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Review article

Dexamethasone as a part of the multimodal perioperative care for thyroid surgery, literature review

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Abbreviations
BSCBP – bilateral superficial cervical plexus block
PONV – postoperative nausea and vomiting
POST – postoperative sore throat
RCT – randomized controlled trial
RLN – recurrent laryngeal nerve
VHI – Voice Handicap Index
VIS – Voice Impairment Score

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Abstract

Background and purpose: *Thyroidectomies are one of the most common elective surgical procedures in modern medicine. Performed under general anesthesia, thyroidectomies are associated with a high incidence of postoperative nausea and vomiting. Other common complications that increase anxiety among the surgical population are pain, postoperative voice dysfunction, and hypocalcemia. Dexamethasone, as a common adjuvant in anesthesia, is recommended as standard of care for prophylaxis of postoperative nausea and vomiting, as well as in the management of postoperative pain. Recent studies recommended the prophylactic use of dexamethasone in order to prevent hypocalcemia, and voice changes after thyroid surgery.*

Materials and methods: *A literature review with 35 studies included was done to investigate and evaluate the effect of dexamethasone on the postoperative nausea and vomiting, pain, and voice dysfunction in patients undergoing thyroid surgery.*

Results: *Dexamethasone seems to be effective for postoperative nausea and vomiting prophylaxis in patients undergoing thyroid surgery in a preoperative single dose of 8-10 mg intravenously. Dexamethasone may have potential in alleviating pain, but the correct dose needs to be determined. Studies supported the prophylaxis with dexamethasone for voice changes and hypocalcemia, but further research is required.*

Conclusion: *A preoperative single intravenous dose of dexamethasone is a safe and effective method for preventing postoperative nausea and vomiting. Further meta-analyses and high-quality trials are needed to determine the optimal dose for pain relief and to assess its impact on voice changes and hypocalcemia.*

INTRODUCTION

Thyroidectomies are among the most common elective surgical procedures in modern medicine, indicated for symptomatic benign diseases, malignant neoplasms, and hyperthyroid conditions *(1,2)*. Mortality and complication rates after thyroid surgery in the specialized thyroid surgery centers, are very low (<1%) *(3)*.

Complications after thyroid surgery can be divided into minor and major *(4)*. Formation of seroma and more pronounced scarring are in the group of minor complications. Seroma is defined as the accumulation of clear fluid secondary to postoperative or post-traumatic exudation. While small seromas may resolve spontaneously without interven-

tion, larger collections often necessitate aspiration or surgical wound dilation under strict aseptic conditions *(4,5).* Pronounced scarring can lead to a sensation of a foreign body in the throat and dysphagia. Postoperative dysphagia is not only the result of scarring; it can also be caused by compromised vascular supply or injury to the small recurrent laryngeal nerve branches innervating the cricopharyngeal muscle. Moreover, endotracheal intubation for general anesthesia can lead to dysphagia and postoperative sore throat *(4).*

Major complications include bleeding and formation of hematoma, hypoparathyroidism, and injury to the recurrent laryngeal nerve (RLN) *(4).* Bleeding and hematoma formation are not very common complications, but can be life-threatening. Bleeding can lead to the formation of a neck hematoma and increase pressure in this small compartment, leading to the compression and dislocation of the trachea and causing respiratory distress, stridor, and hypoxia. This condition requires prompt revision surgery. Endotracheal intubation during revision surgery can be challenging *(4).*

Injury to the RLN can result in paresis or paralysis. Injuries can be unilateral or bilateral, transient or permanent. Unilateral injury usually presents as hoarseness, and bilateral injuries can present as biphasic stridor, respiratory distress, and aphonia. Transient injuries last less than one year, while injuries that last longer than one year are considered permanent. Devices for intraoperative nerve monitoring can be helpful and prevent injuries to the RLN *(4).*

Some patients may experience postoperative voice dysfunction and hoarseness, even in the absence of the recurrent laryngeal nerve injury *(8).* Transient hypoparathyroidism after total thyroidectomy can lead to postoperative hypocalcemia and voice dysfunction, which are the most common complications after thyroidectomy *(9).* Parathyroid glands are positioned next to the thyroid gland. During thyroid surgery, direct trauma, devascularization or accidental removal of parathyroid glands can occur, which can lead to the transient or permanent loss of parathyroid function e.g., hypocalcemia as a result of the lower parathyroid hormone levels produced by parathyroid glands *(4).* Transient hypocalcemia occurs in up to 1.2 to 49% of patients, while permanent hypocalcemia occurs in up to 3% of patients *(4).*

Thyroidectomies performed under general anesthesia are associated with a high incidence of postoperative nausea and vomiting (PONV). PONV and postoperative pain may increase anxiety in surgical population, while vomiting itself increases risk of postoperative bleeding, which may potentially lead to the airway obstruction due to neck hematoma *(6).* The postoperative complications of interest for this literature review, in the context of thyroid surgery, are postoperative nausea and vomiting (PONV), postoperative pain, voice changes, and hypocalcemia.

Glucocorticoids are powerful anti-inflammatory drugs. Dexamethasone is a steroid administered for its glucocorticoid effect, available in oral and parenteral preparations. Its half-life is more than 4 hours, and it has a duration of action of 36 to 54 hours. A single dose of dexamethasone is considered safe, but it may cause an increase in plasma glucose in diabetic and obese patients *(12).* Dexamethasone has a wide range of effects, including its supported use in the management of PONV and as part of multimodal analgesia protocols, although the optimal dose and timing of administration remain uncertain *(12).* The anti-inflammatory action may be the underlying mechanism of antiemetic and analgesic activity of dexamethasone. This effect is mediated by peripheral inhibition of the phospholipase enzyme involved in the cyclooxygenase and lipoxygenase pathways, stabilization of neuronal membranes, and spinal cord nociceptive processing *(11,12).* Central inhibition of prostaglandin synthesis and control of endorphin release may be the mechanism of the antiemetic effect. Furthermore, the release of neuropeptides, such as substance P and calcitonin gene–related peptide, after tissue injury may be suppressed by dexamethasone *(11).*

Another potential effect of dexamethasone is the reduction of vocal fold edema and the minimization of structural damage to the vocal cords caused by endotracheal intubation *(4).* Prevention of symptomatic hypocalcemia after thyroidectomy involves various measures, such as the routine administration of calcium with vitamin D supplements, until the parathyroid glands return their function. If it is permanent, lifelong substitution therapy is needed with calcium or vitamin D3 or recombinant PTH injections. Furthermore, recent randomized controlled clinical trials have shown that hypocalcemia can be prevented by the use of perioperative dexamethasone *(9).* Dexamethasone needs to cross cell membranes to act on cytoplasmic glucocorticoid receptors, which is the reason why it exerts effect approximately 1 to 2 hours after intravenous administration and it should be administered before the start of surgery *(11, 12).*

This article reviews major trials and other studies to determine the effects of a perioperative dexamethasone on the PONV, pain, and voice dysfunction after a thyroid surgery in adult patients.

MATERIALS AND METHODS

A comprehensive search was conducted using the PubMed database. The following search string was used to identify relevant articles:
((("Steroids"[Mesh:NoExp] OR "Dexamethasone"[Mesh] OR "Dexamethasone Isonicotinate"[Mesh] OR "Glucocorticoids"[Mesh]) OR (steroid*[tiab] OR decadron[tiab] OR desametasone[tiab] OR desamethasone[tiab] OR dexacort[tiab] OR dexamethasone[tiab] OR dexamethasonum[tiab] OR dexamethazone[tiab] OR dexason[tiab]

OR dexasone[tiab] OR dexone[tiab] OR DXM[tiab] OR DXMs[tiab] OR fortecortin[tiab] OR hexadecadrol[tiab] OR maxidex[tiab] OR millicorten[tiab] OR oradexon[tiab] OR isonicotinate[tiab] OR HE-111[tiab] OR HE 111[tiab] OR HE111[tiab] OR glucocorticoid*[tiab])))) AND ((("Thyroidectomy"[Mesh]) OR (endocrine surgical procedure*[tiab] OR thyroidectom*[tiab] OR thyroid surger*[tiab])) NOT ("animals"[mh] NOT "humans"[mh]) AND English[lang] AND (1999/01/01[PDAT] : 3000/12/31[PDAT])

Search was limited to papers written in English in the time period from 1999 to 2023. The search was performed on September 11, 2023. The database search resulted in 310 results. After excluding studies, a total of 35 articles were included in this review. For details, see Figure 1. Characteristics of included studies are presented in Table 1. To minimize the risk of bias a professional librarian was involved in the development of the search strategy to ensure comprehensive and unbiased literature retrieval. The PRISMA flow diagram was used to transparently document the study selection process. Two independent reviewers (authors) screened the titles, abstracts, and full texts, and assessed eligibility based on predefined inclusion and exclusion criteria. Inclusion Criteria: male and female patients >16 years undergoing thyroid surgery under general anesthesia (ASA I-III); dexamethasone administered intravenously or as an adjuvant in a peripheral nerve block; studies reporting on at least one of the following outcomes: prevention of PONV, postoperative

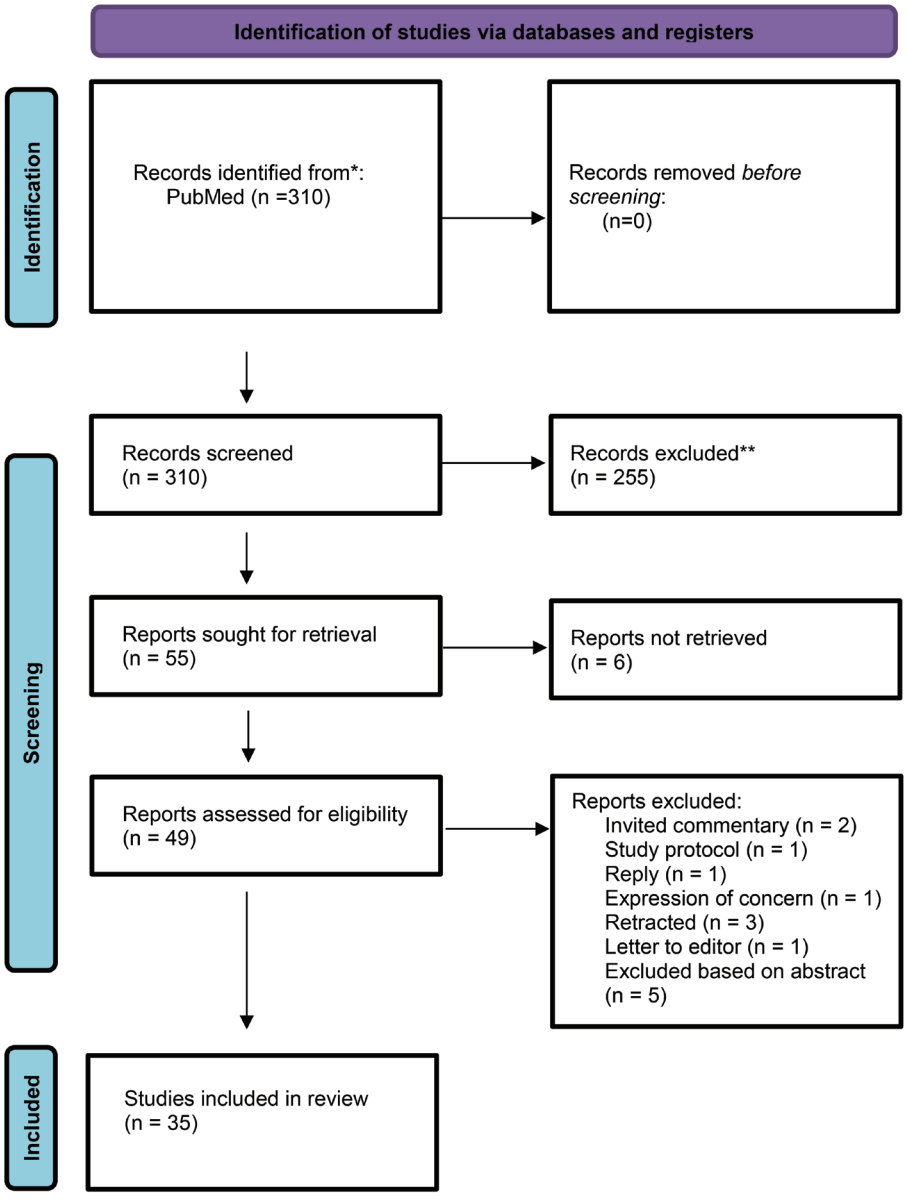

Figure 1. *Flow diagram of study searching and selection process*

Table 1. *Characteristics of the included studies*

Author	Year	Type of study	Interventions	Outcomes
Barros A *(35)*	2013	DB RC prospective study	D 4 mg iv or placebo; both groups received T 1mg/kg at wound closure + tramadol as part of patient controlled analgesia	Dexamethason could have beneficial effect on postoperative pain but not on decreasing tramadol requirement.
Batistaki C (10)	2017	critical review of randomized trials, and prospective consecutive studies 2006-2015	iv D at different doses	Single dose of dexamethasone could have beneficial role on reduction of postoperative analgesic requirements.
Cheng L *(30)*	2020	meta-analysis of RCTs	iv D from 3–8 mg	Dexamethasone resulted in signifcantly reduced pain scores, number of required analgesics, analgesic consumption, nausea and vomiting, as well as rescue antiemetics.
Doksrod S *(36)*	2012	prospective, randomized, DB study	iv D 0.15mg/kg, D 0.30mg/kg or placebo	Dexamethasone resulted in less PONV and a modest increase in blood sugar, but had no additional postoperative analgesic or opioid sparing effect.
Jain N *(34)*	2023	comparative randomized double--blinded clinical study	Rop + NS + Dex OR Rop + NS + D for BSCPB	Analgetic effect was comparable between groups, but dexamethasone as an adjuvant resulted in a statistically significant decrease in the incidence of PONV when compared to dexmedetomidine.
Cheng SP *(39)*	2015	systematic review and meta-analysis	iv D 8 mg	This meta-analysis failed to demonstrate a clinical benefit of dexamethasone in terms of immediate postoperative voice outcomes
Donatini G *(42)*	2019	prospective not randomized study	iv D 4 mg intraoperatively	A single iv D 4 mg bolus injection performed within 10 min from the beginning of a LOS during thyroid surgery exerts a therapeutic action, measurable by EMG modifications, allowing complete recovery of RLN signal in the majority of patients
Kim JS *(40)*	2018	meta-analysis	iv D 8 mg	The observed difference in voice quality on day 1 after steroid administration may not translate into a clinically significant difference given the absence of differences between groups at days 2 and >7.
Lachanas VA *(38)*	2014	retrospective review of prospectively collected data	iv D 8 mg	Single perioperative iv D 8 mg does not seem to add any benefit on voice-related quality of life, even though it may be used for other reasons such as nausea and vomiting prophylaxis or analgesia
Abdel Latif A.M. *(29)*	2020	RCT	iv D 8 mg or placebo	Dexamethasone had significant reduction in postoperative pain, PONV and significantly less voice hoarseness in study group as well as lower occurrence rate in post-operative symptomatic hypocalcemia.
Nasiri S *(41)*	2013	prospective DB RCT	iv D 8 mg or placebo	Preoperative dexamethasone injection decreases early postthyroidectomy voice changes.
Ahmad R *(14)*	2019	DB RCT	iv D 8 mg or placebo	Prophylactic dexamethasone significantly reduces the mean pain score in patients undergoing thyroidectomy, without statistically significant relation in terms of PONV.

Author	Year	Type of study	Interventions	Outcomes
Bononi M *(32)*	2009	RCT	O 4 mg iv OR patients with less than 2 risk factor for PONV received O 4mg iv OR patients with 2 or more risk fatcors received O 4mg and D 4 mg iv	The incidence of postoperative vomiting was significantly reduced in the dexamethasone group, but no relationship between postoperative vomiting and bleeding was evidenced.
Chen CC *(15)*	2012	systematic review of RCTs	iv D 8-10mg	Prophylactic administration of dexamethasone reduces the incidence of PONV, it may decrease the severity of postoperative pain and the need for rescue analgesics and antiemetics. Higher doses are more effective than lower doses.
Cho YJ *(16)*	2020	systematic review and network meta-analysis	Various pharmacologic interventions	In conclusion, propofol, tropisetron, their combination, and ramosetron combined with dexamethasone was effective in preventing PON, POV, PONV, reducing the need for rescue antiemetics, and in enhancing complete response.
Shilpa SN *(17)*	2015	DB RCT	iv O 8 mg + iv D 8 mg OR 150µg of oral clonidine + iv D 8 mg	Clonidine group experienced early PONV while ondansetron group had late onset of PONV. However, combination of oral ondansetron with dexamethsone or oral clonidine with dexamethasone reduced the overall incidence of PONV in thyroidectomy patients
Jeon Y *(18)*	2010	DB RCT	R 0.3 mg OR iv D 8 mg,OR R 0.3mg + iv D 8 mg OR placebo	The combination of R + D was more effective in reducing PONV than was D monotherapy. However, the R +D did not show additional benefits compared with R alone in preventing PONV.
Park JW *(28)*	2012	RCT	iv palonosetron 0.075 mg OR iv palonosetron 0.075 mg and iv D 4 mg	There was no significant difference in terms of the incidence of PONV between the two groups
Song YK *(19)*	2012	RCT	iv D 10 mg OR R 0.30mg iv OR placebo	Ramosetron 0.3 mg was more efficacious than dexamethasone 10 mg for monotherapy against PONV .
Tarantino I *(20)*	2015	randomized, double-blind, placebo-controlled, superiority study	iv D 8 mg OR placebo	Dexamethasone is safe and effective for the prevention of PONV.
Tavlan A *(21)*	2006	randomised, double-blind	placebo + iv D 150mcg/kg OR 0.5g ginger+ iv D 150mcg/kg	Dexamethasone plus ginger was clinically and statistically not superior to dexamethasone alone in preventing PONV
Li B *(22)*	2014	meta-analysis	iv D 5-10 mg OR placebo	D has been effective for reducing incidence and severity of PONV but without significant difference for a reduction of pain severity or analgesic consumption in using dexamethasone
Wang JJ *(23)*	1999	randomized, DB , placebo-controlled study	iv D 10 mg OR IV droperidol 1.25 mg OR placebo	The prophylactic administration of either IV dexamethasone 10 mg or IV droperidol 1.25 mg significantly reduced the incidence of PONV, but patients who received droperidol reported a higher intensity of sore throat and a more frequent incidence of restlessness.
Wang JJ *(24)*	2000	dose ranging study	iv D at doses of 10 mg, 5 mg, 2.5 mg, 1.25 mg, OR placebo	Dexamethasone 5 mg was as effective as dexamethasone 10 mg and was more effective than placebo control for preventing PONV. Dexamethasone 2.5 mg was partially effective and dexamethasone 1.25 mg was ineffective for this purpose. Dexamethasone 5 mg IV is suggested to be the minimum effective dose in this patient population

Author	Year	Type of study	Interventions	Outcomes
Zhou H *(25)*	2011	RCT	iv D 8 mg OR iv tropisetron 5 mg OR iv D 8 mg + tropisetron 5 mg	A combination of dexamethasone and tropisetron offered better prophylaxis for PONV and pain than either drug alone in patients undergoing thyroidectomy, especially during the late postoperative period (6–48 h after operation).
Zou Z *(26)*	2014	meta-analysis	iv D in a single or combination dose ranging from 1.25–18 mg	Prophylactic dexamethasone 8– 10 mg administered before induction of anesthesia should be recommended for patients undergoing thyroidectomy except for those that are pregnant, have diabetes mellitus, hyperglycaemia or contraindications for corticosteroids.
Dhahri AA *(9)*	2022	DB CT	iv D 8 mg or placebo	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
Exarchos ST (43)	2015	Retrospective study	iv D 8 mg or placebo	Swallowing impairment score 48 h after TT was significantly lower in patients who received perioperative dexamethasone.
Feroci F *(1)*	2010	RCT	iv D 8 mg or placebo	8 mg dexamethasone IV is a safe, simple, and inexpensive method to reduce the incidences of postoperative nausea and pain.
Fujii Y *(6)*	2007	randomized, double-blinded, placebo-controlled clinical study	placebo, iv D 4 mg OR iv D 8 mg	Dexamethasone 8 mg effectively decreases PONV and analgesic requirements in patients undergoing thyroidectomy under general anesthesia.
Gamalial J *(8)*	2017	2-armed study	iv D 8 mg or placebo	Dexamethasone group had signifficantly less incidence of PONV and experienced less pain compred to the placebo group. On contrary, dexamethasone was not effective in protecting vocal function.
Kolahdouzan M *(44)*	2019	RCT	iv D 8 mg	The pre-operative administration of dexamethasone reduced post-operative hypocalcemia rate.
Lee MJ (27)	2015	randomized, double-blinded study	iv R 0.3mg or iv R 0.3mg + iv D 5mg or placebo	Combination of ramosetron and dexamethasone was a simple, safe, and effective method to reduce the incidence of PONV, and postoperative pain, as compared to ramosetron alone.
Radovanović D *(31)*	2020	prospective, randomized study	4 mg of O + placebo OR iv O 4 mg + iv D 8 mg	Using dexamethasone is a safe and simple method for reducing the incidence and severity of PONV, pain, and vocal impairment; hence, dexamethasone use could reduce the total treatment cost.
Yang C *(7)*	2016	prospective DB RCT	Placebo OR ketorolac 30 mg iv OR placebo + ketorolac 30 mg iv OR D 10 mg iv + placebo	Prophylactic dexamethasone 10 mg IV significantly reduce the incidence and severity of postoperative sore throat at 24 hours after extubation as compared with placebo in thyroidectomy patients.

Abbreviations: DB RC – double-blind randomized controlled, D – dexamethasone, T – tramadol, iv – intravenous, RCT – randomized controlled trials, DB CT – double-blind controlled trial, BSCPB – bilateral superficial cervical plexus block, Rop – ropivacaine, NS – 0.9% normal saline, Dex – Dexmedetomidine, LOS – loss of the signal on neuromonitoring, RLN – recurrent laryngeal nerve, EMG – electromyography, PONV – postoperative nausea and vomiting, O – ondansetron, R – ramosetron

pain, analgesic consumption, voice changes, or hypocalcemia; published in English between 1999–2023; full-text available for download. Exclusion Criteria: retracted studies; studies not assessing dexamethasone's effect on the outcomes of interest; studies not available for full-text download; studies with no measurable outcome data.

The primary objective of this review was to investigate and critically evaluate the effects of dexamethasone on postoperative nausea and vomiting (PONV), pain, and voice dysfunction in patients undergoing thyroid surgery.

RESULTS

PONV

PONV is the most common and unpleasant complication after general anesthesia and surgery with an estimated incidence of 30% in the general surgical population *(13)*. Incidence of PONV can be as high as 80% after thyroidectomy, without a prophylactic antiemetic given *(14,15,16,17,18,19,20,21,22,23,24,25,26)*. In adults, the most common risk factors for PONV are female sex, a history of PONV and/or motion sickness, non-smoking status, young age, and use of postoperative opioids *(13,15)*. Although, etiology of PONV after thyroidectomy remains unclear, it may be associated with perioperative vagal stimulation during surgical handling of neck structures *(18)*. Edema and inflammation of neck tissue may strengthen aroused parasympathetic impulses through vagal, recurrent laryngeal, and glossopharyngeal nerves to the vomiting centre (*17)*. Sudden motion, changes in position, transport from the postanesthetic recovery unit to the postsurgical ward, and early oral intake can also precipitate nausea and vomiting in patients who have received opioid compounds. Moreover, vomiting after thyroidectomy may lead to a higher incidence of postsurgical complications such as surgical wound dehiscence, postoperative hemorrhage, or neck hematoma *(16)*. The neck hematoma is a risk factor for the development of respiratory distress due to the airway obstruction, neck pain, and dysphagia, requiring reoperation. PONV decreases patients' satisfaction, prolongs days of hospitalization, and increases healthcare costs *(16)*. Severe anxiety before surgery, together with greater fear of PONV than postoperative pain *(15,20),* increases the incidence of PONV.

PONV prevention is an important part of the anesthetic management of patients who undergo thyroid surgery. Current guidelines recommend dexamethasone in doses between 4 and 10 mg for PONV prophylaxis *(13)*. Dexamethasone acts as an antagonist on inflammatory reactions and may trigger release of endorphins, resulting in mood elevation, a sense of well-being, and appetite stimulation *(21)*. Antiemetic activity of dexamethasone, during thyroidectomy, may be by reduction of tissue inflammation and reduction of the ascending parasympathetic impulses to the vomiting centre *(17,23)*.

Of the 35 included studies in this review article, 22 studies measured the antiemetic effect of dexamethasone for thyroid surgery. In 1999, Wang et al. *(23)* compared the antiemetic effect of dexamethasone and droperidol on PONV, in women undergoing thyroidectomy. Although 10 mg dexamethasone and 1.25 mg droperidol significantly reduced the incidence of PONV with no statistically significant differences between these two groups, droperidol led to adverse effects such as restlessness and sore throat. One year later, Wang et al. *(24)* published that 5 mg dexamethasone is the minimum effective dose for PONV prevention in adult female patients undergoing thyroid surgery.

When comparing antiemetic effect of dexamethasone for thyroid surgery with combinations of dexamethasone and different drugs, studies have shown that dexamethasone was superior in reducing incidence of PONV to the combination of dexamethasone and ginger, *(21)* but combination of dexamethasone and ramosetron *(16,18,27)* or tropisetron *(25)* were more effective than either drug alone. On the contrary some results suggested that ramosetron *(19)* and palonosetron *(28)* alone seems to be more effective than dexamethasone for PONV prevention. Furthermore, combination of intravenous dexamethasone with oral clonidine or oral ondansetron may reduce the incidence of PONV, but it was associated with early onset or late onset of PONV *(17)*. One study *(14)* failed to show statistically significant reduction of the PONV incidence, after treatment with dexamethasone in patients undergoing thyroidectomy. To sum up, dexamethasone seems to be safe, effective, economical and widely available for PONV prophylaxis in patients undergoing thyroid surgery, when given intravenously and preoperatively in doses 8-10 mg *(6,8,15,20,22,26,29,30,31)*. Although, Bononi et al. *(32)* failed to demonstrate correlation between postoperative vomiting and bleeding after thyroidectomy, the potential risk of postoperative bleeding still exists and antiemetic strategy is recommended.

Pain

Postoperative pain is an unpleasant complication after surgery with an impact on a patient's well-being *(10)*. Inflammatory, neurogenic, and visceral mechanisms are involved in the pathogenesis of postoperative pain. Pain after thyroid surgery varies from mild to severe *(30,34)*. Adequate management of postoperative pain optimizes postoperative recovery, reduces the length of hospital admission after surgery, decreases preoperative anxiety, and results in fewer sedative medication requests *(10)*. Treatment of postsurgical pain depends on the type and intensity of the pain, and usually requires a multimodal approach. Furthermore, administration of traditional analgesics, such as the non-opioids (acetaminophen), non-steroidal anti-inflammatory drugs and the opioids, in addition to co-analgesics, such as alpha-2-delta calcium subunit modulators (gabapentin, pregabalin), NMDA

antagonists (ketamine, magnesium), serotonin-norepinephrine reuptake inhibitors, a2-adrenergic receptors agonists (clonidine, dexmedetomidine), steroids and more, is usually combined with regional analgesic techniques *(10).*

Recent studies have suggested that dexamethasone may have a beneficial role in management of postoperative pain after surgical tissue trauma (10). After binding the glucocorticoid receptor, dexamethasone suppresses tissue levels of bradykinin and the release of neuropeptides from the nerve endings *(10).* The analgesic effect of dexamethasone is mainly based on its ability to decrease the products of the cyclooxygenase and lipoxygenase pathways in the inflammatory response *(10,25).* Dose of dexamethasone for antiemetic effect seems to be lower than dose required for analgesic effect *(36).*

The analgesic effect of dexamethasone was investigated in 14 out of 35 included studies. In 2007, Fuji et al. *(6)* published that during the postoperative period, patients that have received 8 mg of intravenous dexamethasone preoperatively experienced less pain, and the need for indomethacin for analgesia was less than it was in groups of patients that received either, placebo or 4 mg of dexamethasone intravenously. Furthermore, two randomised controlled trials *(2,25)* published that 8 mg of intravenous dexamethasone administered immediately before induction of anesthesia alleviates severity of postoperative pain after thyroid surgery. Another two studies that primarily compared the effect of dexamethasone and ramosetron on PONV, found out as a secondary outcome that dexamethasone could alleviate postoperative pain after thyroid surgery *(19, 27).*

On the contrary, Li and Wang *(22)* and Doksrod et al. *(36)* failed to show any significant effect of dexamethasone on postoperative pain, regardless of the dose. Barros et al. *(35)* measured pain scores postoperatively with the NRS (0-10) scale. The study has shown that pain scores were significantly smaller in the dexamethasone group at the beginning of patient-controlled analgesia (started when the patient came to the postanesthesia care unit). Patient controlled-analgesia was filled with tramadol in order to measure tramadol requirements after thyroid surgery. In any of the observation periods there were no statistically significant differences in tramadol demand, suggesting that further studies are needed using a higher dose of dexamethasone. Batistaki et al. *(10)* reviewed studies in order to determine the efficacy of dexamethasone on postoperative pain not only during head and neck surgery, but also during general surgery, gynecological/breast surgery, orthopedic/spinal surgery, children's tonsillectomy, and children's orchiopexy. In the framework of this review, researchers concluded that the administration of dexamethasone prior to the thyroid surgery could have a positive effect on the postoperative pain, but exact dose and timing of administration should be further investigated.

In addition, results of the further studies *(8,29,30,31)* supported the administration of perioperative dexamethasone for significant postoperative pain reduction. The minimal effective dose of intravenous dexamethasone was 8 mg *(8, 29, 31),* or ranged between 3-8 mg *(30).* In the context of the multimodal approach for postsurgical pain treatment, to patients undergoing thyroidectomy, after the induction of general anesthesia, the bilateral superficial cervical plexus block (BSCB) was applied *(34).* Patients received either the combination of ropivacaine 0.5% and 0.9% normal saline with dexmedetomidine or dexamethasone for the BSCPB. Dexmedetomidine and dexamethasone used as adjuvants in BSCPB led to a comparable duration of analgesia and reduced the need for opioids postoperatively. Although dexamethasone was not shown to have a greater advantage over dexmedetomidine in reducing postoperative pain, this study offered different preemptive analgesic techniques in thyroid surgeries.

In conclusion, evidence supports the use of intravenous dexamethasone as part of multimodal pain management in thyroid surgery, although further research is needed to determine the optimal dose, timing, and combination strategies for consistent postoperative pain control.

Voice, sore throat, and hypocalcemia

The main goals of thyroid surgery are complete removal of the abnormal thyroid and any involved lymph nodes, preservation of parathyroid gland function, and maintenance or improvement of voice and swallowing *(37,38).* Among patients undergoing thyroid surgery, 87% can experience subjective voice changes in the postoperative period *(9,37,38,39).* Post-thyroidectomy voice change may be a result of nonsurgical and surgical causes. Nonsurgical causes usually include laryngeal irritation, edema, and inflammation around the vocal cords, or injury from airway management, while surgical causes may include direct mechanical injury to recurrent or superior laryngeal nerves or cervical strap muscles *(9,29,37,38,39,40,41*). One of the most dangerous complications is lesion of the recurrent laryngeal nerve, which can be life-threatening if it is bilateral, because it leads to airway obstruction and possible need for tracheostomy and intensive care unit management *(42).* Fortunately, this complication is rare, with the incidence of transient recurrent laryngeal nerve palsy reported in 0.4–12% of cases, permanent palsy in up to 6%, and bilateral recurrent laryngeal nerve injury in 0.1–0.9% *(42).* Owing to the increasing use of intraoperative neuromonitoring, the occurrence of these complications have been progressively declining.

Voice changes may be accompanied with postoperative swallowing impairment and postoperative sore throat (POST) *(7,39,43).* Although postoperative sore throat is a common problem after general anesthesia, the incidence of POST after thyroid surgery is significant and usually ranges from 61 to 100% during the first 24 hours after tracheal intubation *(7).* Symptoms such as non-specific

swallowing changes, occasional dysphagia, painful swallowing, swallowing difficulty and sensation of a lump or coughing usually resolve after a short period, and less commonly may persist long after the surgery *(7,43)*. This is due to the mucosal irritation and inflammation in the trachea as a result of the movement of the endotracheal tube during the neck hyperextension (usual positioning for the thyroid surgery) and manipulation of tissues surrounding the airway during surgery *(7)*.

Hypocalcemia, mainly caused by the damage of the parathyroid glands, is another frequent complication after total thyroidectomy with the incidence of 1.2 – 49% *(9,43,47)*. It can be transient or permanent if it lasts longer than 6 months after the surgery *(4)*.

Dexamethasone modifies the postoperative inflammatory response by inhibiting the effect of inflammatory mediators like tumor necrosis factor alpha, interleukin-1, and interleukin-6 *(7,40,41,42,44)*. Anti-inflammatory effect of dexamethasone may be beneficial in ameliorating post-thyroidectomy voice changes, transient hypocalcemia and POST *(7,38,39,40,41,42,43,44)*.

Among 35 of included studies, 7 investigated the effect of dexamethasone on voice changes after thyroidectomy, 3 investigated preventive effect of dexamethasone on hypocalcemia, and 2 investigated the effect of dexamethasone on the incidence of the sore throat. Nasiri et al. *(41)* measured voice quality with standardised Voice Impairment Score (VIS) questionnaires on postoperative day 1 and 7. They have published that patients who have received 8 mg dexamethasone preoperatively had significantly lower VIS than the control group, but on postoperative day 7 differences between groups were not significant. According to their research, they have suggested that the reduction of VIS score may be the result of administration of dexamethasone, which has decreased perineural or vocal cord edema, since there were no anatomical injury to RLNs. On the other hand, Lachanas et al. *(38)* measured voice quality using the Greek Voice Handicap Index (VHI) on the day before operation, 48 hours and 1 month after the surgery. Greek VHI has been recommended as a voice assessment tool in thyroid surgery because of the high levels of diagnostic precision in predicting significant voice changes pre- and post-thyroid surgery. They have shown that postoperative VHI score was significantly higher at 48 h after surgery in a group that has received a single dose of 8 mg dexamethasone preoperatively, as well as in a group that has received normal saline. Higher VHI score means greater voice-related handicap. One month after surgery, no significant difference was noticed between groups which is similar to the results of Nasiri et. al. *(41)*.

In a meta-analysis published by Kim et al. *(40)*, which included four studies, voice outcomes were measured by different scores (VHI, VIS, visual analog scale) which required integration of the scales for each study. The researchers have suggested that improvement of voice quality on day 1 after surgery in groups that have received dexamethasone may not be clinically significant, since there were no differences between groups on the second and seventh postoperative day. Donatini et al. *(42)* administered 4 mg of dexamethasone intravenously within 10 minutes of a detected loss of signal during nerve-monitoring thyroidectomy, where a persistent loss of signal beyond 20 minutes is predictive of vocal cord palsy. The administration of dexamethasone demonstrated a therapeutic effect, evidenced by measurable improvement in the electromyographic signal. Since this was not a randomized study, future research should aim to conduct a randomized controlled trial to validate these findings. Another meta-analysis conducted by Cheng et al. *(39)*, which included four studies, failed to show the positive effect of perioperative 8 mg dexamethasone on subjective voice quality after thyroidectomy, suggesting that available data are insufficient to draw definitive conclusions about the effectiveness of a single perioperative dose of dexamethasone in reducing voice changes after thyroidectomy. In a study from Abdel Latif et al. *(29)* results regarding the effect of dexamethasone on reducing the incidence of voice changes after thyroid surgery were not statistically significant. Voice function was assessed using Voice Visual Analog Scale. In the same research, results showed that the single dose of preoperative dexamethasone was associated with lower incidence of postoperative symptomatic hypocalcemia compared to the control group. Patients were examined for signs of hypocalcemia. Dharhi et al. *(9)* measured voice function using Voice Analog Score and hypocalcemia was assessed by measuring serum calcium levels (hypocalcemia was defined as serum calcium level less than 8 mg/dL (2 mmol/L)). Researchers have shown that preoperative 8 mg dexamethasone resulted in a 19% lower rate of symptomatic hypocalcemia and 25% lower rate of voice dysfunction compared to the control group.

Kolahdouzan et al. *(44)* measured serum calcium levels (hypocalcemia= 1 serum calcium determination below 8.1 mg/dL) and evaluated patients clinically for signs of hypocalcemia. They have observed that occurrence of postoperative symptomatic hypocalcemia was more often in the control group compared to the dexamethasone group, but results were not statistically significant. Exarchos et al. *(43)* showed that 8 mg dexamethasone given preoperatively was associated with improvement of post-thyroidectomy swallowing symptoms at 48 hours after surgery. Furthermore, Yang et al. *(7)* published that 10 mg dexamethasone administered 5 minutes before the induction of anesthesia was significantly effective in reducing the incidence and severity of postoperative sore throat at 24 hours after extubation in patients undergoing thyroid surgery. They compared the effect of dexamethasone to a single dose of ketorolac, which failed to produce the same effect. Both studies supported the prophylactic effect of 8 - 10 mg of dexamethasone for reducing the incidence of swallowing and sore throat symptoms after thyroid surgery.

DISCUSSION

In reviewed studies dexamethasone was administered in different doses, ranging between 3 to 21 mg. The most common dose was 8 mg intravenous.

High incidence of PONV after thyroid surgery is a reason for effective PONV prophylaxis. Dexamethasone given preoperatively may be effective for PONV prophylaxis *(6,8,15,20,22,24,29,30).* Although 5 mg dexamethasone was suggested as minimum effective dose, majority of studies recommended preoperative 8 mg dexamethasone for PONV prophylaxis in patients undergoing thyroid surgery *(6,8,15,20,26,29,30).* It is possible that dexamethasone may enhance the antiemetic efficacy of 5-HT3 receptor antagonists by inhibiting central or peripheral production or secretion of serotonin and sensitisation of the pharmacologic receptors *(18).* Further research is required in order to investigate the effectiveness of dexamethasone combined with 5-HT3 receptor antagonists in high risk patients for PONV and to determine the cost effectiveness of such treatment.

Complete postoperative recovery requires adequate pain management *(10).* Some of the analysed studies supported the use of 8 mg dexamethasone prior to thyroid surgery in order to reduce postoperative pain intensity and analgesic consumption *(3,8,10,29,31).* Recent meta-analysis *(32)* showed that intravenous dexamethasone in doses 3-8 mg for patients undergoing thyroid surgery resulted in significantly reduced pain scores, number of required analgesics and analgesic consumption. On the contrary, there are studies *(22,36)* that failed to show this benefit of dexamethasone. Furthermore, 8 mg dexamethasone has been shown to be superior to 4 mg in reducing pain scores and the need for analgesic consumption *(6,35).* Studies *(19,25,27)* comparing the combination of dexamethasone and one of the 5-HT3 receptor antagonists on postoperative pain, showed that dexamethasone was superior *(25,27)* or similarly efficient *(19)* for alleviating postoperative pain to 5-HT3 receptor antagonists.

Studies to date support that the administration of dexamethasone prior to thyroid surgery may be beneficial in reducing postoperative pain severity and analgesic requirements. It may also decrease the incidence of adverse effects and the overall cost of analgesic administration in surgical patients. However, no consensus has been reached regarding the optimal dose and timing of administration. Further research is needed to better understand dexamethasone's analgesic effects. Additionally, a matter of future research may be the effect of dexamethasone as adjuvant to the BSCPB, another method for efficacious postoperative analgesia in thyroid surgeries *(34).*

Approximately 87% of patients undergoing thyroid surgery can experience subjective voice changes in the postoperative period due to surgical and nonsurgical causes *(9, 37,38, 39).* Anti-inflammatory effect of dexamethasone can have positive impact on voice changes by decreasing edema and inflammation around the nerve or vocal folds, but without effect on neuropraxia *(9,29,40,41,42).* Unfortunately, majority of studies published that positive effects of dexamethasone on voice changes were significant only on day one after thyroidectomy *(9, 40,41).* Furthermore, different studies used various scoring systems to measure voice changes, and the sample sizes were small, with most studies not being randomized. Additionally, the meta-analyses were conducted on a limited number of studies. This suggests that the existing literature on the impact of dexamethasone on post-thyroidectomy voice outcomes is still limited and inconsistent, indicating the need for further studies using validated methods. Moreover, further studies should include proposed voice assessment tools such as VHI to assess voice outcomes, EMG parameters of intraoperative nerve monitoring, mean phonation time, and robust acoustic voice analysis, to characterize the pathophysiology of voice changes and mechanisms of dexamethasone effects.

Dexamethasone may be beneficial in reduction of postoperative hypocalcemia rate, (9,44) as well as in reduction of the incidence of sore throat and swallowing symptoms after thyroid surgery *(7,43),* but because of the lack of sufficient clinical evidence further studies are needed for definite conclusion.

The long-term therapy with dexamethasone increases the risk of postoperative infections, impaired wound healing, and glucose intolerance, but prophylactic therapy with dexamethasone is considered to be relatively free of side effects *(3,6,11,45).* Single prophylactic dose of dexamethasone appears to induce only mild elevation in blood glucose levels, even in the presence of diabetes *(13).* It also seems that a single preoperative dose of dexamethasone could reduce the drainage volume after thyroidectomy, as well as, the C-reactive protein levels and leukocytes counts in the drainage fluid *(46).* Furthermore, wound healing one month postoperatively seems to be uninterrupted *(4)* which may suggest that anti-inflammatory effect of dexamethasone on wound healing could result in reduced scar formation and better skin colour *(4).*

CONCLUSION

Preoperative dose of dexamethasone is a safe and simple method for the prophylaxis and treatment of postoperative nausea and vomiting. We acknowledge the heterogeneity of findings across studies regarding voice changes, hypocalcemia, and postoperative pain after thyroid surgery, while the beneficial effect of dexamethasone on postoperative nausea and vomiting (PONV) appears to be well established. Given the variability in results for the other outcomes, we suggest that a meta-analysis focused on postoperative pain could help clarify the overall effect of dexamethasone and determine optimal dosing strategies. Additionally, further large-scale, high-quality randomized trials are needed to better understand the poten-

tial impact of dexamethasone on voice changes and hypocalcemia, and to reduce the current uncertainty in clinical practice.

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