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 uncomplicated 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


TOTAL THYROIDECTOMY OR thyroid lobectomy has been accepted as the current surgical therapy for benign and malignant thyroid disorders, but extensive resection might increase the risk of postoperative complications. Recurrent laryngeal nerve (RLN) dysfunction and hypoparathyroidism are well-recognized, important complications of thyroid surgery. Complication rates of thyroidectomy have a varying range for both RLN injury (0% to 1%) and permanent hypoparathyroidism (1% to 11%). Paralysis of vocal cords may cause serious phonyatory, respiratory, and psychological problems that limit working capacities and quality of life of the pa-
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 superiorty 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, Loré 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.

Methods

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 the 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 branches and following its course with care until it entered the larynx. When dissection proceeded to the ligament of Berry area, RLN was identified where it coursed 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 Loré. 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, anesthesia was maintained with oxygen in air, sevoflurane, and remifentanil hydrochloride, 0.25 μg/kg/min.
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 anesthetics 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. 

Nausea and vomiting scores were evaluated separately for the six- through 24-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. 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-
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The identification, careful exposure, and preservation of the RLN throughout its course are important to prevent nerve injury. The approach for the identification of the RLN during surgery on the thyroid gland was described in some previous studies. Although Bergamaschi et al 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. Wagner and Seiler reported that in total thyroidectomy the permanent injury rate significantly increased from 3.8% to 7% when...
the nerve was not identified. Mättig et al\textsuperscript{27} 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 al\textsuperscript{23} 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 al\textsuperscript{22} 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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<tr>
<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 (1.2)</td>
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<td>Hypoparathyroidism</td>
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<tr>
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<td>61 (37.0)</td>
<td>82 (25.0)</td>
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<tr>
<td>Permanent</td>
<td>3 (1.8)</td>
<td>4 (2.4)</td>
<td>7 (2.1)</td>
<td>.97</td>
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</table>

Table 2. Recurrent Laryngeal Nerve Palsy and Hypoparathyroidism

![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 (\textasteriskcentered \textsuperscript{\(P < .01\)). 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 (\textasteriskcentered \textsuperscript{\(P < .05\)). C, Changes in serum CRP levels in patients receiving placebo or dexamethasone. The increase in CRP level was significantly higher in the placebo group (\textasteriskcentered \textsuperscript{\(P = .01\)). Preop indicates preoperation. For CRP, to convert milligrams per deciliter to nanomoles per liter, multiply by 95.24.](https://archotol.jamanetwork.com/article.aspx?articleid=1532588)
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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 is a great need for a more accurate method for evaluating the impact of steroid therapy. However, variability in study populations, surgical procedures, protocols for steroid dosing, and end points of clinical outcome preclude any consensus.

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). 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 glucocorticoid 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 single-dose steroid administration in several studies. This can be explained by a central antinociceptive mechanism involving endogenous prostaglandin and opioid production. In a recent meta-analysis of 17 randomized clinical trials, a single dose of dexamethasone in combination with 5-HT3 receptor antagonists significantly reduced postoperative nausea and vomiting compared with placebo, but the optimal dose of this combination needs to be identified. Furthermore, the role of concomitant use of 5-HT3 receptor antagonist remains to be clarified. In the present study, intravenous dexamethasone was administered 90 minutes before skin incision. Glucocorticoids bind to the intracellular glucocorticoid receptor, and effects are predominantly mediated through an altered pro-

tein synthesis via gene transcription. Therefore, the onset of biological action is generally 1 to 2 hours, depending on the route of administration. Unfortunately, most studies have administered glucocorticoids immediately before induction of anesthesia, including the other trials in patients undergoing laparoscopic cholecystectomy. Because activations of the early mediators of the metabolic response to surgery occur immediately after the surgical incision, administration of glucocorticoids 1 to 2 hours preoperatively may be important to achieve the full postoperative benefit of the treatment.

In conclusion, we demonstrated that a single dose of 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 reoperation 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: Schietroma, 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.

Conflict of Interest Disclosures: None reported.

REFERENCES


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