

Use of Prophylactic Steroids to Prevent Hypocalcemia and Voice Dysfunction in Patients Undergoing Thyroidectomy

A Randomized Clinical Trial

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IMPORTANCE Total thyroidectomy is associated with risks related to temporary hypocalcemia and vocal quality dysfunction. Dexamethasone has been proposed to have a physiological effect on hypocalcemia and voice quality.

OBJECTIVE To assess the effect of preoperative dexamethasone used to improve hypocalcemia and postthyroidectomy voice dysfunction.

DESIGN, SETTING, AND PARTICIPANTS This double-blind, parallel-group, placebo-controlled randomized clinical trial was conducted from January 15, 2014, to December 31, 2019, at the Department of Surgery, Holy Family Hospital in Rawalpindi, Pakistan. All patients with a benign thyroid condition and no preoperative corrected hypocalcemia and voice or vocal quality dysfunction were included. Patients were excluded if they had previous thyroid or neck surgery, known vocal cord dysfunction on laryngoscopy, hearing or voice problems, a history of gastroesophageal reflux, stomach ulcer disease, or contraindications to steroid use.

INTERVENTIONS Corrected serum calcium levels and Voice Analog Score defined and measured preoperatively. The dexamethasone group received a 2-mL intravenous dose of 8 mg of dexamethasone 60 minutes before the induction of anesthesia. In contrast, the placebo group received 2 mL of intravenous normal saline (0.9%) 60 minutes before the induction of anesthesia.

MAIN OUTCOMES AND MEASURES Evidence of hypocalcemia and voice dysfunction. Voice dysfunction was defined as a subjective score of less than 50 on a Voice Analog Score scale of 0 to 100 points.

RESULTS A total of 192 patients (mean [SD] age, 38.9 [12.4] years; 156 women [81.2%]) were included in the study, with 96 patients randomized to each study group (dexamethasone group, mean [SD] age, 39.2 [12.1] years; 75 women [78.1%]; placebo group, mean [SD] age, 38.5 [12.9] years; 81 women [84.5%]). In the first 24 hours after undergoing thyroidectomy, 47 patients (24.4%) developed hypocalcemia and 18 (9.4%) were symptomatic. At 3 days postthyroidectomy, 4 of 96 patients (4.2%) in the placebo group had hypocalcemia compared with no patients in the dexamethasone group. At 24 hours postthyroidectomy, 8 of 96 patients (8.3%) in the dexamethasone group had voice dysfunction compared with 32 of 96 patients (33.3%) in the placebo group. A total of 40 patients (20.8%) reported voice dysfunction. The absolute reduction in the rate of hypocalcemia at 24 hours was 24% (95% CI, 11.9%-35.2%) and at 3 days was 4.2% (-0.44% to 10.0%). The rate of symptomatic hypocalcemia was 19% lower in the dexamethasone group than in the placebo group (95% CI, 11.1%-27.7%). The rate of voice dysfunction was 25% lower in the dexamethasone group than in the placebo group (95% CI, 13.7%-35.7%).

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, a single preoperative dose of dexamethasone was safe and effective in reducing postoperative hypocalcemia and voice dysfunction rates in patients undergoing thyroidectomy.

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Symptomatic benign thyroid diseases are common, and multinodular goiter with concomitant iodine deficiency is the most frequent presentation requiring surgical intervention worldwide. Surgery provides definitive treatment and is the treatment of choice. All surgical options, most commonly total or near-total thyroidectomy, are used to rule out malignancy in a benign-appearing thyroid. However, surgery has some inherent risks, including recurrent hypocalcemia, voice dysfunction, and recurrent laryngeal nerve injury.¹⁻⁴

Voice dysfunction and hypocalcemia are the most common complications after thyroidectomy.⁵⁻⁷ Voice dysfunction, such as hoarseness, has been reported in approximately 80% of cases and is reversible in 58% to 100% of cases.⁸⁻¹⁰ It may result from direct or indirect injury to the recurrent laryngeal nerve leading to transient or permanent vocal cord paralysis. Indirect nerve injury is reported to be more common than direct nerve injury.⁵ Although not wholly acknowledged, it is postulated that after total thyroidectomy, the strap muscles exclusively bear the laryngotracheal unit and are the basis of voice dysfunction.^{6,7} Symptomatic hypocalcemia is the most frequent complication after total thyroidectomy and occurs in up to 50% of cases. Hypocalcemia results from loss of the parathyroid glands, and patients with this condition require supplements such as calcium or vitamin D₃ (cholecalciferol) to recover function.¹¹⁻¹³

Various methods have been evaluated to prevent these complications.^{14,15} The use of steroids (ie, dexamethasone) in the perioperative period has been shown to improve voice function postoperatively. Intraoperative neural monitors have also been used to prevent this complication. The evidence for the use of dexamethasone is supported by previous randomized clinical trials (RCTs); however, its use is not widespread in clinical practice.¹⁶ The use of dexamethasone in the perioperative phase is based on surgeon discretion. Similarly, the use of an intraoperative neural monitor varies in different centers where the surgery is conducted. Neural monitoring is used to detect the location of the recurrent laryngeal nerve intraoperatively so as to prevent direct and indirect damage from diathermy.¹⁷

Prevention of hypocalcemia after thyroidectomy involves various measures, such as the use of perioperative dexamethasone, routine administration of calcium with vitamin D₃, and use of parathyroid hormone extract. None of these interventions have been shown to have any benefit over the other. The usual practice involves measurement of serum calcium and parathyroid hormone levels within 24 hours after thyroidectomy and repeat measurement for the next 3 to 5 days if hypocalcemia is detected within the first 24 hours after surgery. The hypocalcemia is then corrected via oral replacement with calcium and vitamin D.^{4,14,15}

A few RCTs have shown benefit from the use of perioperative dexamethasone in the prevention of voice dysfunction, hypocalcemia, nausea, and vomiting. One study showed that a single intramuscular injection of dexamethasone preoperatively could significantly reduce the incidence of voice dysfunction and symptomatic hypocalcemia. This outcome is particularly important because patients who undergo thyroidectomy are often relatively young, and the development of voice dysfunction and having to take regular medication can

Key Points

Question What is the effect of preoperative dexamethasone on postoperative hypocalcemia and voice dysfunction after thyroidectomy?

Findings In this randomized clinical trial of 192 patients, those in the dexamethasone group had a lower rate of hypocalcemia, less symptomatic hypocalcemia, and less voice dysfunction in the first 24 hours after thyroidectomy than patients in the placebo group.

Meaning These findings suggest that single-dose preoperative dexamethasone is safe and effective in reducing postoperative hypocalcemia and voice dysfunction.

negatively affect their quality of life. Although a few clinical studies have shown the potential benefit of dexamethasone use perioperatively, their results have not changed current clinical practice in many centers.^{7,13,16}

Therefore, it is vital to gather more evidence to evaluate the use of preoperative dexamethasone in patients undergoing thyroidectomy. If newly conducted research demonstrates that the perioperative complications of voice dysfunction and hypocalcemia can be prevented with a single dexamethasone injection before thyroid surgery, the results may have a significant effect on patient care. We hypothesized that the use of a single preoperative injection of dexamethasone could reduce postoperative voice dysfunction and hypocalcemia. We conducted a double-blind controlled trial to assess the effect of preoperative dexamethasone on vocal dysfunction and hypocalcemia after thyroidectomy.

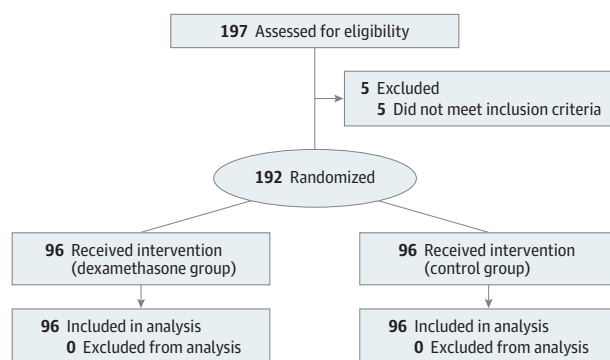
Methods

Setting

This RCT was conducted at the Department of Surgery, Holy Family Hospital in Rawalpindi, Pakistan, from January 15, 2014, to December 31, 2019. The Holy Family Hospital is a 1000-bed tertiary care hospital attached to Rawalpindi Medical University, with surgical services including endocrine surgeries. The Holy Family Ethical Committee approved the study protocol (registration No. 233/HFH12/14), and all patients provided written informed consent. This study has been reported in line with the Consolidated Standards of Reporting Trials Extension (CONSORT Extension) reporting guideline (Figure).¹⁸

We extended our study period over 5 years in an effort to obtain a large sample size. A total of 192 eligible patients were included in the study. The patients were aged between 18 and 60 years and met the following criteria for inclusion: they each had a diagnosis of a benign thyroid condition and no preoperative corrected hypocalcemia or vocal quality dysfunction. Exclusion criteria included patients with a history of Graves disease, previous thyroid or neck surgery, known vocal cord dysfunction on laryngoscopy, hearing or voice problems, gastroesophageal reflux, stomach ulcer disease, and any contraindication to corticosteroid use.

Figure. Study Flow Diagram



Intervention

We created 2 parallel groups and labeled them group A (dexamethasone group) and group B (placebo group). The following method of group assignment was used to distribute patients into the 2 groups: patients were randomly assigned numbers; those with odd numbers were assigned to group A, and those with even numbers were assigned to group B. In group A, 2 mL of 8 mg of dexamethasone was injected intravenously 60 minutes before the induction of anesthesia. In contrast, in group B, 2 mL of normal saline (0.9%) was given intravenously 60 minutes before the induction of anesthesia. Before surgery, investigators (R.A., D.B., and S.H.A.) assessed the serum calcium levels of each patient, and each patient's voice was assessed by Voice Analog Score.

A single surgeon in our study performed all thyroidectomies. In our surgical center, there were 3 dedicated surgeons who performed thyroidectomies. Standard of care was provided preoperatively and postoperatively for all patients. There was no use of recurrent laryngeal nerve monitoring during any of the procedures. The nerve was anatomically identified during the procedure in all cases. The completion of skin closure was considered to be time point 0. At 24 hours, signs and symptoms of hypocalcemia and voice dysfunction were assessed using serial corrected serum calcium levels and the Voice Analog Score (eAppendixes 1 and 2 in Supplement 2).

Outcomes

As described in the trial protocol (Supplement 1), the primary outcomes for this study were serum and symptomatic evidence of hypocalcemia and subjective voice score. Symptomatic hypocalcemia was assessed as a secondary outcome.

Low calcium level was defined as a corrected serum calcium level of less than 8 mg/dL (2 mmol/L).¹⁹ Patients with low corrected calcium levels (<8 mg/dL) were labeled as having hypocalcemia, and treatment was given according to symptoms. The same corrected calcium was again calculated at 72 hours after surgery.

Voice dysfunction was defined by Voice Analog Score on a scale of 0 to 100 points. Dysfunction was defined subjectively as a score of less than 50. Each patient was assessed 24 hours after surgery for voice dysfunction via Voice Analog Score, and those having a score of less than 50 were labeled as having voice dysfunction.²⁰

Table 1. Demographic Details

Variable	Group, No. (%)	
	Dexamethasone (A)	Placebo (B)
Men	21 (21.9)	15 (15.6)
Women	75 (78.1)	81 (84.4)
Age, mean (SD), y	39.2 (12.1)	38.5 (12.9)
Operative time, mean (SD), min	105.3 (12.6)	103.8 (11.1)

Statistical Analysis

No formal sample size or power calculation was performed. The Shapiro-Wilk test was conducted and confirmed a normal distribution of the study participants. The difference in the rates was calculated for the outcomes in categorical variables. The 95% CI around the effect size was used to describe the precision of the estimates and where the true value for the point estimate likely would be found. All calculations were performed using SPSS, version 23 (IBM Corp).

Results

A total of 192 patients (mean [SD] age, 38.9 [12.4] years; 156 women [81.2%] and 36 men [18.8%]) were included in the study, with 96 patients randomized to each study group (dexamethasone group, mean [SD] age, 39.2 [12.1] years; 75 women [78.1%] and 21 men [21.9%]; placebo group, mean [SD] age, 38.5 [12.9] years; 81 women [84.4%] and 15 men [15.6%]) (Table 1). The mean (SD) operative time was 104.6 (11.6) minutes. A total of 40 patients (20.8%) reported voice dysfunction. In the first 24 hours after surgery, 47 patients (24.5%) developed hypocalcemia and 18 (9.4%) were symptomatic. At 3 days after surgery, 4 of 96 patients (4.2%) in the placebo group had hypocalcemia compared with no patients in the dexamethasone group.

The comparison of outcomes is displayed in Table 2. At 24 hours after surgery, 8 of 96 patients (8.3%) in the dexamethasone group had voice dysfunction compared with 32 of 96 patients (33.3%) in the placebo group. The absolute reduction in the rate of hypocalcemia at 24 hours was 24% (95% CI, 11.9%-35.2%) and on postoperative day 3 was 4.2% (-0.44% to 10.0%). The rate of symptomatic hypocalcemia was 19% lower in the dexamethasone group than in the placebo group (95% CI, 11.1%-27.7%). The rate of voice dysfunction was 25% lower in the dexamethasone group than in the placebo group (95% CI, 13.7%-35.7%). During the study and follow-up period, no unintended effect was observed secondary to dexamethasone use, and none of the participants were excluded or lost to follow-up after randomization.

Discussion

In this RCT, patients who received dexamethasone before thyroidectomy had a lower rate of hypocalcemia in the first 24 hours after surgery than those who received a placebo. Additionally, only 4 patients (2.1%) had hypocalcemia on the third day after surgery. This study also confirmed the efficacy of intraoperative dexamethasone for avoiding vocal

Table 2. Comparison of Outcomes Between the 2 Groups

Outcome	Group, No. (%)		Difference in proportion, % (95% CI)
	Dexamethasone (group A)	Placebo (group B)	
Hypercalcemia, postoperative			
24 h	12 (12.5)	35 (36.4)	24.0 (11.9 to 35.2)
3 d	0	4 (4.2)	4.2 (−0.44 to 10.0)
Symptomatic hypercalcemia (24 h postsurgery)	0	18 (18.8)	18.8 (11.1 to 27.7)
Voice dysfunction (24 h postsurgery)	8 (8.3)	32 (33.3)	25 (13.7 to 35.7)

nerve palsy, with a significantly lower voice dysfunction rate seen during the first 24 hours after surgery. Thus, a single preoperative 8-mg dose of dexamethasone was safe and effective in reducing transient postoperative hypocalcemia and ameliorating postthyroidectomy voice dysfunction.

Total thyroidectomy is considered a safe surgical procedure for benign thyroid diseases, such as Graves disease or multinodular goiter, with only a slight risk of complications. Temporary hypocalcemia and postthyroidectomy voice dysfunction are 2 of the few frequently encountered complications.^{19,21} Dexamethasone is a corticosteroid and has a well-established immune-modulating effect at the surgical site; it reduces inflammation, edema, and physiological stress.^{6,7,13} However, to our knowledge, no clear guidelines have been published about its use in the prevention of hypocalcemia and vocal cord dysfunction. Our study compared the effect of preoperative dexamethasone with placebo in patients undergoing total thyroidectomy to improve hypocalcemia and prevent vocal cord dysfunction. Although we administered dexamethasone 1 hour before the induction of anesthesia, the exact timing of its preinduction administration is still not clear.²²

Dexamethasone and Hypocalcemia

We defined hypocalcemia biochemically as an adjusted serum calcium level of less than 8 mg/dL (2 mmol/L) during the postthyroidectomy period. This level of corrected calcium is in contrast to a serum level less than 8.42 mg/dL (2.10 mmol/L) as defined by The British Association of Endocrine and Thyroid Surgeons.^{12,19} Temporary hypocalcemia can have a dynamic pathophysiology. It can result unintentionally from trauma-induced edema, from compromised blood supply, or as the result of an autoimmune disease (eg, Graves disease). Hypocalcemia can be asymptomatic or symptomatic, with features consistent with neuromuscular prodromes to psychosis.^{23,24} There has been minimal discussion of the effect of dexamethasone on postoperative transient hypocalcemia. Results of 2 different RCTs^{13,25} showed that dexamethasone, when given in a single preoperative dose, reduces the chance of hypocalcemia. The effectiveness of a single preoperative dexamethasone dose was evident in our study. However, Feroci et al¹⁶ did not find a significant difference in symptomatic or asymptomatic hypocalcemia with perioperative dexamethasone use.

Dexamethasone and Voice Dysfunction

Like hypocalcemia, postthyroidectomy voice dysfunction can also be temporary or permanent. The incidence of temporary, unilateral recurrent laryngeal nerve palsy after total thyroidectomy was found to be 1.3% by Efremidou et al.²⁶

Although still not fully understood, laryngeal nerve palsy can result from injury or bruising of the strap muscles. It is postulated, that during surgery, the strap muscles are at risk of injury during retraction or dissection and thus can lead to temporary voice quality dysfunction.^{6,10}

The literature has shown that a single preoperative dose of dexamethasone can shorten and reduce the incidence of temporary, recurrent laryngeal nerve palsy, thus preventing postoperative voice dysfunction.^{27,28} In an RCT by Worni et al,⁷ the use of a single dose of dexamethasone resulted in an improvement in postoperative voice quality function after thyroidectomy within the first 48 hours. That study further found that improvement was more evident within 16 hours after surgery. Abdel Latif et al²⁵ also found that a single dose of dexamethasone during the preoperative period effectively prevented temporary, recurrent laryngeal nerve palsy. Another recently published prospective nonrandomized study²⁹ compared the outcome of dexamethasone use in 2 groups during intraoperative neural monitoring. The results of that study confirmed the efficacy of intraoperative dexamethasone in avoiding vocal nerve palsy. Our study found a significantly lower voice dysfunction rate during the first 24 hours after surgery in patients who received dexamethasone. To date and to our knowledge, no previous studies in the literature have compared the cost of 1-time dexamethasone use compared with long-term administration of calcium and vitamin D in the affected population.

Limitations

We recognize a few limitations to our study. First, there was no long-term follow-up; however, similar studies have also had no long-term follow-up. Second, the lack of a sample size estimate led to a longer duration of patient recruitment into the study, and the resulting recruitment process was difficult. Third, no nerve monitor was used; however, during each thyroidectomy, the nerve was anatomically identified and safely preserved. Fourth, patients' characteristics were not fully recorded owing to their socioeconomic status and regional language differences, which resulted in incomplete medical records. Information regarding patient characteristics was mainly gathered from the patients' history.

Conclusions

This RCT demonstrated that a single 8-mg dose of dexamethasone during the preoperative period was safe and effective in improving transient, immediate postoperative hypocalcemia as well as temporary voice dysfunction in patients undergoing thyroidectomy.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Dhahri, R. Ahmad, Rao, S. H. Ahmad, Ghufuran.

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