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ORIGINAL SCIENTIFIC REPORT

A Perioperative Small Dose of Dexamethasone Enhances Postoperative Recovery by Reducing Volume and Inflammatory Contents in Wound Drainage After Thyroid Surgery: A Double-Blinded, Randomized, Prospective Study

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Abstract

Background The aims of this study were to assess the effect of perioperative dexamethasone on postoperative thyroid surgery recovery using measures of wound drainage volume and C-reactive protein (CRP) levels and leukocyte counts.

Materials and methods From January to September 2014, healthy patients, aged between 18 and 65 years, had elective thyroid surgery in the tertiary hospital. Eligible patients were randomized into either group D (dexamethasone 0.1 mg/kg IV) or group S (saline IV) after anesthesia induction. At the end of surgery, a drainage tube was placed at the thyroid bed with a negative pressure ball connected outside the wound. Drainage fluids were collected after thyroid surgery. The fluid volume and the levels of C-reactive protein and leukocyte counts inside were analyzed. All patients were followed up for 1 month.

Results The median total drainage in group D (n = 103) was 43 ml (IQR: 21–83 ml), and 68 ml (IQR: 35–104 ml) in group S (n = 111), P = 0.002. More patients in group D were discharged on postoperative day 2 (74.8% vs. 54.1%, P = 0.002). The CRP levels and leukocyte counts were much less in group D than in group S (P = 0.002 and $P < 0.001$, respectively). Two patients (one in each group) had wound infections 1 week after surgery that healed one additional week later.

Conclusions One perioperative small dose of dexamethasone reduced wound drainage volume and inflammatory content after thyroid surgery, thereby possibly contributing to early recovery. The effects of dexamethasone have never been evaluated before under these conditions.

Registration number: NCT02304250 (http://www.clinicaltrials.gov).

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Introduction

A perioperative low dose of dexamethasone has been reported to have many benefits after thyroid surgeries, including preventing postoperative nausea and vomiting (PONV), relieving shivering, sore throat and pain, preventing recurrent laryngeal nerve damage, improving voice change, increasing appetite and reducing discomfort [1–5], but its effects on postoperative recovery as measured by wound drainage and infection are unknown.

Wound ooze is inevitable during healing. Persistent wound ooze is responsible for delay in discharge and thus leads to prolonged hospital stay [6]. The amount of inflammatory cells in wound ooze may imply an early and subtle wound infection before systemic response starts. Although the quality and quantity of drains used after thyroid surgery is debated [7], in some geographical areas, non-evidence-based use of drains is still used by some surgeons [7, 8]. Since the withdrawal of the drain is often determined by the amount of drainage [8], the amount of drainage could itself be used as a marker for postoperative recovery after thyroid surgery. We used drainage amount and inflammatory content as outcome measures to evaluate the effects of a small perioperative dose of dexamethasone on postoperative recovery after thyroid surgery.

The primary outcomes in the study were the daily and total amount of postoperative wound drainage. The secondary outcomes included the C-reactive protein (CRP) levels and leukocyte counts in the drainage, the length of postoperative hospital stay, postoperative pain scores and wound complications.

Materials and methods

Ethics approval

This was a prospective, randomized, double-blinded, controlled study performed at a single center. Ethical approval for this study was provided by the Ethics Committee of Shanghai Jiaotong University, affiliated with Shanghai Sixth People's Hospital, Shanghai, China (Chairperson Prof. Weiping Jia) on September 30, 2013. The study was registered at clinicaltrials.gov (NCT02304250). Written informed consent was obtained from all patients.

Patient population

Patients, aged between 18 and 65 years, in good health (ASA I–II) who presented to the tertiary center for elective thyroid surgery, were eligible. Exclusion criteria included thyroid tumor with symptoms of Grave's disease, thyroid tumor size over 4 cm, previous thyroid surgery, pharyngitis and long-term use of dexamethasone or other cortisones.

Conduct of the study

The study was conducted from January 2014 to September 2014. The trial protocol is provided in the Supplementary material of trial protocol (Supplements). Enrolled patients were randomized into two groups: group D received dexamethasone 0.1 mg/kg IV in the concentration of 5 mg/ml, and group S, serving as the control group, received an equivalent volume of saline. Sequentially numbered opaque sealed envelopes technique is used for randomization. An anesthesia assistant who was not involved in data collection and data analysis prepared the medication by labeling the syringes with "test drug" to preserve blinding. The test drug was administered right after general anesthesia induction.

All patients received open thyroid surgery, either total thyroidectomy or hemithyroidectomy, with central lymphadenectomy or total lymphadenectomy, performed by a team. At the time of thyroid surgery, identical surgical instruments, including a general electrocautery, were used. After completion of the hemostasis and irrigation procedure, a Jackson-Pratt drain (Sunmoonstar medical Co, Suzhou, China) with a 7-mm lumen was inserted at the thyroid bed prior to the completion of the surgery in both groups. A total of ten layers of dressing covered the incision with the drainage bag left outside. The day of surgery was defined as day 0 (POD0), the first day after surgery was defined as postoperative day 1 (POD1) and so on.

The wound, negative pressure and dressing were checked at 6 h after operation, as well as the patency of the drainage tube. The drainage bag was emptied and the amount of fluid was recorded every morning, with the drainage tube in situ. The tube was kept in the wound for at least 2 days after the operation. If the bag was empty on POD1, the patency of the drainage tube was checked and then the tube was left in situ. On the morning of POD2, the tube was pulled out if there were less than 25 ml fluid in the bag, and the amount of fluid in the bag was recorded. If the bag was empty (i.e., zero ml) on both POD1 and POD2, then drainage tube blockage and/or no actual drainage was suspected. In such a case, the tube was pulled out and only drainage accumulated on the dressing, if any, was calculated for drainage volume analysis. Because no drainage from the bags could be collected, these patients were excluded from inflammatory markers analysis, and only

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length of hospital stay was recorded. When there was more than 25 ml of fluid in the bag, the bag was emptied, the amount of fluid was recorded and the tube was kept in situ until the next day. The dressing was changed on every postoperative morning, and the bloodstained area in each layer was calculated and summed each day. Every 10 cm * 10 cm bloodstain on a single layer of gauze was calculated as 10 ml of drainage fluid. All these drainage collections were done by a researcher who did not know the group allocations. Patients checked out of the hospital on the day drain output ceased, with the condition the tube was not blocked. No fluid in the tube or bag and a large stained area on the dressing were considered signs of blockage.

Inflammatory content in drainage

Two milliliters of drainage fluid from POD1 to POD2 was collected to measure C-reactive protein (CRP) concentrations and total leukocyte counts using latex-enhanced immunonephelometry on a Siemens BN-ProSpec Nephelometer (Siemens, Germany) and a Sysmex XE-5000 (Sysmex, Japan), respectively.

Data collection

The demographics of participants included age, gender, height, weight, ASA status. Surgery types and duration were recorded. Drainage in the tube, bag and bloodstained gauze was collected on every postoperative day. The total drainage amount was the sum of daily drainage for each patient.

The researcher who collected drainage fluid also asked for pain scores. Pain was evaluated for sore throat at rest, while swallowing, and for incision pain using a visual analog scale (VAS) (0 = none, 10 = severe), all at the same time points. Postoperative pain was controlled by flurbiprofen 50 mg IV if any pain scores were larger than five. The number and percentage of patients who required flurbiprofen treatment were also recorded.

All patients were followed up at the outpatient clinic for 1 month after discharge to check for wound complications, which included purulent and local pain, as well as swelling, redness or heat around the incision site.

Statistics

Using a power analysis based on the results from previous studies, we anticipated an average difference of 25 ml in drainage between the two groups with a SD (standard deviation) of 40 ml for both groups (G-power). With a power of 0.95 and a significance level of 0.05, at least seventy-one patients per group were needed. Some factors, such as blocked tubes and operation times longer than 2 h which resulted in routine administration of antibiotics, could not be predicted; we decided to recruit at least 120 patients in each group to ensure adequate statistical power. All analyses were conducted as modified intention to treat. Proportional data were presented as numbers in each group, and were evaluated using the Chi-square test. For continuous data, the Kolmogorov–Smirnov test was performed first. If continuous data were skewed, the Mann–Whitney U test was used; otherwise, Student's t test was used for comparing the two groups. For drainage volume and pain scores analysis, two-way repeated ANOVA with factors of time and treatment was performed. Mixed models allow for the incorporation of all data points from a subject, even if observations are missing for that subject; so a mixed model was used for checking the drainage volume analysis, as many patients were discharged on POD3 and POD4. P value <0.05 was considered statistically significant. SPSS 22.0 (IBM) was used in all statistical analyses.

Results

Among the 240 patients who met the inclusion criteria and enrolled in the study, 26 cases with operation times longer than 2 h and who had antibiotics were excluded from the study. Among the remaining 214 cases, 15 patients (ten in group D, five in group S) had zero drainage in tube and bag for two postoperative days. These 15 patients were included for drainage volume analysis and the length of postoperative hospital stay, but not the inflammatory content analysis (Fig. 1). Demographic and clinical characteristics of 103 patients in group D and 111 patients in group S were similar (Table 1).

The primary outcomes

The median total drainage in group D was 43 ml (IQR: 21–83 ml) and 68 ml (IQR: 35–104 ml) in group S ($P = 0.002$). The square root of the original data shows that the raw data pass the normal test (K–S test: $P = 0.2$). Transformed data from the total drainage volume also showed a statistically significant difference between the two groups (6.61 ± 3.44 in group D vs. 7.91 ± 3.12 in group S, $P = 0.004$). Seventy-seven, or 74.8% of patients in group D and 60 or 54.1% of patients in group S, were discharged on POD2 as their drainage amounts were less than 25 ml ($P = 0.002$). The number of patients with drainage tubes and their drainage volumes on each postoperative day are shown in Fig. 2. All the patients had their tube removed on POD4. Two-way repeated ANOVA analysis showed there were significant differences in time and group (time: $P < 0.001$, time * group: $P = 0.177$,

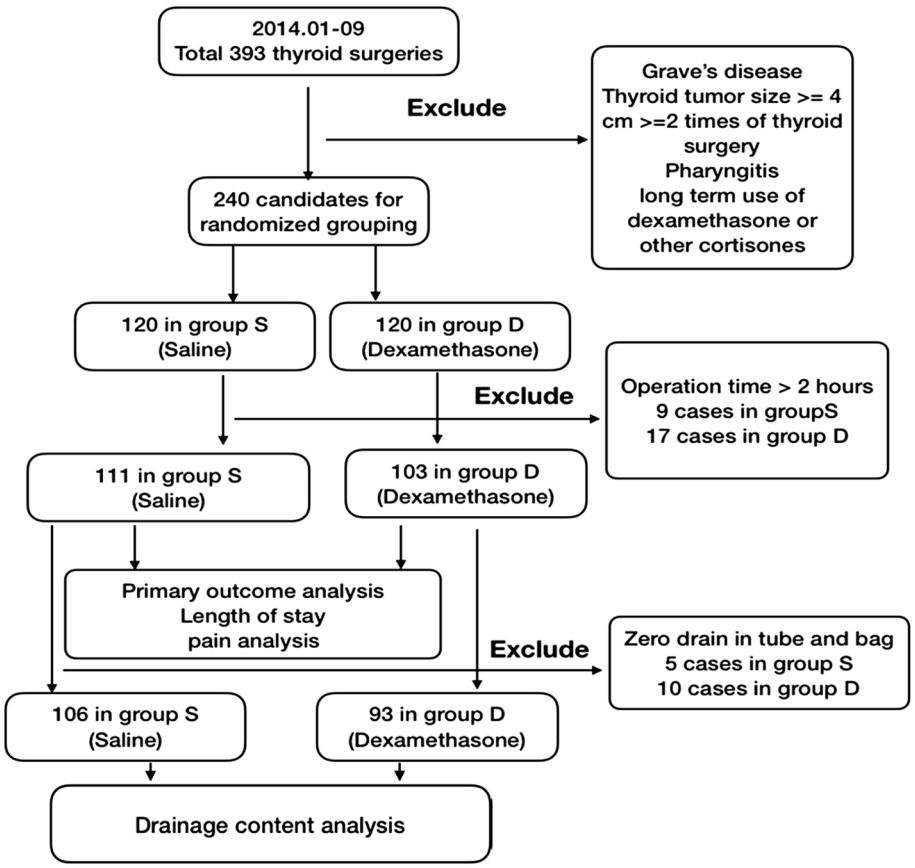

Fig. 1 Consort diagram describing patients' inclusion and exclusion from the study

Table 1 Demographic and clinical characteristics of patients in two groups

Characteristic	Group D (n = 103)	Group S (n = 111)	P value
Age (years) (mean ± SD)	46.32 ± 12.12	44.34 ± 12.34	0.24
Gender (male/female) (n)	25/78	26/85	1.00
Height (cm) (mean ± SD)	165.82 ± 7.88	166.98 ± 8.13	0.29
Weight (kg) (mean ± SD)	63.87 ± 9.33	63.82 ± 9.97	0.97
ASA I/II (n)	74/29	92/19	0.07
Operation duration (min) (mean ± SD)	72.67 ± 23.77	70.44 ± 24.56	0.50
Tumor size (cm) (mean ± SD)	1.53 ± 0.92	1.32 ± 1.01	0.11
Total Fentanyl dosage (ug) (mean ± SD)	362.99 ± 71.95	363.24 ± 75.20	0.98
Types of thyroid surgery (Uni/bilateral thyroidectomy)	59/42	72/39	0.40

ASA American Society of Anesthesiologists, Unilateral thyroidectomy included one-side total thyroidectomy and one-side subtotal thyroidectomy; bilateral thyroidectomy included two-side total thyroidectomy and two-side subtotal thyroidectomy

group: $F_{(3,848)} = 102.6$, $P < 0.001$). A mixed model of repeated measures also demonstrated a significant difference between the two groups ($F_{(1,\ 212)} = 9.22$; $P = 0.003$).

The secondary outcomes

Ten cases in group D and five cases in group S had zero drainage. So, only 199 cases had drainage content analysis. The CRP levels were much lower in group D than that in group S (two-way repeated ANOVA, $F_{(1,197)} = 9.86$, $P = 0.002$). And a similar discrepancy between the two

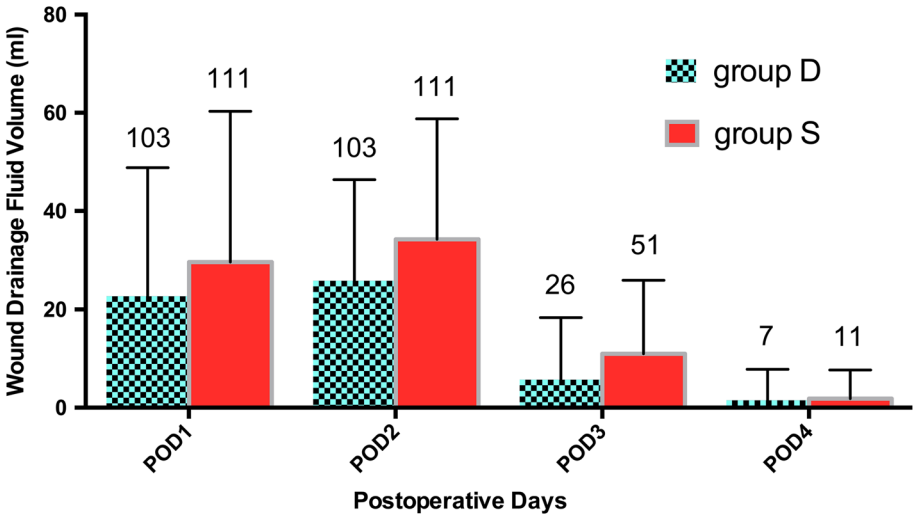

Fig. 2 Drainage volume on each postoperative day after thyroid surgery in patients receiving dexamethasone 0.1 mg/kg IV (blue patterned) or saline (red blank). Data were shown as mean and standard deviation. The volume included fluid in drainage tube and drainage bag and gauze stains (10 cm * 10 cm stain was counted as 10 ml drainage fluid). The numbers on each bar indicated the number of patients who had their drainage tube in situ. Two-way repeated ANOVA analysis showed there were significant differences in time and group (time: $P < 0.001$, time * group: $P = 0.177$, group: $F_{(3,\ 848)} = 102.6$, $P < 0.001$). Mixed model of repeated measures also demonstrated a significant difference between the two groups ($F_{(1,212)} = 9.22$; $P = 0.003$)

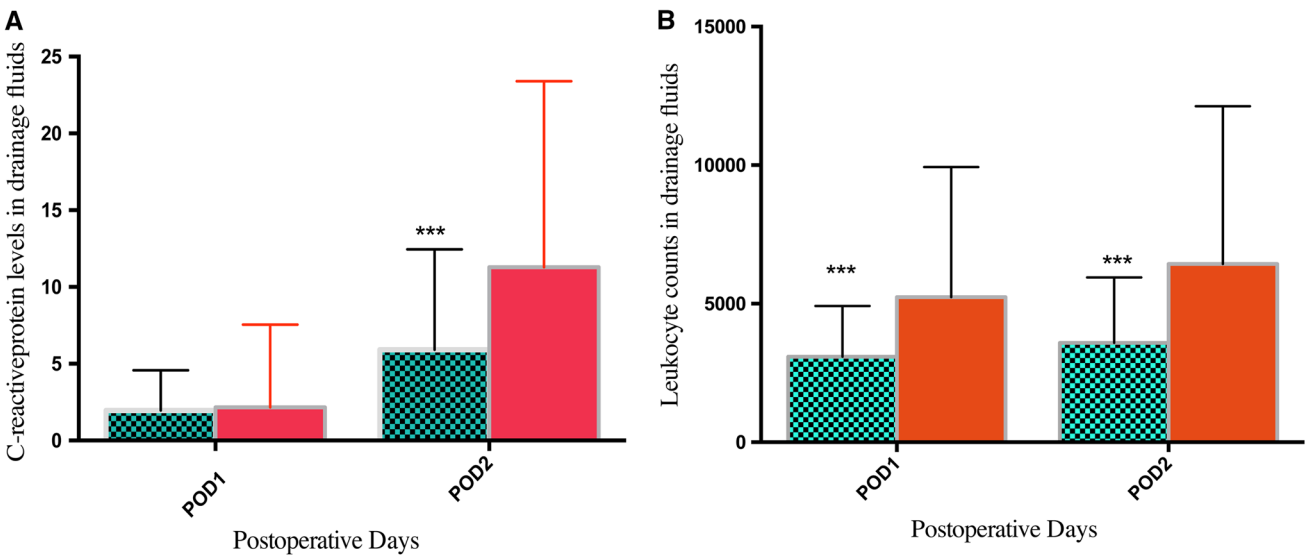

Fig. 3 C-reactive protein levels and leukocyte counts in drainage fluids after thyroid surgery in patients receiving dexamethasone 0.1 mg/kg IV (blue patterned) or saline (red blank). Data were shown as mean and standard deviation. There were significant differences between groups in time (two-way repeated ANOVA: time: $P < 0.001$, time * group: $P < 0.001$, group: $F_{(1,\ 197)} = 9.86$, $P = 0.002$) and in C-reactive protein levels in postoperative drainage fluids (**a**). There were significant differences between groups in time (two-way repeated ANOVA: time: $P < 0.039$, time * group: $P = 0.393$, group: $F_{(1,\ 197)} = 37.19$, $P < 0.001$) and in leukocyte counts in postoperative drainage fluids (**b**). ***indicates a significant difference between the two groups on that day

groups was found in total leukocytes (two-way repeated ANOVA, $F_{(1,197)} = 37.10$, $P < 0.001$) (Fig. 3).

The average lengths of postoperative stay between the two groups were statistically different (2.66 ± 0.65 days in group S vs. 2.38 ± 0.61 days in group D, $P = 0.002$) (Table 2). The pain scores, including wound incision pain, sore throat at rest and swallowing pain, on POD0 and POD1 were significantly lower in the dexamethasone group

Table 2 Scores of postoperative pain and PONV in two groups

	Group D (n = 103)	Group S (n = 111)	P value
Sore throat (rest) (mean ± SD)			
POD0	1.21 ± 1.32	2.15 ± 1.55	<0.001
POD1	0.68 ± 1.24	1.58 ± 1.69	<0.001
POD2	0.56 ± 0.38	0.61 ± 0.28	0.27
Sore throat (swallow) (mean ± SD)			
POD0	3.86 ± 1.89	4.59 ± 2.86	0.005
POD1	2.85 ± 1.57	3.38 ± 1.76	0.021
POD2	1.38 ± 1.02	1.22 ± 0.97	0.242
Incision pain (movement) (mean ± SD)			
POD0	1.34 ± 1.32	2.34 ± 1.63	<0.001
POD1	0.96 ± 1.25	2.08 ± 1.58	<0.001
POD2	0.12 ± 0.60	0.16 ± 0.37	0.555
Patients required analgesics (n) (%)	22 (21.35%)	68 (61.13%)	<0.001
Length of hospital stay* (Median, IQR) (Days)	2, 2–3	3, 2–3	0.001

POD postoperative day, *IQR* interquartile range

*The average lengths of postoperative hospital stays were 2.66 ± 0.65 days in group S vs. 2.38 ± 0.61 days in group D, P = 0.002

than in the saline group ($P < 0.001$). But on the POD2, almost no pain scores were over 3. The number and percentage of patients who needed rescue pain medicine were significantly less in group D than in group S ($P < 0.001$) (Table 2).

There were two wound inflammation cases, one in each group (0.97% in group D and 0.9% in group S), found at one-week follow-up. They were treated with antibiotics and dressing changes every day. The one in group D and the other in group S were cured after 5 and 7 days, respectively.

Discussion

This study focused on the effects of single low dose of dexamethasone, administered perioperatively, on postoperative recovery, as measured by wound drainage volume and inflammatory content in drainage fluid after thyroid surgery. The main findings of the study were that perioperative small single doses of dexamethasone reduced the drainage volume and the CRP levels and leukocytes counts in the drainage fluid, along with the postoperative pain. All these results, in turn, were related to early hospital discharge. The role of dexamethasone has never been evaluated before in those conditions. A possible causal mechanism was the drug's anti-inflammatory properties, which reduce vascular permeability.

These results are consistent with many previous reports in which perioperative dexamethasone appeared to enhance recovery after major noncardiac surgeries [9] and orthopedic operations [10]. However, one study found that perioperative dexamethasone (60 mg for 3 days) caused more harm than benefit after head and neck cancer surgery [11]. A possible reason for this difference could be the dosage of dexamethasone used.

Both blood CRP and leukocytes are commonly used inflammatory markers. Although their diagnostic accuracy in drainage after thyroid surgery is unknown, synovial WBC counts and CRP levels were reported to be useful in diagnosing acute periprosthetic joint infection after primary knee arthroplasty [12]. Our results are consistent with previous reports in other types of surgery. Preoperative dexamethasone was reported to attenuate early peritoneal cytokine response and was associated with early postoperative recovery after colectomy [13].

The analgesic effect of dexamethasone has been reported in many studies for incision pain and sore throat [14]. This study confirmed the analgesic effect of a perioperative single dose of dexamethasone after thyroid surgery in which a sore throat might be one major source of pain for some patients. Due to its analgesic effect and reduced amount of drainage fluid, a single small dose of dexamethasone in our study was related to early recovery from thyroid surgery.

Postoperative infection rate in thyroid surgery is rare at 0.3–1% [15]. The infection rates in the study were at the high end, 0.97% in the D group and 0.90% in the S group. Tracing back their total drainage volume (75 ml in group D and 95 ml in group S), both of them were discharged on POD4. Their CRP levels and leukocyte counts on POD1 and 2 were not outliers. Due to their delayed onset, the

reasons for the infections were complex and unclear, and unlikely related to the use of dexamethasone. Another study found that drainage tubes were an independent risk factor for surgical site infection after thyroid surgery [16].

There were some limitations in this study. First, the study focused on drainage volume and CRP levels and leukocyte counts inside drainage after surgery. Both blood CRP and leukocytes are commonly used inflammatory markers. The association between inflammatory markers in drain fluid and in blood is worth further study. Second, the levels of inflammatory content in drainage fluid were secondary outcomes. The sample size was not calculated by the related changes. A type II error may exist. Third, the types of drainage, serous or purulent, signs of wound infection, were not recorded. Finally, lengthy surgeries were excluded in this study. Operation duration is a factor associated with postoperative recovery and wound infection.

In conclusion, a perioperative small dose of dexamethasone could enhance recovery after thyroid surgery by reducing wound drainage volume and inflammatory content, in addition to reducing postoperative pain.

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Authors contribution Study conception was given by QZ. Study design was done by all authors. Participant recruitment was done by BW, QW, JL, CX. Data collection was done by HZ, QZ. Data analysis was given by HZ, YF. The first draft and the final paper were written by QZ, HZ.

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Compliance with ethical standards

Conflict of interest There is no conflict of interest in the manuscript.

Human and animal rights Statement of human rights was approved by Shanghai Jiaotong University affiliated Shanghai Sixth People's Hospital ethics committee.

Informed consent Informed consent was obtained from all individual participants included in the study.

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