https://doi.org/10.31925/farmacia.2024.6.10 **ORIGINAL ARTICLE**

LOW MOLECULAR WEIGHT HEPARIN IN THE PROTECTION OF PARATHYROID FUNCTION AFTER THYROID SURGERY

YOUSONG ZENG [1,2], MENGYUAN WANG [3]*

[1]*Jinzhou Medical University Postgraduate Education Base (Chongqing University Three Gorges Hospital), Wanzhou, 404199, Chongqing, China*
[2]*The Thirteenth People's Hospital of Chongqing, Department of General Surgery, Jiulongpo, 400053, Chongqing, China*
[3]*Chongqing University Three Gorges Hospital, Department of Breast, Wanzhou, 404199, Chongqing, China*

**corresponding author: mengyuanwang199@163.com*

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Abstract

Permanent hypoparathyroidism is a severe complication of thyroid surgery, affecting postoperative quality of life. This study investigated the protective effects of low molecular weight heparin (LMWH) on parathyroid function in 92 patients undergoing total thyroidectomy (June 2019-June 2023). Patients were divided into a control group (CG) receiving standard care and an experimental group (EG) receiving prophylactic calcium LMWH. LMWH (4000 AXaIU enoxaparin) was administered subcutaneously before and after surgery. Coagulation markers, parathyroid indicators and inflammatory markers were assessed pre- and post-operatively. EG showed improved coagulation function and reduced postoperative inflammation (lower IL-6 and CRP levels) compared to CG. Although both groups experienced transient reductions in parathyroid function, recovery was comparable by day 180, with no permanent hypoparathyroidism observed. LMWH improved postoperative outcomes by mitigating hypercoagulability, reducing inflammation and supporting parathyroid function, suggesting its potential benefit in thyroid surgery.

Rezumat

Hipoparatiroidismul permanent este o complicație severă a chirurgiei tiroidiene, afectând calitatea vieții postoperatorii. Acest studiu a investigat efectele heparinei cu greutate moleculară mică (LMWH) asupra funcției paratiroidiene la 92 de pacienți supuși tiroidectomiei totale (în perioada iunie 2019-iunie 2023). Pacienții au fost împărțiți într-un grup de control (CG), care a primit terapie standard și un grup experimental (EG) care a primit LMWH și calciu profilactic. LMWH (4000 AXaIU enoxaparina) a fost administrată subcutanat înainte și după operație. Markerii de coagulare, indicatorii paratiroidieni și markerii inflamatori au fost evaluați înainte și după operație. EG a prezentat o activitate de coagulare îmbunătățită și inflamație postoperatorie redusă (niveluri mai scăzute de IL-6 și CRP) comparativ cu CG. Deși ambele grupuri au prezentat reduceri tranzitorii ale funcției paratiroidiene, recuperarea a fost comparabilă până în ziua 180, fără a se observa hipoparatiroidism permanent. LMWH a îmbunătățit rezultatele postoperatorii prin atenuarea hipercoagulabilității, reducerea inflamației și susținerea funcției paratiroidiene, sugerând potențialele avantaje în chirurgia tiroidiană.

Keywords: hypercoagulable states, low molecular weight heparin, parathyroid function thyroid surgery

Introduction

The thyroid gland is an important part of the endocrine system and plays a vital role in human metabolism, growth and development [1]. Thyroid disorders include hyperthyroidism, hypothyroidism, nodular thyroid disease and thyroid cancer [2]. Thyroid cancer is a malignant tumour that arises from thyroid tissue, and its incidence is increasing every year [3, 4]. Common subtypes include papillary thyroid cancer, follicular thyroid cancer, medullary thyroid cancer and un-differentiated thyroid cancer [5-7]. Surgery is the primary treatment for most thyroid cancers and includes total thyroidectomy, partial thyroidectomy and neck lymph node dissection [8]. However, postoperative patients may face several complications, including hypoparathyroidism, vocal cord injury and postoperative hypercoagulability. These complications can affect patients' quality of life and rehabilitation process. Therefore, research into effective postoperative management strategies is essential.

Low molecular weight heparin (LMWH) is a class of anticoagulants widely used in clinical practice and belongs to the subclass of heparins. Its primary action is inhibiting coagulation Factor Xa's activity to achieve anticoagulation, with a molecular weight between 4000 and 6000 Daltons. Due to its smaller molecular size, LMWH has a more controllable anticoagulant effect and higher bioavailability [9-11]. In clinical use, LMWH is commonly used for the prevention and treatment of venous thromboembolism, including deep vein thrombosis and pulmonary embolism, acute coronary syndromes, anticoagulant therapy after cardiac surgery and anticoagulant therapy during pregnancy and puerperium [12]. Studies have shown that LMWH has anti-inflammatory and antioxidant biological effects in addition to the anticoagulant effects. Following thyroid surgery, tissue trauma and inflammation can impair parathyroid function. The anti-inflammatory and anti-oxidant effects of LMWH are critical in attenuating the postoperative inflammatory response, thereby helping to protect parathyroid function [13]. Clinical assessment of parathyroid function includes evaluation of indicators such as blood calcium (Ca), blood phosphorus (P) and parathyroid hormone (PTH). LMWH, through its anti-inflammatory and antioxidant effects, helps to reduce inflammation induced by surgery, thereby influencing indicators of parathyroid function. In addition, research has shown that LMWH can promote angiogenesis, positively affecting damaged tissue repair and the regeneration. LMWH promotes angiogenesis and helps to improve blood supply, thereby affecting T3 and T4 levels [14]. In addition, the anticoagulant mechanism of LMWH plays a regulatory role in maintaining TSH levels and other thyroid indicators. Based on this, LMWH may also have a similar effect on post-operative parathyroid repair and regeneration, stabilising parathyroid function after surgery.

Thyroid surgery often requires bed rest, which can increase the risk of venous thrombosis. Considering this situation, the widespread use of LMWH as a prophylactic measure for DVT becomes an effective strategy to help reduce postoperative complications, maintain the patient's overall health and protect parathyroid function [15]. Therefore, LMWH has a potentially critical role in managing thyroid surgery. Along with maintaining coagulation balance, it promotes tissue repair, alleviates post-operative inflammatory responses and ultimately improves the overall success of surgery. The primary objective of this work was to investigate the use of LMWH in thyroid surgery to assess its protective effects on parathyroid function and its potential mechanisms. Investigating the anti-inflammatory, antioxidant and angiogenic biological effects of LMWH was hoped to provide better treatment options for patients after thyroid surgery. The study aimed to improve their quality of life, reduce the risk of post-operative complications and minimise the occurrence of permanent hypoparathyroidism.

Materials and Methods

Patients

Between June 2019 and June 2023, 92 patients who underwent total thyroidectomy for thyroid cancer at the Thirteenth People's Hospital of Chongqing, Jiulongpo, China, were selected as study participants. All patients and their families were informed about the study, and informed consent was obtained from each participant. The study was approved by the hospital's medical ethics committee.

Inclusion criteria were as follows: i). met the diagnostic criteria for thyroid cancer outlined in the Guidelines for the Diagnosis and Treatment of Thyroid Nodules and Differentiated Thyroid Cancer and confirmed by surgical pathology; ii). first presentation and underwent surgery; iii). no history of previous mental illness, capable of independently completing the scales required for the study; iv). patients' preoperative parathyroid function was expected; and v). both the patient and family members signed the informed consent form.

The exclusion criteria were: i). concurrent presence of other diseases that may cause disturbances in parathyroid function, such as hyperthyroidism and hypothyroidism; ii). patients with concurrent other malignant tumours; iii). patients with abnormal liver or kidney function; iv). patients who have undergone radiotherapy or chemotherapy; v). patients allergic to LMWH; and vi). use of anticoagulant drugs in the two months before surgery.

Treatment schemes

The 92 patients were randomly assigned to the control group (CG) and the experimental group (EG), with 46 patients in each group. The CG consisted of 13 male patients aged 42 - 63 years (53.5 ± 9.4 years) and 33 female patients aged 31 - 72 years (53.3 ± 11.5 years). In terms of cancer classification, 43 patients had papillary thyroid cancer and 3 patients had follicular thyroid cancer. In the EG, there were 12 men aged 37 to 65 years (51.4 ± 7.9 years) and 34 women aged 25 to 74 years (54.1 ± 9.3 years). In terms of cancer classification, 44 patients had papillary thyroid carcinoma and 2 patients had follicular thyroid carcinoma, with no notable differences ($p > 0.05$).

All patients underwent routine open thyroid surgery and cervical lymph node dissection according to the specific situation. The operation was performed under general anaesthesia with the patient in the supine position and the operative area in the middle of the lower neck. Before surgery, the patient was disinfected and draped, and then a small 8 cm arcuate incision was made in the neck to expose the thyroid gland fully. The thyroid capsule was then dissected. The recurrent laryngeal nerve and the parathyroid gland were identified and safeguarded with special attention. The thyroid lobe was then removed, and the cervical lymph nodes were dissected. The surgical area was irrigated with normal saline. Bleeding was stopped by electrocoagulation or ligation. After thyroidectomy, the drainage tube was placed in the surgical area and sutured to the skin on the body surface. Finally, the surgical incision was sutured. After the operation, the drainage tube was removed if the drainage fluid was less than 20 mL for three consecutive days.

Postoperatively, both groups were closely monitored for incisional bleeding, exudate and dysphagia. Pain management was provided after surgery, and patients with severe pain symptoms were given 2 mg/d of fentanyl (Chengdu Techpool Pharmaceutical Co., Ltd., China) for analgesia. Routine physical recovery exercises, including light walking, stretching, deep breathing and upper limb activities, were started 24 hours post-operatively to promote rehabilitation and prevent complications. They were performed under the supervision of a physician.

The postoperative medication plan for CG patients included levothyroxine sodium (China Limited, China). After surgery, the patient took 2 tablets orally *per* day (a total of 100 mg) and underwent a follow-up examination after 1 month of use. Adjustments were made based on thyroid function and TSH suppression targets, usually by adding or subtracting half a tablet or 1/4 tablet. The patient continued to take the medication for one month and then underwent another follow-up examination until the desired thyroid function and TSH suppression targets were achieved. It should be noted that this medication had to be taken for life to replace the thyroid hormones that cannot be secreted after total thyroidectomy, which was equivalent to life-long replacement therapy.

Patients in the EG received prophylactic calcium LMWH in addition to the standard treatment given to the CG. This consisted of a single subcutaneous injection of 4000 AXaIU enoxaparin 2 to 4 hours before surgery and a daily single subcutaneous injection of 4000 IU LMWH on days 1 to 5 after surgery.

Observation indicators and detection methods

Perioperative indicators. Perioperative indicators for all patients were statistically analysed and compared. These indicators included operative time (minutes), intraoperative blood loss (millilitres), number of lymph nodes dissected, postoperative drainage volume (millilitres), time to first postoperative oral intake (hours), time to first postoperative ambulation (hours), time to first postoperative functional training (hours) and length of hospital stay (days). In addition, visual analogue scale (VAS) scores were recorded and compared for both groups 24 hours postoperatively [16]. In the VAS scoring system, a score of 0 indicates no pain, while 10 indicates excruciating pain. Patients choose a numerical value to express their subjective perception of pain.

Coagulation function. A total of 5 mL of fasting venous blood was collected from the patient on the day before surgery and the mornings of postoperative days 1, 3, 5 and 7 (6:00 - 8:00 a.m.). Considering the actual situation, patients who have undergone total thyroidectomy can usually be discharged at least four days after surgery. Given the situation, patients who were discharged but needed to have their blood drawn had to return to the hospital to complete the blood draw. Blood samples were placed in a Centrifuge CR22N high-speed centrifuge (Eppendorf, Germany) and centrifuged at 3000 rpm for 15 minutes. PT (prothrombin time), APTT (activated partial thromboplastin time), PLT (platelet count), D-D (D-dimer) and Fib (fibrinogen) levels were measured using an XL3600c fully automated coagulation analyser (Beijing Zhongchi Weiye Technology Development Co., Ltd., China).

Parathyroid function. The PTH, Ca and P levels of the two groups of patients were statistically analysed before surgery and on postoperative days 1, 4, 30 and 180. Fasting venous blood (FVB) samples (5 mL) were collected from the patients early in the morning (6:00 - 8:00 a.m.). After clotting for 30 minutes in clotting tubes, the samples were centrifuged at 3000 rpm for 15 minutes in a Centrifuge CR22N high-speed centrifuge, and the supernatant was stored at -80°C for subsequent analysis. The Ellume-A fully automated chemiluminescence immunoassay analyser (Shenzhen Guosai Biotechnology Co., Ltd., China) was used to analyse the parathyroid function of the patients using the electrochemi-luminescence immunoassay method. Serum calcium was measured using the Arsenazo III method using the SYNCHRON series biochemical analysis system (Beckman Coulter, USA).

Inflammatory factors. FVB samples (5 mL) were collected one day before surgery and 24 hours post-operatively. The samples were centrifuged at 3000 rpm for 15 minutes, and the supernatant was stored at -20°C for further analysis. Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of interleukin (IL-6) and CRP in the patients [17]. The plate was allowed to equilibrate at room temperature for 20 minutes before removal. Standard and sample wells were established by adding 50 μL of different concentrations of standards to each standard well, 50 μL of the test sample to each well, and no addition to the blank wells. Then 100 μL of horseradish peroxidase-labelled antibody was added to each standard and sample well, followed by sealing of the plate and incubation at 37°C for 60 minutes. The plate was then washed using a plate washer, and 50 μL of substrate was added. The plate was incubated for a further 15 minutes at 37°C. Finally, 50 μL of stop solution was added, and the OD values at 450 nm were determined for each well. The results were compared. IL-6 and CRP kits were purchased from Shanghai Jianglai Industrial Co.

Complications. Post-operative complications were assessed before discharge, including nausea and vomiting, subcutaneous fluid accumulation, hypo-calcaemia, dysphagia, bleeding and venous thrombo-embolism.

Statistical analysis. Data were processed using SPSS 26.0 (IBM, USA). Descriptive statistics for continuous variables were expressed as mean ± standard deviation and compared using the t-test. Categorical data were presented as frequencies or percentages and compared using the chi-squared test. A $p < 0.05$ was considered statistically significant.

Results and Discussion

The intraoperative indicators during the perioperative period for both groups of patients are shown in Figure 1. For CG patients, the duration of surgery was 103.2 ± 10.4

minutes, intraoperative blood loss was 40.2 ± 6.2 mL and the number of dissected lymph nodes was 3.83 ± 0.42. In EG patients, these values were 105.1 ± 9.8 minutes, 40.6 ± 5.9 mL and 3.65 ± 0.39, respectively. When comparing these data, there were no apparent differences between patients in the different groups ($p > 0.05$).

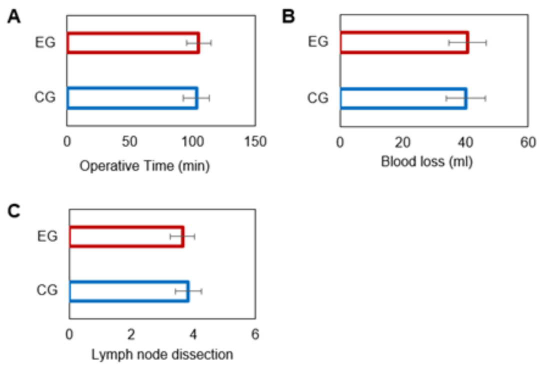

Figure 1.
Perioperative indicators of patients in CG and EG
A: surgical duration; B: intraoperative blood loss;
C: number of lymph nodes dissected

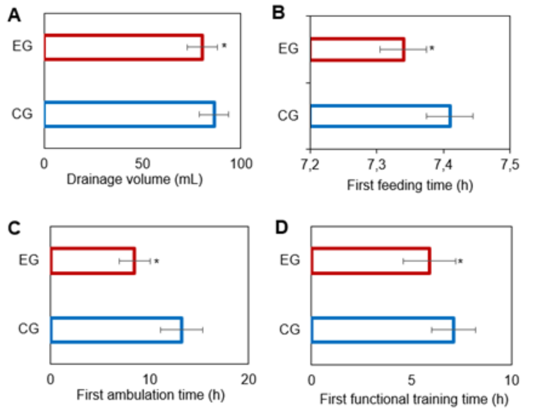

Figure 2.
Changes in postoperative phase indicators
A: postoperative drainage volume; B: the time to first postoperative meal; C: the time to first postoperative ambulation; D: the time to first postoperative functional training. * $p < 0.05$ compared with the value in CG

The perioperative and postoperative indicators for both groups of patients are detailed in Figure 2. For CG patients, the postoperative drainage volume was 86.42 ± 7.42 mL, the time to first postoperative meal was 7.34 ± 2.05 hours, the time to first postoperative ambulation was 13.24 ± 2.12 hours and the time to first postoperative functional training was 7.11 ± 1.12 hours. For EG patients, the postoperative drainage volume was 80.39 ± 7.83 mL, the time to first post-operative meal was 7.41 ± 1.32 hours, the time to first postoperative ambulation was 8.48 ± 1.58 hours and the time to first postoperative functional training was 5.95 ± 1.28 hours. These data showed that the post-operative indicators for EG patients were significantly shorter than those for CG patients ($p < 0.05$).

The VAS score for CG patients was 3.63 ± 0.95 and the length of hospital stay (LOS) was 8.79 ± 0.98 days. The VAS score 2.01 ± 0.42 and LOS 7.62 ± 0.45 for EG patients were much lower in contrast to those for CG, showing obvious differences with $p < 0.05$, as illustrated in Figure 3.

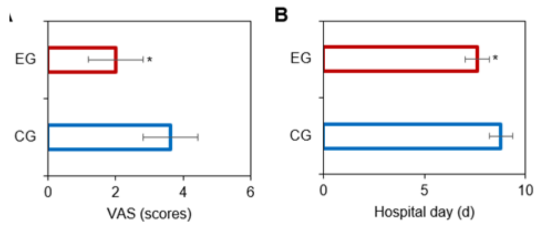

Figure 3.
Comparison of pain and length of hospital stay indicators
A: VAS; B: LOS. * $p < 0.05$ compared with the value in CG

Changes in coagulation function indicators

LMWH can effectively inhibit platelet aggregation. The coagulation function indicators for both EG and CG of the patients are shown and compared in Figure 4. After surgery, PT, APTT and D-D in CG increased significantly and were significantly higher than the preoperative values ($p < 0.05$). Under the influence of LMWH, PT and Fib in EG showed an increase after surgery but with no visible difference from preoperative levels ($p > 0.05$). D-D on the first postoperative day was much higher compared to the preoperative levels ($p < 0.05$), while on the third postoperative day, no significant difference was seen compared to the preoperative levels ($p > 0.05$). The PLT levels of all patients in different groups showed minimal variations with no significant difference. It showed a trend of first decreasing and then increasing, reaching the lowest point on the third postoperative day, and was significantly different from the preoperative levels ($p < 0.05$). APTT for patients in both EG and CG showed a decreasing trend but no significant changes from preoperative levels and between EG and CG ($p > 0.05$).

Alternations in parathyroid function

Parathyroid function, as shown in Figure 5, showed that on postoperative day 1, there was a varying degree of decrease in PTH and Ca in all patients, accompanied by an increase in P. The differences between the two groups were statistically significant ($p < 0.05$). On postoperative day 4, there was a variable degree of recovery of PTH, Ca and P in all patients, with significant differences in the recovery rates ($p < 0.05$). On postoperative day 30, most patients in both groups had largely normalised PTH, Ca and P levels, with significant differences between the two groups ($p < 0.05$). At day 180, there were no significant differences in the recovery of PTH, Ca and P between the two groups, indicating comparable recovery outcomes ($p < 0.05$).

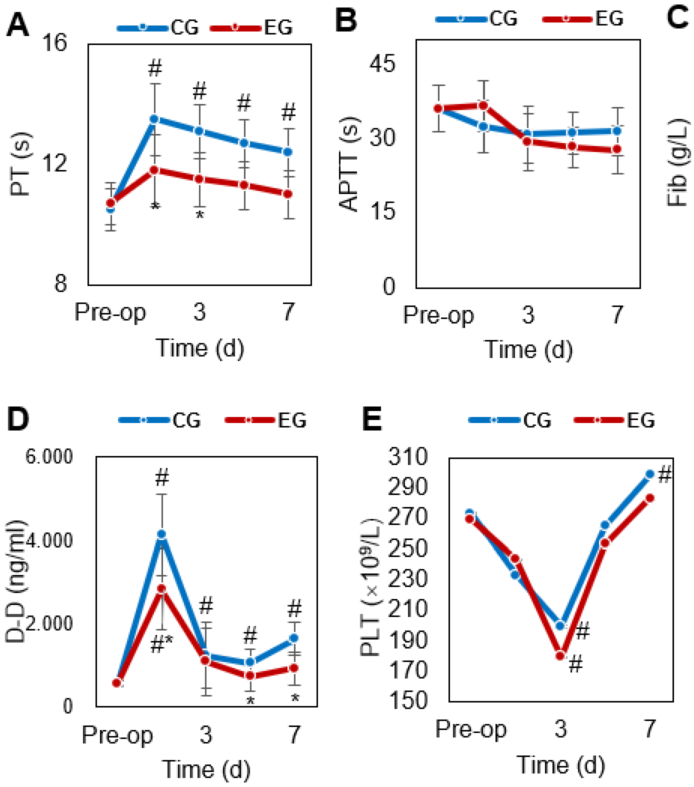

Figure 4.

Changes in coagulation function indicators of patients

A: PT; B: APTT; C: Fib; D: D-D; E: PLT. * $p < 0.05$ compared with the value in CG; # $p < 0.05$ compared with preoperative values

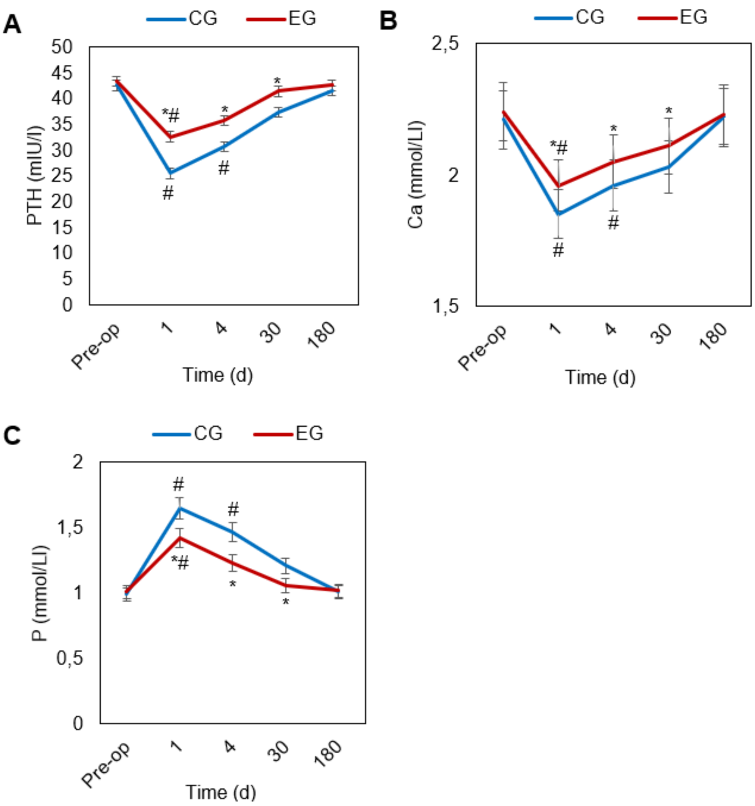

Figure 5.

Comparison of the parathyroid function of patients in different groups

A: PTH; B: Ca; C: P. * $p < 0.05$ compared with the value in CG; # $p < 0.05$ compared with preoperative values.

Changes in inflammatory factors of patients before and after different treatments

Figure 6 below compares the levels of inflammatory factors in the patients 24 hours after surgery. After surgery, patients' IL-6 and CRP levels were all elevated, which was more pronounced in CG compared to pre-operative levels ($p < 0.05$). In EG, CRP levels were upregulated after treatment ($p < 0.05$), while IL-6 levels changed slightly ($p > 0.05$). In the intergroup comparison, 24 hours postoperatively, EG had significantly downregulated IL-6 and CRP compared to CG patients ($p < 0.05$).

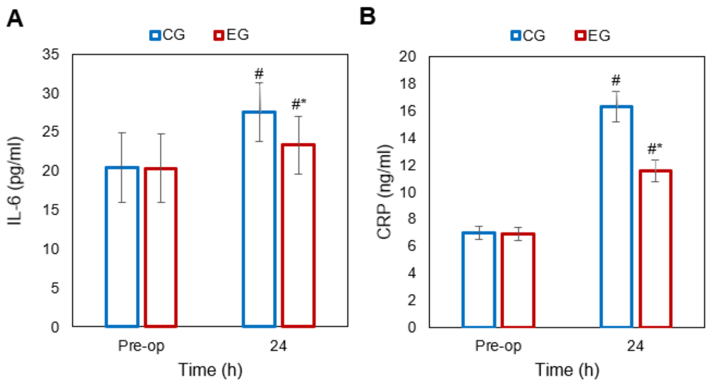

Figure 6.

Changes in inflammatory factors of patients

A: IL-6; B: CRP. * $p < 0.05$ compared with the value in CG; # $p < 0.05$ compared with preoperative values.

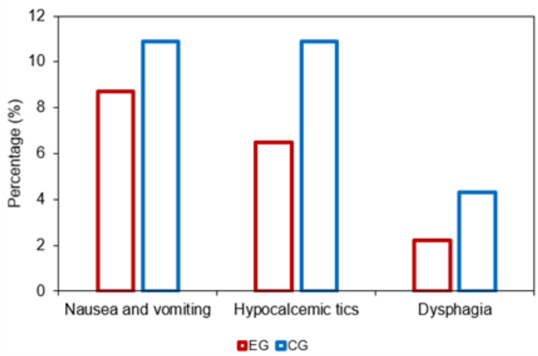

Figure 7.

Complications after thyroid surgery

Complications after thyroid surgery

Before discharge, a statistical analysis was performed on the incidence of postoperative complications between the two groups of patients during treatment (Figure 7). The probability of nausea and vomiting was 10.9%. CG patients had higher rates of hypercalcaemic seizures (10.9%) and dysphagia (4.3%) than EG patients, and the differences were statistically significant ($p < 0.05$).

Thyroid cancer accounts for about 1% of all malignant tumours, and thyroidectomy is a standard surgical procedure for its treatment [18, 19]. Based on the extent of resection, thyroidectomy can be divided into total thyroidectomy and thyroid lobectomy. Regardless of the type of surgery chosen, there is a 6.9% to 46.0% chance of developing postoperative complications such as hypoparathyroidism, recurrent laryngeal nerve injury and calcium metabolism disorders [20-22]. This work aimed to investigate the potential protective effects of LMWH on parathyroid function after thyroid surgery. Answering this question is crucial to improving patients' postoperative recovery and quality of life.

In this study, patients treated with LMWH showed significant advantages in postoperative recovery and rehabilitation compared to the control group. EG showed significantly shorter postoperative drainage volume, time to first meal, time to first ambulation and time to first functional training. In addition, LMWH promotes angiogenesis by improving blood supply to damaged tissues, accelerates the recovery process, and promotes the restoration of parathyroid function. Regarding coagulation function, PT is used to assess the functionality of the extrinsic coagulation pathway, and D-D represents a fibrinolytic product. Fib is a protein involved in fibrin formation. Elevated D-D and Fib levels indicate a state of hypercoagulability and increased fibrinolysis [23-26]. The D-D and Fib levels in EG patients were significantly lower than those in CG, suggesting that LMWH effectively reduces the risk of thrombosis and improves the postoperative recovery rate. This is consistent with the findings of Shiqing *et al.* [27], who observed that LMWH is beneficial in alleviating postoperative hypercoagulability, increased viscosity and inflammatory response and reducing the incidence of lower extremity deep vein thrombosis in patients with spinal trauma. Although the literature on complications and recovery after thyroid surgery is relatively extensive, research on the specific role of LMWH in this process and its protective effect on parathyroid function is relatively limited [28, 29].

Postoperative parathyroid function indicators showed that EG patients treated with LMWH maintained relatively stable parathyroid hormone levels, with no significant difference from preoperative levels, whereas CG patients had impaired parathyroid function. This provides new insights into clinical practice and suggests that LMWH may be a potential therapeutic approach to protect postoperative parathyroid function, reduce the risk of complications and facilitate a faster recovery process.

PTH is a hormone synthesised and secreted by the parathyroid cells [30, 31]. Under normal circumstances, low Ca, high P and a decrease in 1.25-dihydroxy vitamin D levels are all stimulatory factors that cause the synthesis and release of PTH by the parathyroid glands. This constitutes a negative feedback mechanism to maintain the balance of calcium and phosphorus metabolism through the action of PTH [32]. The primary functions of PTH in the body include promoting the release of calcium and phosphorus from bone, increasing renal tubular reabsorption of calcium and stimulating the kidneys to excrete phosphorus [33]. Hypoparathyroidism typically leads to a decrease in PTH levels. PTH regulates Ca^{2+} levels by stimulating calcium release from bone, increasing renal tubular calcium reabsorption, inhibiting phosphorus reabsorption and increasing phosphorus excretion by the kidneys [34]. If there is a deficiency in PTH synthesis or release due to hypoparathyroidism, this leads to a decrease in Ca levels. The regulation of phosphorus by PTH primarily involves the inhibition of renal tubular reabsorption of phosphorus and increasing phosphorus excretion. Hypoparathyroidism can lead to a decrease in PTH levels, which attenuates phosphorus excretion and leads to an increase in P levels [35].

After treatment with LMWH, EG showed relatively stable parathyroid hormone levels, with no significant difference compared to preoperative levels. This may be due to the anti-inflammatory, antioxidant and immunomodulatory effects of LMWH, which alleviate postoperative inflammation and damage, contributing to the protection of parathyroid function. Foreign studies suggest concurrent LMWH treatment during anti-tumour therapy can effectively improve patient survival [36].

Although the results are promising new treatment options, this study has several limitations, including a relatively small sample size, limited study duration and insufficient mechanistic exploration. Future research could improve the understanding of the potential effects of LMWH in thyroid surgery by increasing the sample size, extending the duration of the study and conducting in-depth investigations of the detailed mechanisms of action, particularly concerning immune and inflammatory responses. The results suggest that low-molecular-weight heparin may potentially protect the parathyroid gland after thyroid surgery. This helps alleviate post-operative hypercoagulable states, improve coagulation function and significantly reduce post-operative inflammatory responses. In addition, the beneficial effect of LMWH on parathyroid function minimises the risk of parathyroid dysfunction, contributing to a favourable long-term prognosis for patients. Future research could further explore the detailed mechanisms of action of LMWH after thyroid surgery. Comparisons of different doses and routes of administration of LMWH may help to determine the optimal treatment regimen and provide more helpful information about recovery after thyroid surgery. Addressing the current study's limitations may lead to a better understanding of the clinical prospects of LMWH in thyroid surgery.

Conclusions

LMWH showed a potential protective effect after thyroid surgery. LMWH had a beneficial effect on parathyroid function, reducing the risk of parathyroid dysfunction. The stability of Ca, P and PTH levels suggested that LMWH would likely maintain more normal parathyroid function. Using LMWH helped alleviate postoperative hypercoagulable states, improve coagulation function and significantly reduce post-operative inflammatory reactions. There were no significant adverse reactions in this work, suggesting that the postoperative use of LMWH was safe. However, further research and large-scale clinical trials are needed to validate these findings and provide a complete understanding of the potential role and safety of LMWH in thyroid surgery.

Conflict of interest

The authors declare no conflict of interest.

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