

RESEARCH PROPOSAL

Version No:3

Version Date: 4/7/2024

Intra-operative Steroid Irrigation for Reducing Recurrent Laryngeal Nerve Palsy Post-thyroidectomy – A Pilot Study

Study Duration: 1/11/2024 – 31/10/2026

Kah Seng Khoo^a
MBBS (UM)
MRCS (Edinburgh)
MSurg (UM)

Joanne Aisha Mosiun^a
MBBS(UM)
MRCS (Edinburgh)
MSurg (UM)

Redzwan Shah Bin John Mohd^b
MBBS (UM), MSORLHNS
(UM)

Yoke Kiet Doon^a
MD (MOSCOW)
MSurg (UM)

Khoon Leong Ng^a
MBBS (S'pore)
FRCS (Glasg) FRCS (Ed)
AM (Mal)

Mee Hoong See^a
MD (UPM)
MSurg (UM)

a Breast & Endocrine Surgery Unit, Department of Surgery, University of Malaya, Malaysia

b Department of Otorhinolaryngology, University of Malaya, Malaysia

*Corresponding author: Kah Seng Khoo, Tel: +6017-2489272, Email: kahseng901209@gmail.com

TABLE OF CONTENTS

| | |
|--|--------------|
| Title Page | 1 |
| Table of Contents | 2 |
| List of Abbreviations | 3 |
| Introduction | 4 |
| Literature Review | 5 |
| Objective and Hypothesis | 6 |
| Methodology: | 7-8 |
| Study Type and Design | |
| Inclusion Criteria | |
| Exclusion Criteria | |
| Withdrawal Criteria | |
| Study Duration and Timeline | |
| Data Collection Tools and Techniques | |
| Data Analysis | |
| Risk and Benefit to Study Participants | |
| Flow Chart | 9 |
| Ethics of Study | 9 |
| Informed Consent | 9 |
| Privacy and Confidentiality | 10 |
| Conflict of Interest | 10 |
| Gantt Chart | 11 |
| References | 12-13 |

List of Abbreviations

Endocrine Surgery - ECS

GS – General Surgery

Recurrent Laryngeal Nerve - RLN

UMMC – University Malaya Medical Centre

WHO – World Health Organization

Introduction

Recurrent laryngeal nerve palsy is a common and feared complication that can happen during thyroidectomy, with incidence reported varies between 1-30% being transient and 0.5-5% being permanent injury¹⁻². Unilateral nerve palsy can lead to hoarseness of voice, choking episodes whereas bilateral nerve palsy can lead to airway compromise and subsequently require tracheostomy. This complication has significant impact to quality of life of patient, health care expenditures and lastly, mental health of operating surgeon.

Manipulation of nerve during thyroid surgery may lead to oedema of the neuron and subsequently dysfunction, ranging from neuropraxia to axonotmesis. Various studies supporting the fact that steroid administration may prevent or reduce neural oedema (facial nerve palsy/ recurrent laryngeal nerve palsy)³⁻⁵. Conflicting data in the past regarding benefit of intraoperative steroids in thyroid surgery in preventing nerve palsy, some proven beneficial⁶, whereas another prospective case controlled clinical trial proven not different in rate of nerve palsy⁷. A pilot study in dental surgery proven intra-operative hydrocortisone irrigation is a useful and low cost method to control oedema in inferior third molar removal⁸.

Retrospective review of data from UMMC Endocrine Surgery Unit (ECS), the incidence rate of post thyroidectomy recurrent laryngeal nerve palsy were 10%, 7.2%, 5% in year 2021, 2022 and 2023 respectively. Majority of the cases (80% in 2021, 100% in 2022, 67% in 2023) were intact nerve during surgery but dysfunction post-operatively (neuropraxia to axonotmesis).

The main aim of this study is to elucidate whether the topical irrigation of steroid during thyroid surgery can reduce the rate of recurrent laryngeal nerve palsy as majority of nerve dysfunction was due to neuropraxia to axonotmesis.

Literature Review

According to the 'Sixth National Audit Report 2021' of The British Endocrine and Thyroid Surgeons (BAETS), the overall rate of recurrent laryngeal nerve (RLN) palsy following thyroidectomy was 6.7-7.8%⁹. Persistent RLN palsy was more common after total thyroidectomy (2.8%) than thyroid lobectomy (1.2%)⁹. Numerous research initiated by surgeons to find a way to reduce RLN palsy in thyroid surgery as this feared complication can impact greatly to the patient and the surgeon as well.

The most common type of RLN palsy is due to manipulation of nerve during thyroid surgery, which lead to oedema of the neuron and subsequently dysfunction, ranging from neuropraxia to axonotmesis. This type of RLN palsy usually will recover overtime. Majority of the treatment of this group of palsy are speech therapies, steroids administration, injection laryngoplasty, thyroplasty and etc. Various studies supporting the fact that steroid administration may prevent or reduce neural oedema (facial nerve palsy/ recurrent laryngeal nerve palsy)³⁻⁵. A randomized double blind controlled study involving prednisolone administration to patient with idiopathic facial nerve paralysis (n=66), showed that patients received prednisolone have less denervation than placebo patients and also significant improvement in facial grade at recovery as well⁵.

However, conflicting data in the past regarding benefit of intraoperative steroids in thyroid surgery in preventing nerve palsy, some proven beneficial⁶, whereas another prospective case controlled clinical trial proven not different in rate of nerve palsy⁷. A randomized clinical trial involving 64 patients were divided into two groups (preoperative dexamethasone and placebo) to study effect on voice change after thyroidectomy. There were no significant complication from the intervention group but the intervention group decrease voice change after thyroidectomy¹⁰.

A cohort study published by Emre AU, et al, studied the efficacy of intraoperative single dose methylprednisolone on recurrence laryngeal nerve function after thyroidectomy. 438 nerves at risk was included and divided into intervention group and placebo group. They concluded single intraoperative dose of steroid does not seem to effect the rate and recovery period of RLN palsy in thyroid surgery¹¹.

With regards to the possible impact of perioperative intravenous dexamethasone side effects, a systematic review and meta-analysis performed by Waldron NH, et al. involving 45 studies (5796 patients) receiving a single dose of dexamethasone. It showed that patients received dexamethasone had significant analgesic benefits without increase in infection or delayed wound healing issue. However, blood glucose levels were higher at 24H in the dexamethasone group¹².

Lately, a pilot study conducted in dental surgery proven intra-operative hydrocortisone irrigation is a useful and low cost method to control oedema in inferior third molar removal which mimic the effect of intravenous steroid in reducing oedema and swelling of soft tissue and nerve⁸. By avoiding intravenous steroid administration, it could avoid the potential side effect of steroid such as wound complication and hyperglycaemia.

Research Question

As majority of RLN palsy in thyroid surgery are due to neuropraxia and axonotmesis, and one of the modality of treatment involving steroid administration or perhaps given prophylactically to reduce the incidence of nerve palsy. With the evolving evidence that steroid irrigation proven to reduce oedema at the operative field, will steroid irrigation help to reduce oedema of the RLN and hence help in reduce the incidence of nerve palsy without its systemic side effect?

Objectives

Primary Objectives

- To investigate whether intraoperative steroid irrigation post thyroidectomy reduces the rate of recurrent laryngeal nerve palsy compared to placebo

Secondary Objectives

- To investigate whether intraoperative steroid irrigation post thyroidectomy hasten the time interval for complete recovery of RLN palsy compared to placebo

Hypothesis

- Null hypothesis: Intraoperative steroid irrigation does not reduce the rate of recurrent laryngeal nerve palsy post thyroidectomy
- Alternative hypothesis: Intraoperative steroid irrigation reduces the rate of recurrent laryngeal nerve palsy post thyroidectomy

Methodology

Study Type and Design

This is a single centre, double blinded and prospective randomized controlled trial which will be conducted in University Malaya Medical Centre (UMMC), Breast and Endocrine Surgery Unit. The duration of the study will be from November 2024 until October 2026 (2 years duration).

Patient will be recruited from the endocrine surgery outpatient clinic who scheduled for elective thyroidectomy. There are several inclusion and exclusion criteria for recruitment into this study. After fulfilling the inclusion criteria, patients will be required to give consent and agree to participate in this study after explanation by the investigator in charge. Participants will be randomized into an intervention group (Group A) and a control group (Group B) with the ratio of 1:1 during admission for surgery by online computer system. The method of randomization utilised will be random randomization. Before and after thyroidectomy, vocal cord will be assessed by single otolaryngologist using indirect laryngoscopy who participate in this study. All surgery will be performed by 3 surgeons (Lectures) in Breast and Endocrine Surgery Unit (ECS).

Intra-operatively, all participants recruited must have the recurrent laryngeal nerve identify and confirm with Intraoperative Nerve Monitoring (IONM) device. Participant will be excluded from the study if the nerve is being transected, unable to identify or no signal after stimulation with IONM. After removal of thyroid gland, 8mg of dexamethasone will be diluted in 100cc of irrigation water and irrigate the operative field for the intervention group. However for the placebo group, they will receive water irrigation over the operative field only which is the current standard of practice at the moment. If there are objective vocal cord paresis during indirect laryngoscopy post thyroidectomy (within 24-48H), the participant will be labelled as nerve palsy. Recurrent laryngeal nerve palsy will then be classified into temporary (<6 months) or permanent (>6months) based on the duration of palsy and will be managed accordingly by otolaryngologist team.

Both the assessor and patient are blinded throughout the whole study. Only the investigators and assistants of the surgery will be aware of the randomization of a patient.

Inclusion Criteria

- The target population are patients who scheduled for thyroidectomy (include both total or hemithyroidectomy) between November 2024 until October 2026 in UMMC.
- Age between 18 years old till 80 years old

Exclusion Criteria

- Vocal cord paresis before surgery
- No consent
- Allergy towards dexamethasone

Withdrawal Criteria

Subjects can choose to withdraw at any time during the study.

Study Duration and Time-line (refer to Gannt Chart)

The research period is from November 2024 till October 2026. After the proposal has been approved by the MREC, data collection will tentatively start from November 2024 till October 2026. Data analysis will take 2 months and the report writing and submission to appropriate journal will take approximately 4 months.

Data Collection Tools and Techniques

As this is a prospective randomized controlled trial, relevant participants information and the outcomes will be recorded and documented in the Electronic Medical Record (EMR). These data will then be transcribed into SPSS for analysis.

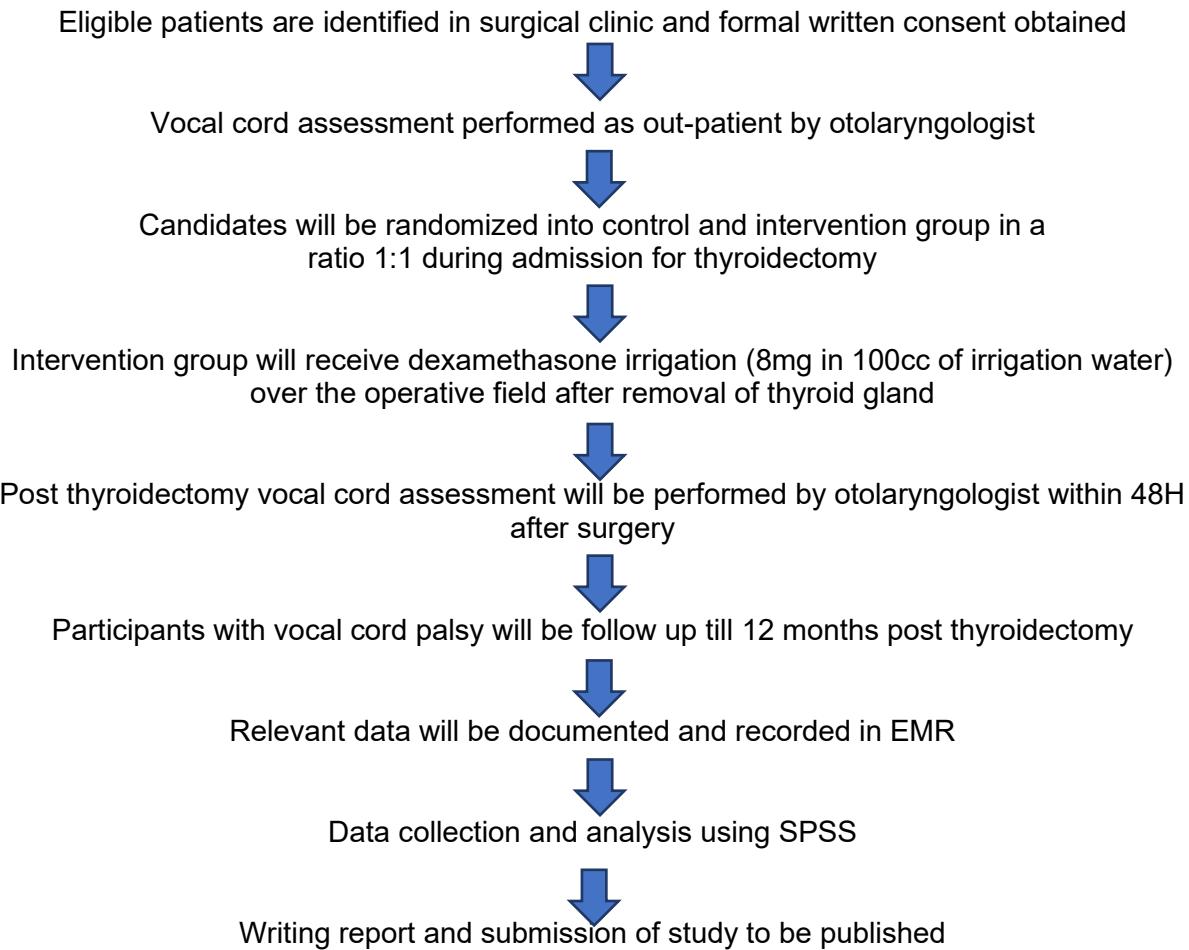
Data Analysis

Data recorded will be analysed using SPSS Statistics Version 25. Continuous data will be expressed as Mean+/- standard deviation unless otherwise stated. Paired T- test was used for comparison of paired samples. The students's T- test was used for comparison of continuous variables between different groups. Chi-square test will be used for categorical data analysis. A value of $P<0.05$ will be considered statistically significant. The data collected will be analysed using an intention to treat analysis.

Risk and Benefits to Study Participants

No risks will be imposed to the study participants as the dexamethasone is not administrated to the patient's systemic circulation but instead of diluted irrigation over the operative field. In the other hand, this study does not present any direct benefit to the participants who involved in this study. However, information obtained from this study will help to formulate a better prophylactic measure and treatment to reduce complication post thyroidectomy.

Flow Chart



Ethics

This study will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline.

Informed Consent

Eligible patients will be identified during clinic visits. Information regarding the study will be given and explained to them during clinic visit. They will be allowed to take the patient information sheet home and consult with their family members. Informed consent will be obtained during clinic visits.

Privacy and Confidentiality

Subject's names will be kept private and an identification number instead of patient identifiers will be used on subject data sheets. Strict confidentiality will be maintained. All identification labels will be anonymised in any future presentations or publications. All data will be entered

into a computer that is password protected. On completion of study, data in the computer will be copied to a thumb-drive/USB drive and the data in the computer erased. Thumb-drive/USB drive and any hardcopy data will be stored in a locked office of the investigator in the Department of Surgery and securely disposed after 7 years on conclusion of the study.

Conflict of Interest

The investigators declare that they have no conflict of interest.

Gantt Chart

| | Apr-May 2024 | Jun-Aug 2024 | Nov 2024- Oct 2026 | Nov-Dec 2026 | Jan-Oct 2027 |
|---------------------------------------|-----------------|-----------------|-----------------------|-----------------|-----------------|
| Literature review & research proposal | ■ | | | | |
| Ethnics approval | | ■ | | | |
| Data collection | | | ■ | | |
| Data analysis | | | | ■ | |
| Report writing and journal submission | | | | | ■ |

References

1. Uruno T, et al. A prophylactic infusion of calcium solution reduces the risk of symptomatic hypocalcemia in patients after total thyroidectomy. *World J Surg*, 2006. 30(3): p. 304-8.
2. Joliat GR, Guarnero V, Demartines N, et al. Recurrent laryngeal nerve injury after thyroid and parathyroid surgery. *Medicine*, 2017 96:17.
3. Bansberg SF, McCaffrey TV. The effect of systemic triamcinolone acetonide on nerve repair. *Otolaryngol Head Neck Surg*, 1987; 96(2): 158-164.
4. Stankiewicz JA. A review of the published data on steroids and idiopathic facial paralysis. *Otolaryngol Head Neck Surg*, 1987; 97(5):481-486.
5. Austin JR, Peskind SP, Austin SG, et al. Idiopathic facial nerve paralysis: a randomized double blind controlled study of placebo versus prednisone. *Laryoscope*, 1993; 103(12): 1326-1333.
6. Lore JM Jr, Farrell M, Castillo NB. Endocrine surgery. In: Lore JM Jr, Medina JE (eds). *An atlas of Head and Neck Surgery*, 4th edn. Elsevier, Philadelphia, 2005:963-965.
7. Wang LF, Lee KW, Kuo WR, Wu CW, Lu SP, et al. The efficacy of intraoperative corticosteroids in recurrent laryngeal nerve palsy after thyroid surgery. *World Journal of Surgery*, 2006 (30):299-303.
8. Rodrigues VP, Deboni MCZ, Cecchetti MM, Ocana RP, Frare JG, et al. Hydrocortisone irrigation for postoperative control of oedema in inferior third molar removal-A pilot study. *Journal of Oral and Maxillofacial Surgery, Medicine, and Pathology*, 2020 (32): 351-355.
9. Aspinall S, Mihai R, Kinsman R, Walton P. The British Association of Endocrine and Thyroid Surgeon Sixth National Audit. 2021.
10. Nasiri S, Shafiq S, Hedayat A, Khorgami Z, Sodagari N, et al. Does corticosteroid have any beneficial effect on voice change after thyroidectomy? *The American Surgeon*, 2013;79 (12):1258-1262.
11. Emre A, Cakmak GK, Arpacı DK, Ilikhan SU, Damar M. The efficacy of intraoperative single dose methylprednisolone on recurrent laryngeal nerve function after thyroidectomy. *International Surgery*, 2016, 101 (3-4):116-120.

12. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. *British Journal of Anaesthesia*, 2013, 110 (2): 191-200.