One-way analysis of variance (ANOVA) was used for continuous data analyses of three groups. Tukey’s post hoc test was performed for further analysis of significant group differences. Nonnormally distributed variables are presented as medians and interquartile range (IQR) and were compared using the Mann–Whitney U test. The qualitative data are expressed as numbers or percentages.
and were analysed using χ² tests. The significance level was \( P \) less than 0.05.

**RESULTS**

The study assessed 128 patients for eligibility. Six patients did not meet the inclusion criteria, and two patients refused to participate in the present study. Therefore, 120 subjects were enrolled for follow-up. The details are shown in Fig. 1. The baseline general characteristics of patients, including age, height, weight, ASA physical status, duration of surgery and anaesthesia, time to awareness and length of PACU stay, were not significantly different (Table 1). The remifentanil total dose (mean, SD) was significantly lower in group L (720.8 μg, 120.1 μg) and group D (745.8 μg, 144.9 μg) than group C (464.8 μg, 189.8 μg) (\( P = 0.000 \)) (Table 1).

The QoR-15 score is shown in Table 2. At POD1, the total score of the QoR-15 (median, IQR) was higher in group L (128.0, 122.0–132.8) and group D (127.5, 122.5–132.5) than group C (118.5, 113.0–123.5) (\( P = 0.000 \)). There was no significant difference in the total QoR-15 score between group L and group D.

Fig. 1 CONSORT flow diagram for the study. group L, i.v. lidocaine; group D, i.v. dexmedetomidine; group C, i.v. equal volume normal saline. 

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The VAS pain score was lower at each time point in group L and group D than group C during the first 24 h after surgery \((P = 0.000)\) (Table 3). As shown in Table 4, the time to first required rescue analgesia (mean, SD) was longer in group L (8.1 h, 1.2 h) and group D (8.5 h, 1.9 h) than group C (5.9 h, 0.9 h) \((P = 0.000)\). The number of patients requiring rescue analgesia was longer in group L (8.1 h, 1.2 h) and group D (8.5 h, 1.9 h) than group C (5.9 h, 0.9 h) \((P = 0.000)\).
analgesia was lower in group L (8/40, 20%) and group D (6/40, 15%) than group C (16/40, 40%) (P = 0.029), and the cumulative consumption of tramadol (mean, SD) was lower in group L (44.0 mg, 17.1 mg) and group D (51.7 mg, 14.1 mg) than group C (73.9 mg, 18.4 mg) (P = 0.000). The remifentanil total dose, VAS pain score and cumulative consumption of tramadol were not significantly different between group L and group D.

As detailed in Table 4, the incidence of PONV in group L (7/40, 17.5%) and group D (9/40, 22.5%) was lower than group C (18/40, 45.0%) (P = 0.016). Twenty-five patients (25/40, 62.5%) had bradycardia in group D during surgery. After intravenous administration of atropine 0.5 mg, the heart rate of these patients gradually recovered to between 60 and 70 beats/min, but no patients had bradycardia in group L or group C (P = 0.000). Hypotension, need for vasopressors or prolonged respiratory support was not observed.

**DISCUSSION**

Our results showed that the total QoR-15 score decreased less in patients who received lidocaine and dexmedetomidine than those in group C. Treatment with lidocaine or dexmedetomidine also decreased the consumption of intraoperative remifentanil, lowered the VAS pain score and reduced the incidence of PONV. At the dose selected in the study, bradycardia was noted in 25 patients in group D, but no bradycardia was recorded in group L or group C.
Reducing postoperative pain and PONV are important factors for improving the quality of recovery after surgery [12, 13]. Satisfactory postoperative analgesia may contribute to improving the postoperative emotional state [14]. However, many patients suffer mild-to-moderate postoperative pain following total thyroidectomy [3]. Tissue inflammation and C-fibre activation cause postoperative pain, and cytokines influence the development of postoperative hyperalgesia [15]. Intravenous lidocaine infusion reduced the severity of postoperative pain in various surgeries and effectively inhibited the inflammatory response [16, 17]. Systematic infusion of dexmedetomidine also provided satisfactory postoperative analgesia and attenuated the proinflammatory response [9, 18]. In addition to morbidity or mortality, a more appropriate measurement method, such as the QoR-15 scale, was used to comprehensively evaluate the quality of postoperative recovery and patient levels of satisfaction using specific and patient-rated questionnaires [19], and it has been widely used in clinical situations. Compared to the QoR-40, the QoR-15 scale is read and completed more quickly [20]. A previous study showed that a change of 8.0 points or more in the QoR-15 score indicated a significant difference and manifested a clinically relevant improvement in the quality of recovery after surgery [11]. There was a 10.2-point difference in the QoR-15 score on POD1 in our pilot study, and the present study found that the total QoR-15 score was higher in groups L and D than group C on POD1, and a significant difference existed in the dimension of emotional state and pain. We speculated that the main cause was related to the analgesic and anti-inflammatory properties of lidocaine and dexmedetomidine [21]. Therefore, our study indicated that both interventions led to a significantly better postoperative health status after thyroid cancer surgery.

Sore throat is the predominate pain after thyroidectomy, and endotracheal tube, inflammation and reflux laryngopharyngitis may contribute to sore throat after surgery [22]. In addition, conventional open thyroidectomy via cervical incision often results in pain, hyperesthesia, and discomfort in the cervical area [23]. Patients in group C showed higher VAS pain score and required more rescue analgesics than groups L and D at each time point during the first 24 h after surgery. The median time to first required rescue analgesia was longer in the present study, and the number of patients requiring rescue analgesia was lower in groups L and D compared to group C. A previous study showed that remifentanil infusion for thyroid surgery was associated with higher postoperative pain and postoperative narcotics requirements [24], but our study observed a significantly reduced total remifentanil dose, and the cumulative consumption of tramadol was lower in groups L and D than group C. Several studies also demonstrated that intravenous lidocaine and dexmedetomidine administration during anaesthesia alleviated the intensity of pain after surgery [25, 26]. A study reported that lidocaine administration helped reduce the production of inflammatory cytokines and improved surgery-induced immune alterations [27]. The benefits of dexmedetomidine infusion may help improve postoperative outcomes, including the attenuation of pain intensity and the reduction of narcotic consumption. Therefore, the results of our study indicated that lidocaine and dexmedetomidine administration offered satisfactory postoperative analgesia, reduced narcotic consumption [28] and improved postoperative outcomes.

Variables of patient discomfort other than postoperative acute pain, such as PONV, should also be considered. Compared to other surgeries, a higher rate of PONV was common in patients undergoing thyroid, parathyroid and other cervical surgeries [29]. Postoperative drainage is inserted routinely to detect severe bleeding after thyroid surgery, which may lead to a higher demand for antiemetic drugs [30]. Several drugs, such as ondansetron (5-HT3 receptor antagonists) and dexamethasone, prevent early PONV after thyroid surgery [31], but dexamethasone was not used in our study. Opioids are traditionally used to relieve postoperative acute pain. However, the occurrence of PONV increases after opioid medication application, which may delay recovery after surgery [32, 33]. The opioid-sparing and
analgesic effects of lidocaine and dexmedetomidine resulted in a lower rate of PONV by minimising perioperative opioid consumption [7, 34], and the aforementioned factors may contribute to reducing the occurrence of PONV in groups L and D.

Neurological and cardiac side effects are the primary side effects of lidocaine [35, 36]. One study reported that lidocaine infusion (bolus followed by continuous infusion) typically yielded therapeutic plasma levels in the range of 1.5–5 μg/ml, with toxicity expected above these levels [37]. Therefore, no side effects occurred in any patient in group L. A loading infusion of dexmedetomidine may produce some adverse events, and an excessive loading dose and infusion rate may cause hypotension, bradycardia and oversedation [38]. Therefore, slow bolus loading or the omission bolus loading may decrease the incidence of side effects. Bradycardia was noted in 25 patients in group D, which was treated with atropine (0.5 mg).

There were several limitations in this study. First, although no side effects occurred in group L, the actual serum concentrations of lidocaine were not measured. Second, the multimodal analgesia (MMA) protocol enhances recovery after surgery. However, the MMA regimen was not used in this study. Third, the incidence of thyroid cancer surgery complications, such as fever, infection, haematoma, cardiopulmonary and thromboembolic events, may be high, but these adverse events were not observed and recorded in the study. Therefore, the results of the study are limited to generalisation. Further studies should be performed to address these limitations.

CONCLUSIONS

Systemic lidocaine and dexmedetomidine had similar effects on enhancing the quality of recovery, alleviating the intensity of pain and reducing the occurrence of PONV after thyroid cancer surgery. However, dexmedetomidine may result in bradycardia. Therefore, lidocaine was superior to dexmedetomidine.

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Authorship Contributions. All authors contributed to data analysis, drafting, or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Compliance with Ethics Guidelines. The study protocol was conducted at Anqing Medical Center of Anhui Medical University from October 1, 2020 to November 30, 2021, in accordance with the Declaration of Helsinki and its later amendments. The study was approved by the Ethics Committee of Anqing Medical Center of Anhui Medical University. Written informed consent was obtained from all subjects before surgery. This study was prospective registered in the Chinese Clinical Trial Registry (ChiCTR2000038442). Initial registration date was September 22, 2020.

Data Availability. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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