Dexamethasone for the Prevention of Recurrent Laryngeal Nerve Palsy and Other Complications After Thyroid Surgery

A Randomized Double-Blind Placebo-Controlled Trial

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Importance: Recurrent laryngeal nerve dysfunction and hypoparathyroidism are well-recognized, important complications of thyroid surgery. The duration of convalescence after noncomplicated thyroid operation may depend on several factors, of which pain and fatigue are the most important. Nausea and vomiting occur mainly on the day of operation. Glucocorticoids are well known for their analgesic, anti-inflammatory, immune-modulating and antiemetic effects. However, there is little information in the literature on the use of steroids in thyroid surgery, and the information that is available is conflicting.

Objective: To investigate whether preoperative dexamethasone could improve surgical outcome in patients undergoing thyroid surgery.

Design: A randomized double-blind placebo-controlled trial. A 30-day follow-up for morbidity was performed in all cases.

Setting: All patients were hospitalized in a public hospital.

Participants: From June 2008 through August 2011, 328 patients were randomized to receive either intravenous dexamethasone, 8 mg, administered 90 minutes before skin incision, or saline solution (placebo).

Interventions: Intravenous dexamethasone, 8 mg.

Main Outcomes and Measures: The primary end points were temporary or permanent recurrent laryngeal nerve palsy. Transient and definitive hypoparathyroidism, pain and fatigue scores, nausea, and the number of vomiting episodes were also registered. Preoperatively and at several times during the first 24 postoperative hours, we measured C-reactive protein, interleukin 6, and interleukin 1β levels.

Results: In the dexamethasone group, the rate of temporary recurrent laryngeal nerve palsy (4.9%) was significantly lower compared with the placebo group (8.4%) (P = .04). Also, postoperative transient biochemical hypoparathyroidism occurred more frequently in the placebo group (37.0%) than in the dexamethasone group (12.8%). Dexamethasone use significantly reduced postoperative levels of C-reactive protein (P = .01) and interleukin 6 and interleukin 1β (P = .02), fatigue (P = .01), and overall pain during the first 24 postoperative hours (P = .04), as well as the total analgesic (ketorolac tromethamine) requirement (P = .04). Dexamethasone use also reduced nausea and vomiting on the day of operation (P = .045).

Conclusions and Relevance: Preoperative administration of dexamethasone, 8 mg, reduced postoperative temporary recurrent laryngeal nerve palsy and hypoparathyroidism rates and reduced pain, fatigue, nausea, and vomiting after thyroid surgery. However, these data require further analysis in randomized prospective studies.

Trial Registration: clinicaltrials.gov Identifier: NCT01690806

tients. Complications especially related to the RLN and parathyroid glands can be prevented with the appropriate surgical technique during total thyroidectomy.

The surgical technique is one of the important factors affecting the outcome of thyroidectomy. In the past, most surgeons avoided dissections in close proximity to the RLN to prevent its injury. Recently, endocrine surgeons consider this unacceptable. The identification and preservation of the RLN are essential to avoid its injury. Meticulous hemostasis and delicate technique are required to prevent nerve injury. Once found, the nerve, with all the identified branches, must be followed superiority through the entire course until it enters the larynx. This surgical technique, which requires more dissections, may harm the RLN and parathyroid glands. In fact, recurrent laryngeal nerve palsy (RLNP) may result from direct mechanical damage without disruption. This disparity between anatomic neural integrity and actual RLN function probably results from trauma to the intact nerve. Nerve manipulation during thyroid surgery may cause neural edema and consequent dysfunction, resulting in anything from neurapraxia to axonotmesis.

The duration of convalescence after noncomplicated thyroid operation may depend on several factors, of which pain, fatigue, and sociocultural factors are the most important. Pain and fatigue are most intense on the day of operation and the following day. Nausea and vomiting occur mainly on the day of operation and only rarely contribute to prolonged convalescence.

Glucocorticoids are well known for their analgesic, anti-inflammatory, immune-modulating, and antiemetic effects, although the mechanism by which glucocorticoids exert their action is yet to be clarified. There are both experimental and clinical data supporting the notion that the steroid administration may prevent or reduce neural edema. Patients with idiopathic facial palsy have shown improved facial nerve function after an empirical course of corticosteroids. Several randomized clinical trials in many different major and minor surgical procedures have been conducted to examine the effects of a perioperative single-dose glucocorticoid administration on surgical outcome. The overall results on postoperative outcome have either been positive and in favor of glucocorticoid use, with postoperative nausea and vomiting and pain outcome parameters most significantly improved, or shown no difference between study groups.

Regarding the use of steroids in thyroid surgery, there is little information in the literature, and the information that is available is conflicting. In their book, Lorè et al have mentioned the benefit of intraoperative steroids in thyroid surgery. Wang et al reported a study that found no statistically significant benefit.

We undertook the present study to investigate whether preoperative use of dexamethasone could improve surgical outcome in patients undergoing either total thyroidectomy or total lobectomy with routine identification of RLN. Our primary end points were to evaluate the role of dexamethasone in preventing or treating postoperative RLNP and in preventing hypoparathyroidism. We also investigated the effects of dexamethasone on pain, fatigue, nausea, vomiting, and the duration of convalescence.

From June 2008 through August 2011, 336 patients were randomized. Exclusion criteria were American Society of Anesthesiologists (ASA) physical class III or IV, age older than 75 years, and pregnancy. Patients were not included if they had chronic pain due to a disease other than thyroid disease; if they had any signs of renal, hepatic, and immunological disease; if they received opioids or tranquilizers (>1 week of treatment before thyroidectomy); if they spoke only a foreign language or had mental disorders; or if they had a history of alcohol or drug abuse. Finally, because the development of surgical complications might influence the chosen outcome parameters, we decided before the start of the study to exclude these patients, and the results were analyzed according to the protocol. The study protocol was approved by the ethical committee of the Faculty of Medicine of the University of L’Aquila, and all patients gave their written informed consent to participate in the study.

Patients were followed from the day before the operation and daily during the first postoperative week. The day of operation was defined as day 0 and the first day after operation as day 1, the second day after as day 2, and so on. A 30-day follow-up for morbidity was performed in all cases. The present study included several contacts between patients and study observers during the first postoperative 24-hour period.

Total thyroidectomy or lobectomy was performed by a technique of capsular dissection. The delicate technique was performed by seeking, identifying, and exposing the RLN with all its branches and following their course with care until it entered the larynx. When dissection proceeded to the ligament of Berry area, RLN was identified where it crossed through the ligament or close to it. Where a large thyroid mass or substernal goiter was encountered, RLN was identified and traced from the recurrent nerve triangle, as advocated by Lorè. However, special care was not given to identify superior laryngeal nerves. All the parathyroid glands were identified, if possible.

All patients were operated on by 2 surgeons (M.S. and G.A.). All patients received preoperative and postoperative flexible laryngoscopic examinations of the vocal cords. If vocal cord palsy was identified, initial follow-up examinations were performed weekly and then every 3 to 4 weeks thereafter until recovery; the dysfunction was considered permanent if it persisted after 6 months. Patients were excluded from the study if they had preoperative RLNP or nerves encased by cancer, in which case the nerves were intentionally removed. Postoperatively total serum calcium concentrations were obtained at 24, 48, and 72 hours (also at 96 and 120 hours in patients with hypocalcemia). Hypocalcemia was defined as at least 1 serum calcium measurement below 8.1 mg/dL (reference range, 8.1-10.4 mg/dL) (to convert to millimoles per liter, multiply by 0.25). Oral calcium supplementation with or without vitamin D analogue was given if patients developed symptomatic hypocalcemia or when the serum calcium level was less than 8.1 mg/dL. An intravenous calcium gluconate, 10%, infusion was administered for significant hypocalcemic symptoms or when oral therapy proved inefficacious. Patients were discharged when the serum calcium level was higher than 8.1 mg/dL. Hypocalcemia was considered permanent if it persisted after 6 months.

All patients received general anesthesia similarly. Preanesthesia was accomplished with atropine sulfate, 0.01 mg/kg, plus promethazine hydrochloride, 0.5 mg/kg; induction with sodium thiopental, 5 mg/kg, and atracurium besylate, 0.5 mg/kg; and tracheal intubation and assisted ventilation with nitrogen dioxide and oxygen in a 2:1 ratio. After intubation, ventilation was accomplished with atropine sulfate, 0.01 mg/kg, plus remifentanil hydrochloride, 0.25 μg/kg/min.

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Amoxicillin-clavulanic acid, 2200 mg, was given at the beginning of surgery. In the postoperative anesthesia care unit (PACU), vital signs (blood pressure, pulse, respiration, pulse oximetry, and adequate answering) were monitored every 15 minutes by a consultant. Patients were discharged from the PACU when vital signs were normalized. We used a prophylactic multimodal analgesic technique for treatment of postoperative pain. Thus, patients received incisional local aesthetics using 13 mL (75 mg) of bupivacaine hydrochloride, 0.3%. Intravenous ketorolac tromethamine, 30 mg, was administered every 6 hours on the first day after operation, and afterwards, on demand. Intravenous ondansetron hydrochloride, 4 mg, was administered for antiemetic treatment on demand. Pain was registered preoperatively, several times during the first 24 postoperative hours, and daily during the first postoperative week. Pain was measured on a visual analog scale (VAS) with end points labeled “no pain,” and “worst possible pain,” and on a verbal rating scale (VRS) (0= no pain; 1= light pain; 2= moderate pain; and 3= severe pain). Moreover, the pain was recorded at rest (supine position) and during mobilization (supine to sitting position) preoperatively and 1, 2, 3, 6, and 24 hours after operation (ie, investigator-recorded instant pain scores). In addition, the patients themselves registered the pain (VAS and VRS) (self-reported registration). Self-reported registrations were completed the day before operation (at 8 PM), on the day of operation (at 6 hours preoperatively and then at 6 hours postoperatively), both the investigator-recorded instant pain score and the patients’ self-registered pain score were recorded, and daily until postoperative day 7 at 8 PM. At the same intervals, patients also noted fatigue on a 10-point ordinal scale (1 = fit; 10 = fatigued).25 Patients were instructed that self-reported registrations should cover pain and fatigue within the period since the last measurements.

Patients evaluated nausea and vomiting over 2 postoperative intervals: 0 through 6 hours and 6 through 24 hours after operation.26 Nausea was rated on a VRS (0 = no nausea; 1 = mild nausea; 2 = moderate nausea; and 3 = severe nausea), and the number of vomiting episodes were registered (0 = no episodes [none]; 1 = 1 episode [mild]; 2 = 2 or 3 episodes [moderate]; 3 = >3 episodes [severe]).

Serial venous blood samples were taken at 0, 30, 60, 90, 120, and 180 minutes, at 12 and 24 hours, and then daily until postoperative day 6. The plasma concentration of C-reactive protein (CRP) was measured using a competitive CRP enzyme-linked immunosorbent assay (ELISA) kit. Serum concentration of interleukin 1 (IL-1β) and interleukin 6 (IL-6) were measured using a quantitative “sandwich” ELISA kit (R&D System) according to the manufacturer’s description (ranges: IL-1β, 3-9-250 pg/mL; and IL-6, 3.13-300 pg/mL). Serum samples (100 μL) were dispensed into the wells of 96-well microtiter plates, which had been coated with the relevant monoclonal cytokine antibody. After incubation for 2 hours at room temperature, unbound proteins were washed away from the wells, to which subsequently an enzyme-linked antibody was added and directed against the relevant cytokine for another 2 hours at room temperature. After further rinsing to remove unbound antibody, a substrate solution was added to each well, and the mixture was incubated for 20 minutes at 37°C. The reaction was terminated with the addition of a stop solution. Adsorption was determined by using an ELISA plate reader at 450 nm. Serial dilution of the relevant recombinant cytokine provided the standard curve. Assays were performed on duplicate samples. Samples were diluted appropriately with the diluent provided in the kit if the levels of neat samples were beyond the linear measuring range.

Patients were randomized by means of a sealed envelope method (on the basis of a block-randomized computer-generated list), and the randomization code was kept unknown to any of the investigators until the study was complete. Patients were randomized to receive intravenous dexamethasone, 8 mg (Decadron; Merck Sharp & Dohme), 90-minutes before skin incision, or saline placebo. The drug or placebo solution was drawn into a syringe by a nurse not participating in the study and was delivered to the investigator (M.S.) who was outside the medicine room and unaware of the content. The saline and dexamethasone solutions appeared transparent and completely identical at the time the syringes were given to the investigator. Thus, the patients, the anesthesiologist, the surgeon, and the study observer were all blinded with respect to the study group. The study drug was administered to the patient within 5 minutes after being drawn into the syringes.

For statistical analyses, we used the Mann-Whitney, Friedman, Fisher exact, χ², Spearman rank correlation coefficient and log-rank tests when appropriate. Postoperative 24-hour results were specifically analyzed for intergroup differences. In addition, postoperative fatigue and pain scores from repeated assessments at different time points were added together for intergroup comparison (added total pain scores and added total fatigue scores).

Nausea and vomiting scores were evaluated separately for the through 6-hour period and the 6- through 24-hour period. From each period, the highest severity score and the highest incidence of nausea and vomiting were used as a measure of nausea and/or vomiting for the entire 24-hour period. P < .05 was considered statistically significant. Data are given as median (range) if not stated otherwise.

### RESULTS

A total of 328 patients were available for analysis (Table 1); 8 patients (4 in each treatment group) were excluded from the study. There were 163 patients in the dexamethasone group and 165 in the placebo group (Table 1).

The overall risk of temporary RLNP was 6.7% (22 of 328) and permanent RLNP was 1.2% (4 of 328) (Table 2). The risk of temporary and permanent RLNP in the dexamethasone group was 4.9% (8 of 163) and 1.2% (2 of 163), respectively. The risk of temporary and permanent RLNP in the placebo group was 8.4% (14 of 165) and 1.2% (2 of 165), respectively (Table 2). In the dexamethasone group, the rate of temporary RLNP was significantly lower compared with the placebo group (Table 2) (P = .04, Mann-Whitney test), whereas the difference did not reach statistical significance between the 2 groups for permanent RLNP (P = .20). Among the 22 patients who had temporary RLNP, the recovery times ranged from 7 to 41 days (mean, 24.2 days) and from 18 to 72 days (mean, 48.6 days) for patients with or without preoperative dexamethasone, respectively (P = .048 Mann-Whitney test). Postoperative transient biochemical hypoparathyroidism occurred more frequently in the placebo group than in the dexamethasone group (Table 2). In the dexamethasone group and placebo group, 21 (12.8%) and 61 (37%) patients, respectively, required oral calcium carbonate supplementation postoperatively, although these patients showed no clinical symptoms of hypocalcemia. This difference was statistically significant (P = .045) (Table 2). The lowest serum calcium level was 7.2 mg/dL in the placebo group vs 7.6 mg/dL in the dexamethasone group. Also, postoperative definitive hy-
Fatigue increased significantly in both groups (P < .01, Friedman test) (Figure 1A). In the dexamethasone group, fatigue scores were significantly lower 24 hours after operation (P < .01, Mann-Whitney test) and throughout the postoperative week compared with the placebo group (P = .01, Friedman test). The added median total postoperative fatigue scores were 28 (range, 10-62) in the dexamethasone group and 39 (range, 16-64) in the placebo group (P = .01, Mann-Whitney test).

In the dexamethasone group, self-reported VAS scores for pain were significantly lower on day 1 after operation compared with the placebo group (Figure 1B) (P = .04, Mann-Whitney test). The added median total VAS scores of pain (covering the first postoperative week) were 52 (range, 0-251) in the dexamethasone group and 148 (range, 13-406) in the placebo group (P < .05, Mann-Whitney test). In both treatment groups, self-reported scores of pain increased during the first postoperative week (P < .01, Friedman test), but differences between groups did not change significantly during the test period (P = .12, Friedman test).

Nine patients in the dexamethasone group and 21 in the placebo group required supplementary doses of ketorolac during their hospital stay (P = .10, Fisher exact test), with a significantly lower total dose in the dexamethasone group (P = .04, Mann-Whitney test) (Table 1). Spearman correlation coefficients for the association between the total dose of postoperative supplementary analgesic during hospital stay and pain (first 24-hour period) were 0.53 (P = .01) and 0.58 (P = .01) for the dexamethasone and placebo groups, respectively. After hospital discharge, 2 patients in the dexamethasone group and 9 in the placebo group required supplementary analgesic (in total, analgesics were taken 18 times by 11 different patients [P = .08, Fisher exact test]).

During the first 6 postoperative hours, the incidence and severity of nausea was significantly lower (P = .045, χ² test and Mann-Whitney test) in the dexamethasone group, and vomiting was significantly reduced during the entire 0 through 24-hour period compared with placebo (P = .045, χ² test and Mann-Whitney test). Eight patients in the dexamethasone group vs 21 in the placebo group received intravenous ondansetron for antiemetic treatment once or multiple times during their hospital stay (P = .11, Fisher exact test) (Table 1).

Serum CRP level increased significantly in both treatment groups during the study period (P = .01, Friedman test), but the increase was significantly higher in the placebo group (P = .01, Friedman test) (Figure 1C).

Before the operation, serum IL-1β and IL-6 levels were not significantly different between the 2 groups. Figure 2 shows the chronological changes in serum IL-1β and IL-6 levels after surgery. In the placebo group, the serum IL-1β and IL-6 levels began to significantly increase as early as 1 hour from the beginning of operation, revealing a peak at the sixth hour (approximately 4 hours after operation) and, thereafter, declining to preoperative levels by 6 days. However, in the dexamethasone group, the increase in the serum IL-1β and IL-6 levels was delayed and the peak values were significantly lower in the placebo group (P < .05, Friedman test).

No apparent signs of adverse effects of the study drugs were observed. Four patients in each group were excluded from the study. In the dexamethasone group, 2 patients had preoperative RLNP and 2 patients developed a wound infection. In the placebo group, 2 patients had the RLN encased by cancer and 2 patients developed a wound infection. Thus, 4 patients (2 from each study group) developed postoperative wound infections.

### DISCUSSION

The identification, careful exposure, and preservation of the RLN throughout its course are important to prevent nerve injury.11 The approach for the identification of the RLN during surgery on the thyroid gland was described in some previous studies.11,27,28 Although Bergamaschi et al29 reported that the RLN identification failed to reduce injury rate, there are many studies demonstrating a significant decrease in the rate of RLN injury maintained by the identification of the nerve.5,7,27,30 Wagner and Seiler31 reported that in total thyroidectomy the permanent injury rate significantly increased from 3.8% to 7% when...
the nerve was not identified. Mättig et al27 demonstrated that routine preparation of the RLN decreased the permanent injury rate from 5.99% to 0.88%.

Empirically, some surgeons use steroids during thyroid operations in an attempt to reduce postoperative neural edema resulting from inevitable nerve manipulation during identification of RLN, as well as to promote recovery of nerve function when nerve paralysis occurs. However, there have only been few published data concerning the efficacy of preoperative or intraoperative steroid use in the management or prevention of nerve dysfunction resulting from operation. Wang et al23 used a single intravenous dose of intraoperative corticosteroids (100-mg hydrocortisone) and concluded that intraoperative steroids did not produce benefit in terms of reducing postoperative temporary and permanent RLNP rates, but it did shorten the recovery time for patients with temporary RLNP. This study was prospective but not randomized. On the contrary, Loré et al22 said that the rate of temporary RLNP can be reduced from 9% to 2.6% with the use of preoperative or/intraoperative steroids. In addition, the use of steroids reduces the longest duration of temporary vocal cord paralysis from 9 to 2 months.

<table>
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<th>Variable</th>
<th>Dexamethasone Group (n = 163)</th>
<th>Placebo Group (n = 165)</th>
<th>Total (n = 328)</th>
<th>P Value</th>
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<td>4 (2.4)</td>
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Figure 1. Changes in fatigue and overall pain scores and serum C-reactive protein (CRP) levels. A, Changes in fatigue scores (10-point ordinal scale: 1 = fit, 4 = slightly tired, 7 = tired, and 10 = fatigued) in patients receiving placebo or dexamethasone. Patients who received dexamethasone were significantly less fatigued on postoperative day 1 (*P < .01). B, Changes in overall pain scores (visual analog scale) in patients receiving placebo or dexamethasone. Patients who received dexamethasone experienced significantly less overall pain on postoperative day 1 (*P < .05). C, Changes in serum CRP levels in patients receiving placebo or dexamethasone. The increase in CRP level was significantly higher in the placebo group (*P < .01). Preop indicates preoperation. For CRP, to convert milligrams per deciliter to nanomoles per liter, multiply by 95.24.
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We routinely identify RLN in every case when performing thyroidectomy. There will be RLN dysfunction after thyroid surgery relating to axonal discontinuity, functional impairment of the intact nerve, or a combination of these factors resulting from nerve manipulation. In the present study, the integrity of all RLNs was ensured after operation. However, there were still 4 patients (2 in the placebo group and 2 in the dexamethasone group) who had permanent RLNP in our study. This study showed that a single dose of preoperative steroids (dexamethasone) was effective in preventing temporary RLNP during thyroid operation. The risk of temporary RLNP in the dexamethasone and placebo groups was 4.9% and 8.4%, respectively (P = .04, Mann-Whitney test). Moreover, the number of days to recovery for patients using preoperative steroids was significantly lower (24.2 vs 48.6 days, P = .048 Mann-Whitney test). Also, postoperative transient biochemical hypoparathyroidism occurred less frequently in the dexamethasone group (12.8%) than in the placebo group (37.0%). This difference was statistically significant (P = .045).

The reason may have been that dexamethasone decreases the chance of traumatic edema or vasospasm, which might have led to neurapraxia (edema) and/or temporary hypoparathyroidism (vasospasm). In fact, glucocorticoids are important modifiers of the postoperative physiologic inflammatory, humoral, and immunologic responses by regulation of the trauma-induced humoral mediators. The usual physiological reaction to injury, surgical or nonsurgical, is an early rise in serum stress hormone levels, together with a decrease in cellular immune response. The overall immune response to surgery in general is reflected mainly in terms of alteration in cytokine functions and the cellular messenger system. The acute phase response and cytokines are important and necessary components of immunological function. Although cytokine levels do not indicate immune status directly, they are a good guide in the assessment of the activation of the systemic immune system. However the overproduction of cytokines, or their production at noninflammatory sites, may lead to deleterious effects on tissues, so a decreased production of cytokines (reduced inflammatory reaction) might be considered beneficial during the postoperative period.

The cytokines IL-1 and IL-6 play a major role in the acute phase response. The expression of IL-6 is believed to be directly proportional to the extent of surgical trauma. C-reactive protein is also a dependable marker of acute phase response. C-reactive protein levels usually rise approximately 4 to 12 hours after operation and peak at 24 to 72 hours, thereafter remaining raised for approximately 2 weeks.

In the present study, significant increases in IL-1β, IL-6, and CRP levels were observed in both treatment groups, but these levels (and fatigue scores) increased significantly less in the dexamethasone group compared with placebo. Thus, our findings suggest that intravenous dexamethasone administered 90 minutes preoperatively reduced the postoperative inflammatory response after thyroid surgery in accordance with observations from other procedures. Our findings of reduced levels of CRP, IL-1β, and IL-6 and fatigue scores in the dexamethasone group support that early fatigue may be associated with the short-lasting inflammatory response after thyroid surgery. These results are supported by the finding of increased fatigue and reduced sleep after IL-6 infusion in human volunteers. Only trials including patients undergoing major abdominal surgery have studied the effect of preoperative glucocorticoids (high-dose methylprednisolone) on fatigue. There was no significant difference in fatigue scores, but postoperative mobilization was significantly improved in the glucocorticoid groups.

Nonetheless, the simple, inexpensive, and apparently innocuous dose of preoperative steroid delivered more benefit to patients than those not receiving preoperative steroid. What is not clear is why it did. To understand this, one can begin by considering the clinical efficacy of single-dose steroid therapy in elective major and minor surgery. There are several published trials available; however, variability in study populations, surgical procedures, protocols for steroid dosing, and end points of clinical outcome preclude any consensus. Holte and

**Figure 2.** Interleukin levels in patients receiving placebo or dexamethasone. A. Interleukin-1β (IL-1β) levels in patients receiving placebo or dexamethasone. P < .05 for all values compared with baseline (Mann-Whitney test). For the dexamethasone group at 6 hours, *P < .05 compared with placebo group (Mann-Whitney test). B. Interleukin-6 (IL-6) levels in patients receiving placebo or dexamethasone. *P < .05 for all values compared with baseline (Mann-Whitney test). For the dexamethasone group at 6 hours, *P < .05 compared with placebo group (Mann-Whitney test).
Kehlet provide a comprehensive review of these trials and endorse the use of a single-dose preoperative steroid. As an immune modulation strategy, such therapy appears to shift the balance of inflammation in favor of anti-inflammatory mediators in a variety of surgical procedures. Some aspects of cardiac and pulmonary function have been shown to improve, but usually in small studies with insufficient statistical power to detect reliable clinical differences. Trials aimed at evaluating adverse effects of preoperative single-dose steroids have also been inconclusive because of size and design. When considered together, however, it appears that this therapy (dexamethasone, 8 mg) is safe; it particularly does not increase complications one might expect, such as infections and impaired wound healing. A recent meta-analysis concluded that perioperative administration of high-dose methylprednisolone (30-35 mg/kg), a dose approximately 50 times the dose used in our study, was not associated with significant adverse effects. In our study, we found no apparent adverse effects or complications caused by dexamethasone treatment because only 2 patients in each surgical group developed a postoperative wound infection. It also appears that the timing of steroid administration is important (1-2 hours preoperatively) if excess inflammatory activations and related postoperative morbidity are to be attenuated.

The analgesic effect of glucocorticoids is provided by inhibiting phospholipase enzymes and, accordingly, blocking both the cyclooxygenase and the lipoxygenase pathway in the inflammatory chain reaction, as well as suppressing tissue levels of bradykinin and releasing neuropeptides from nerve endings, both of which may enhance nociception in inflamed tissue and the surgical wound. In the present study, dexamethasone reduced pain. Our results are in accordance with the analgesic effect of dexamethasone, 8 mg, in patients undergoing gynecologic operation and dental extractions. In a recent review, the effects of perioperative single-dose glucocorticoid administration, randomized trials from several minor and major surgical procedures were analyzed. The authors concluded that glucocorticoid administration in major abdominal surgery probably has no or limited analgesic effect, but may have an analgesic effect in minor surgical procedures, and that glucocorticoid administration definitely has an analgesic effect in dental surgery.

The incidence and severity of postoperative nausea and vomiting have been significantly decreased by preoperative dexamethasone (administered 90 minutes before skin incision) was effective in preventing temporary RLNP during thyroid operation and in reducing the duration of temporary RLNP. This is especially important for the patients with locally advanced cancer, patients with Graves disease, and patients undergoing re-operation in which the incidence of RLNP may be triple or more. Also postoperative transient biochemical hypoparathyroidism occurred less frequently with preoperative single-dose dexamethasone.

Moreover, dexamethasone improved surgical outcome after thyroid surgery in terms of significantly less pain, fatigue, nausea, and vomiting, and patients resumed their recreational activity significantly faster compared with the placebo group. This simple therapy, in the absence of increased morbidity from the single dose of steroids, warrants broader application in thyroid surgery.

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Author Contributions: Dr Schietroma had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Carlei. Acquisition of data: Cecilia, Sista, De Santis, and Lancione. Analysis and interpretation of data: Schietroma and Amicucci. Drafting of the manuscript: Cecilia, Sista, De Santis, and Lancione. Critical revision of the manuscript for important intellectual content: Schietroma, Carlei, and Amicucci. Statistical analysis: De Santis and Lancione. Administrative, technical, and material support: Schietroma, Cecilia, Carlei, Sista, and Amicucci.

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