Trial Protocol

Version No:2

Version Date: 9/5/2020

Article information: https://dx.doi.org/10.21037/gs-24-190

The Use of Prophylactic Infusion of Calcium Gluconate Compared to Placebo in Reducing the Rate of Early Hypocalcaemia After Total Thyroidectomy: A Double-Blinded, Randomized Controlled Trial

Study Duration: 1/6/2020—13/5/2022

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List of Abbreviations

b.d.- twice a day

ECS- endocrine surgery unit

EMR- electronic medical record

FDA- Food and Drug Administration

MREC- Medical Research Ethics Committee

PTH- parathyroid hormone

i-PTH- serum parathyroid hormone

o.d.- once a day

q.i.d.- four times a day

t.d.s.- three times a day

UMMC- University Malaya Medical Centre

WHO- World Health Organization

Introduction

Total thyroidectomy is a commonly performed procedure nowadays. It is the treatment option for thyroid malignancies and also for benign disease such as symptomatic multinodular goitre[2]. Hypocalcaemia is one of the most common complications associated with total thyroidectomy and it has been reported to occur in 13%- 49% of cases in a meta-analysis, causing transient and permanent hypocalcaemia[5].

In the UMMC Endocrine Surgery Unit (ECS), the incidence rate of post total thyroidectomy symptomatic hypocalcaemia within 48 hours after surgery in 2018 and 2019 were 40% and 23% respectively. The group of patients that required rescue doses of intravenous calcium gluconate infusion within 48 hours after surgery was 40% and 33% in 2018 and 2019 respectively. None of the patients that received intravenous calcium gluconate experienced any adverse effects in 2018 and 2019.

Post-thyroidectomy hypocalcaemia arises due to either parathyroid removal, parathyroid devascularization or gland damage[4]. Even with experienced surgeons and preservation of the parathyroid glands at the time of surgery, symptomatic hypocalcaemia can still occur[2]. General consensus suggests that only one half of a normal parathyroid gland needs to be preserved to yield adequate parathyroid hormone.

Hypocalcaemia causes symptoms such as paraesthesia, muscle spasms, nervousness and anxiety. Classical signs would be Chvostek's and Trousseau's signs. Persistent symptomatic hypocalcaemia will lead to prolonged hospital stay, with increased patient cost and patient dissatisfaction.

There has been multiple reports that prophylactic administration of oral calcium supplement and vitamin D post-surgery is effective in reducing the rate of post-operative hypocalcaemia. However, there is a paucity of literature regarding the role of prophylactic infusion of calcium prior, during or after surgery in reducing the risk of developing post-operative hypocalcaemic symptoms.

The main aim of this study is to establish whether the administration of prophylactic infusion of calcium gluconate as compared to placebo reduces the rate of post-total thyroidectomy hypocalcaemia in the first 48 hours after surgery.

Literature Review

According to the 'Firth National Audit Report 2017' of The British Endocrine and Thyroid Surgeons (BAETS), the overall rate of early hypocalcaemia is 23.6%, compared to 27.4% in the 2012 report and 29.6% in the 2009 report[1]. These figures probably represent an under-estimate of the true rate of early hypoparathyroidism as some patients would have received prophylactic calcium supplements in order to prevent post-operative hypocalcaemia. In the BAETS audit, the rate of early hypocalcaemia was as high as 30.4% in total thyroidectomy plus central node dissection group[1]. The standard post-operative stay in that audit was a two-night stay and currently, in the UK, they are moving towards the trend of a one-night stay depending on the serum calcium level.

Several risk factors have been identified to cause temporary hypocalcaemia post-total thyroidectomy and common causes include accidental parathyroid removal and disruption of blood supply to the parathyroid glands. The treatment of symptomatic hypocalcaemia is intravenous infusion of calcium gluconate. There is limited data on the prophylactic use of intravenous calcium gluconate in preventing or reducing the rate of hypocalcaemia. A prospective cohort study by Urono, *et al* in 2006 showed that a significantly lower rate of post-total thyroidectomy hypocalcaemia was achieved by giving prophylactic infusion of calcium solution within 3-8 hours after surgery. The serum calcium level for the intervention group on the first post-operative day was 7.91+/- 0.49 mg/dL while in the control group it was 7.65 +/- 0.54 mg/dL. There was no difference in the serum intact parathyroid hormone (i-PTH) level in both groups on the first post-operative day. This was the first prospective study that evaluated the role of prophylactic calcium infusion in reducing the rate of hypocalcaemia after total thyroidectomy[2].

Hafez, *et al* in the year 2014 found that in a randomized controlled trial involving 40 patients, prophylactic intravenous infusion of calcium gluconate during total thyroidectomy was effective in minimizing the risk for post-operative symptomatic hypocalcaemia[3]. These are the research currently available on the role of prophylactic intravenous calcium gluconate infusion after total thyroidectomy. Multiple factors can influence the rate of post-operative hypocalcaemia including patient characteristics or surgical technique. Rio PD, *et al* reported that females are at double risk of developing hypocalcaemia as compared to the male gender. Apart from that, the total thyroidectomy group have higher rates of hypocalcaemia as compared to the sub-total thyroidectomy group[4]. Total thyroidectomy plus central nodes dissection will increase the rate of post-operative hypocalcaemia even further as compared to total thyroidectomy alone (44% vs 14.3% of laboratory proven hypocalcaemia)[7].

A meta-analysis by Xing TF, *et al* involving 10 randomized controlled trials suggested that routine post-operative calcium and vitamin D supplementation significantly reduced the rate of hypocalcaemia and the demand for intravenous calcium supplementation as compared to either no treatment or calcium alone[5,12]. While there is evidence regarding the role of post-operative supplementation, there is little

literature reporting on the role of routine pre- and post-total thyroidectomy calcium and vitamin D supplementation in preventing post-operative hypocalcaemia. Routine pre- and post-total thyroidectomy calcium and vitamin D supplementation have been shown to reduce the rate of post-operative hypocalcaemia and length of hospital stay[6,7].

Interestingly, there was a randomized controlled trial performed by Besic, *et al* who studied whether magnesium infusion prior to total thyroidectomy will influence the onset of transient hypocalcaemia. This is as normomagnesaemia is needed for the normal secretion of parathyroid hormone. However, no statistical difference was identified between the intervention and control groups[9,12]. It is essential to measure serum magnesium in any patient who is hypocalcaemic, as the correction of hypomagnesaemia must occur to overcome parathyroid hormone (PTH) resistance before serum calcium can normalised with calcium supplementation[14].

Pre-operative parathyroid hormone level can help to predict and anticipate post-operative hypocalcaemia. If the pre-operative PTH is less than 4.7pmol/L, the risk of developing transient hypoparathyroidism is 2.4 times higher than the normal population and thus there is a higher risk of developing post-operative hypocalcaemia[10]. Pre-operative calcium levels can also help to predict post-operative hypocalcaemia. A retrospective study by Amir , *et al* found that corrected pre-operative serum calcium levels of less than 2.27 mmol/L was associated with a 63% chance of developing post-thyroidectomy hypocalcaemia whereas those with calcium levels above 2.27 mmol/L have a 24% chance of developing hypocalcaemia[11].

Luo Han, *et al* performed a retrospective study of protocols for the post-thyroidectomy management of patients who underwent thyroidectomy between 2013 and 2015 in West China Hospital[14]. All patients were given routine 2-days of intravenous calcium infusion, 2g on the day of surgery and 4g on post-operative day 1. All patients were also prescribed with calcium carbonate 600mg t.d.s or q.i.d. on post-operative day 1. Extra calcitriol 0.25mcg b.d. was added into the therapeutic plan on a case-by-case basis. The patients were usually discharged on the third day after surgery depending on their serum calcium levels and the relative decrease in percentage between pre-operative i-PTH and postoperative i-PTH level (the cut-off percentage used was 70% decrease in i-PTH level). On the basis of their findings in this study, routine 2-day intravenous infusion of calcium with or without oral supplement plus extra supplement of calcitriol according to the relative decrease percentage and absolute value of post-operative PTH was an effective protocol that could identify patients needing longer hospitalization[14].

Hypocalcaemia can present either as an asymptomatic laboratory finding or as a severe, life-threatening condition[15]. The ability to distinguish acute from chronic hypocalcaemia and asymptomatic from severely symptomatic hypocalcaemia is essential to determine the appropriate therapy. In the setting of

acute hypocalcaemia, rapid treatment may be necessary. In contrast, chronic hypocalcaemia may be well tolerated, but treatment is necessary to prevent long-term complications. Post total thyroidectomy hypocalcaemia is one of the causes of acute hypocalcaemia. The hallmark of acute hypocalcaemia is neuromuscular irritability. Patients often complain of numbness and tingling in their fingertips, toes, and the perioral region. Paraesthesia of the extremities may occur, along with fatigue. Muscle cramps can be very painful and progress to carpal spasm or tetany. In extreme cases of hypocalcaemia, bronchospasm and laryngospasm with stridor may occur. All these symptoms can be corrected by calcium replacement either in the oral or intravenous form depending on the clinical picture.

Clinically, neuromuscular irritability can be demonstrated by eliciting Chvostek's or Trousseau's signs. Chvostek's sign is elicited by tapping the skin over the facial nerve anterior to the external auditory meatus. Ipsilateral contraction of the facial muscles occurs in individuals with hypocalcaemia. It has to be noted that Chvostek's sign is also present in 10% of normal individuals[15]. Trousseau's sign is elicited by inflation of a blood pressure cuff to 20 mm Hg above the patient's systolic blood pressure for 3-5 minutes. Carpal spasm presents as flexion of the wrist and of the metacarpal phalangeal joints, extension of the interphalangeal joints, and abduction of the thumb. Cardiac manifestations such as prolonged QT interval, abnormal T wave and cardiac arrhythmias could be one of the features of acute hypocalcaemia. Thus, by classifying hypocalcaemia into mild or severe, depending on the clinical symptoms and biochemical results can be useful to direct treatment strategy (**Appendix 3**).

Calcium gluconate is the intravenous calcium salt of choice to correct hypocalcaemia as calcium chloride often causes local irritation. In most hospital settings, only calcium gluconate is readily available. Calcium gluconate contains 90 mg of elemental calcium per 10 mL ampoule, and usually 1 to 2 ampoules (180 mg of elemental calcium) diluted in 50 to 100 mL of 5% dextrose is infused over 10 minutes. This can be repeated until the patient's symptoms have resolved. With persistent hypocalcaemia, administration of a calcium gluconate infusion over a longer period of time may be necessary. Infusion rates of 0.5-2.0 mg/kg/hour are recommended[15].

The most common adverse effects of intravenous calcium infusion are hypertension, nausea, vomiting, and flushing. Bradycardia and heart block may occur in rare cases. Patients receiving intravenous calcium should be placed on cardiac monitoring and administration should be discontinued if bradycardia ensues. Patients may complain of tingling sensation, a sense of oppression or heat wave and a calcium or chalky taste following administration of intravenous calcium gluconate. As extravasated calcium may cause severe tissue irritation and necrosis, it should be given through a well-functioning intravenous catheter[16,17].

Objectives

Primary Objectives

- To determine whether prophylactic infusion of calcium gluconate reduces the rate of early hypocalcaemia after total thyroidectomy as compared to placebo treatment

Secondary Objectives

- To determine whether prophylactic infusion of calcium gluconate reduces the length of hospital stay as compared to placebo group

Study Endpoint

- The level of corrected calcium in the first 48 hours after total thyroidectomy between intervention and control group

Hypothesis

- Null hypothesis: prophylactic infusion of calcium gluconate does not reduce post-total thyroidectomy hypocalcaemia and length of hospital stay as compared to placebo group

- Alternative hypothesis: Prophylactic infusion of calcium gluconate reduces the rate of post-total thyroidectomy hypocalcaemia in the first 48 hours and shorten the length of hospital stay as compared to placebo group

Methodology

Current Protocol in UMMC

All patients admitted or scheduled for total thyroidectomy in UMMC will have their baseline serum calcium and i-PTH levels checked one day before surgery. Subsequently, all patients will have their serum calcium levels checked at the 6-hour, 12-hour, 24-hour, 36-hour and 48-hour mark post-surgery. The i-PTH level will be tested at the 12-hour post-surgery mark together with the serum calcium level. Oral calcium supplements 2g a day (Calcium Carbonate 1g b.d.) and Rocaltriol 0.25mcg o.d. will be started once the patients are able to tolerate orally. If a patient experiences symptoms of hypocalcaemia and the serum calcium level is less than 2.0mmol/L, the patient will be administered a rescue dose of intravenous calcium gluconate (3g of calcium gluconate in 50mls of normal saline) over 4 hours duration. However, if a patient experiences hypocalcaemia symptoms and the serum calcium level is more than 2.0mmol/L, the patient will be continued on oral supplements at an increased dosage (3-4g of calcium carbonate a day). The usual hospital stay for a total thyroidectomy patient is 48 hours post-surgery. If a patient is asymptomatic and the serum calcium level is normal at 48-hours post-surgery, the patient can be discharged with an appointment at the outpatient clinic in two weeks time.

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), Endocrine Surgery Unit. The duration of the study will be from June 2020 until May 2022 (2 years duration).

Patient will be recruited from the endocrine surgery outpatient clinic and in-patient referrals for total 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 clinician and 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 (**Appendix 2)**. The method of randomization utilised will be random randomization. Both the surgeon and patient will not be aware of the randomization arm of any particular patient. Only the primary investigator and assistants will be aware of the randomization of a patient. Before surgery, baseline serum calcium, magnesium and i-PTH will be obtained. If intra-operatively, all 4 parathyroid glands are accidentally removed during the total thyroidectomy, these patients will be excluded from the study as this will definitely affect their serum calcium levels post-surgery.

After total thyroidectomy, the intervention group will receive a calcium gluconate infusion over one hour (1g of intravenous calcium gluconate, diluted in 100mls of normal saline) within 4 hours after skin closure. On the other hand, the control group will receive a saline infusion (100 ml of normal saline) infused over one hour within 4 hours of skin closure. Both groups will be put on cardiac monitoring

during the administration of the intravenous infusion. The dosing, dilution and infusion rate for the calcium gluconate are within the safety limits as recommended by FDA and WHO model formularies.

Post-total thyroidectomy, both groups of patients will receive the same regime of oral calcium carbonate 1g t.d.s. and oral Rocaltriol 0.25mcg o.d. as per current protocol in the endocrine surgery unit. Serum calcium levels will be obtained at the 6-hour, 12-hour, 36-hour, 48-hour mark post-surgery. The blood samples collected will be sent to the biochemical laboratory of UMMC.

During blood taking and review, the patient will be assessed for symptoms of hypocalcaemia such as perioral numbness, spasm, etc. During assessment, if there are clinically suggestive symptoms of hypocalcaemia, the symptoms will be classified into mild or severe symptoms (**Appendix 1**). If a patient exhibited signs of mild hypocalcaemia like perioral numbness, limbs numbness and positive Chvostek's sign, then immediate biochemical investigations including corrected serum calcium level will be performed and the results traced. If the results show serum hypocalcaemia (less than 2.0mmol/L) and patient is experiencing mild hypocalcaemic symptoms, a rescue dose of intravenous calcium gluconate (3g of intravenous calcium gluconate infusion over 4 hours) will be given as per current unit protocol. After completion of the rescue dose of calcium infusion, the serum calcium level will be repeated and further action will be taken based on the post-correction serum calcium level.

However, if the patient developed severe hypocalcaemia symptoms such as carpo-pedal spasm, bronchospasm/laryngospasm or cardiac manifestation, then an immediate biochemical investigation (corrected serum calcium level) will be obtained and an immediate rescue dose of intravenous calcium gluconate will be administered to the patient before the result are available. According to current unit protocol, if a patient developed severe hypocalcaemia symptoms, an immediate intravenous calcium slow bolus (1g of calcium gluconate) will be given over 20 minutes. This will be followed by intravenous calcium infusion (3g of intravenous calcium gluconate infusion over 4 hours) after biochemical confirmation of hypocalcaemia. After completion of the slow calcium bolus and calcium infusion, serum calcium levels will be repeated and further action will be determined based on the post-correction serum calcium level. The management of hypocalcaemic patients can be referred to **Appendix 3**. Both groups of patients will be followed-up until 48 hour post-operation. In the event of an emergency and there is a need to break the code, the clinician in charge of the patient will contact the principal investigator immediately to facilitate the rescue process.

In the endocrine surgery unit, the current practice is that all patients who had total thyroidectomy performed will be kept as an in-patient routinely for at least 48 hours so that their serum calcium levels can be monitored at the intervals mentioned above (6-hour, 12-hour, 24-hour, 36-hour & 48-hour). Therefore, this study will not incur an additional stay or prolonged admission.

Target Population

The target population is from the endocrine surgery clinic and UMMC ward. Target population consists of all patients scheduled for total thyroidectomy during the period of 1st June 2020 to 31st May 2022.

Sample Size

A pilot study will be conducted after obtaining approval from MREC (Medical Research Ethics Committee) UMMC. 10 patients will be recruited for the pilot study and randomized into 5 patients each arm. Sample size calculation will then be derived from the mean and standard deviation obtained from the pilot study.

Inclusion Criteria

-Age between 18-80 years old

-Scheduled for total thyroidectomy in UMMC

Exclusion Criteria

-Their age outside the range of 18-80

-Have parathyroid disorders or end stage renal failure

-On calcium or vitamin D supplements prior to surgery

-Have deranged calcium homeostasis pre-operatively (outside the normal range of 2.2-2.6 mmol/L)

-Scheduled for total thyroidectomy plus lymph node dissection

Withdrawal Criteria

Subjects can choose to withdraw at any time and withdrawn subjects will not be replaced.

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

The total research period is from October 2019 till February 2023. The first two months will be spent on literature review of the relevant papers and the next two months will be on preparation of the research proposal. Subsequently, the research proposal will be summited to MREC for approval.

After the proposal is approved by MREC, data collection will tentatively start from June 2020 till May 2022. Subsequently, data analysis will start from June 2022 till October 2022. Another two months will be spent on the final report writing and finally thesis presentation and submission on January to February 2023. (please refer to the Gantt chart)

Data Collection Tools and Techniques

As this is a prospective randomized controlled trial, relevant participants information and blood investigations 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 per-protocol analysis.

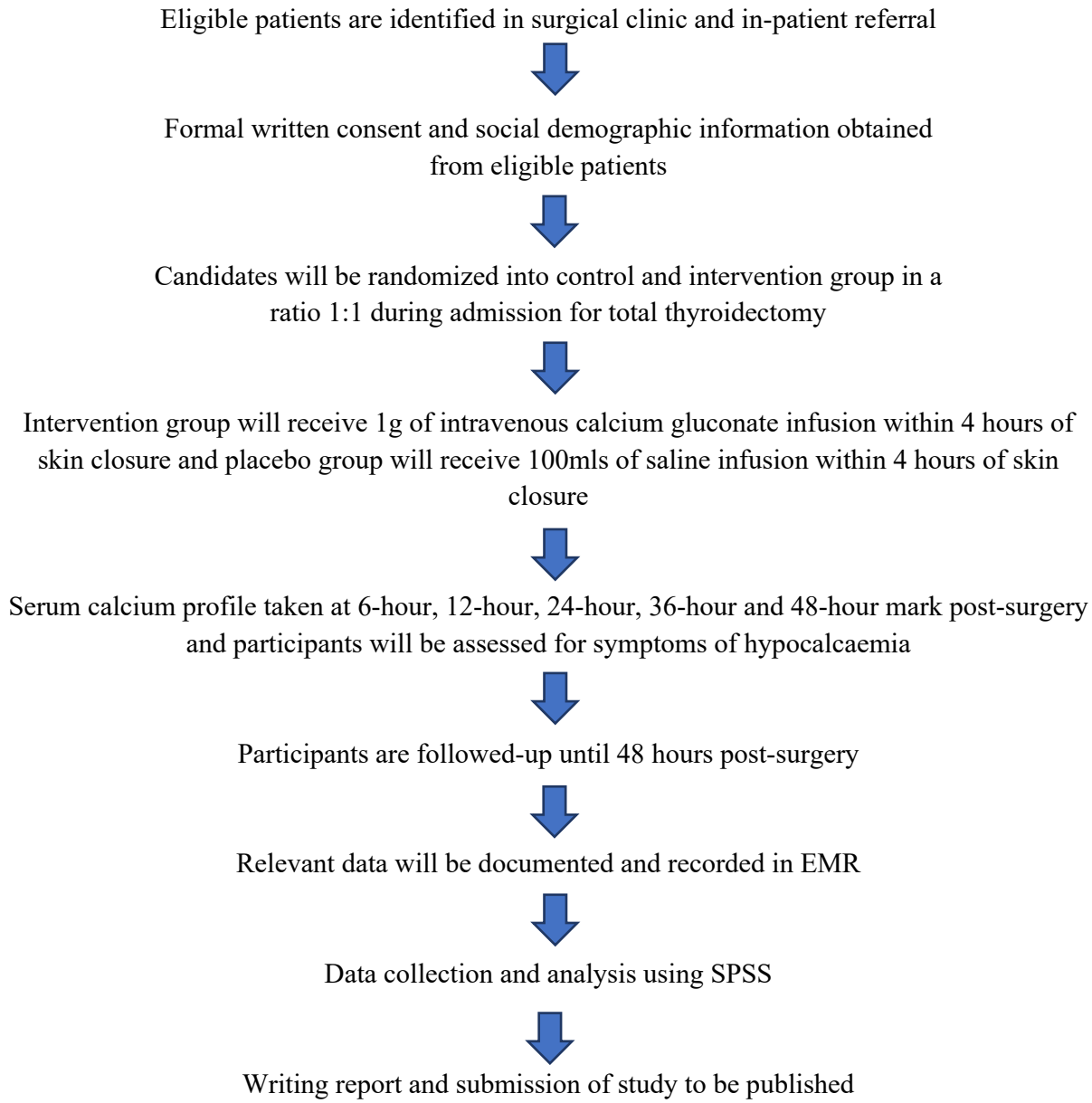
Risk and Benefit to Study Participants

The dose and infusion rate of calcium used in this study is within the safety limits proposed by the World Health Organization (WHO). The adverse effects of calcium infusion are rare and may range from mild to severe. Common adverse effects including nausea, vomiting, hypertension, flushing and local inflammation over the infusion site. Severe adverse effects such as heart block and slow heart rate may occur but are extremely rare with this regime and dosage of calcium infusion. All study participants will be placed on cardiac monitoring and administration will be discontinued if adverse effects supervene. None of the patients in the endocrine surgery unit, UMMC experienced

any adverse effect after receiving intravenous calcium gluconate in the year 2018 and 2019. Therefore, there is very minimal risk for subjects who choose to participate in this study.

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 treatment protocol/plan to reduce and prevent incidences of hypocalcaemia after total thyroidectomy.

Flow Chart



Ethical Consideration of Study

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 when they are admitted for surgery.

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. The expense for the cost of the investigational product will be borne by the principal investigator.

Gantt Chart

	OCT –NOV 2019	DEC 2019-JAN 2020	FEB-APRIL 2020	JUNE 2020-MAY 2022	JUNE-OCT 2022	NOV-DEC 2022	JAN-FEB 2023
LITERATURE REVIEW							
THESIS PROPOSAL							
ETHICS APPROVAL							
DATA COLLECTION							
DATA ANALYSIS							
REPORT WRITING							
THESIS SUBMISSION							

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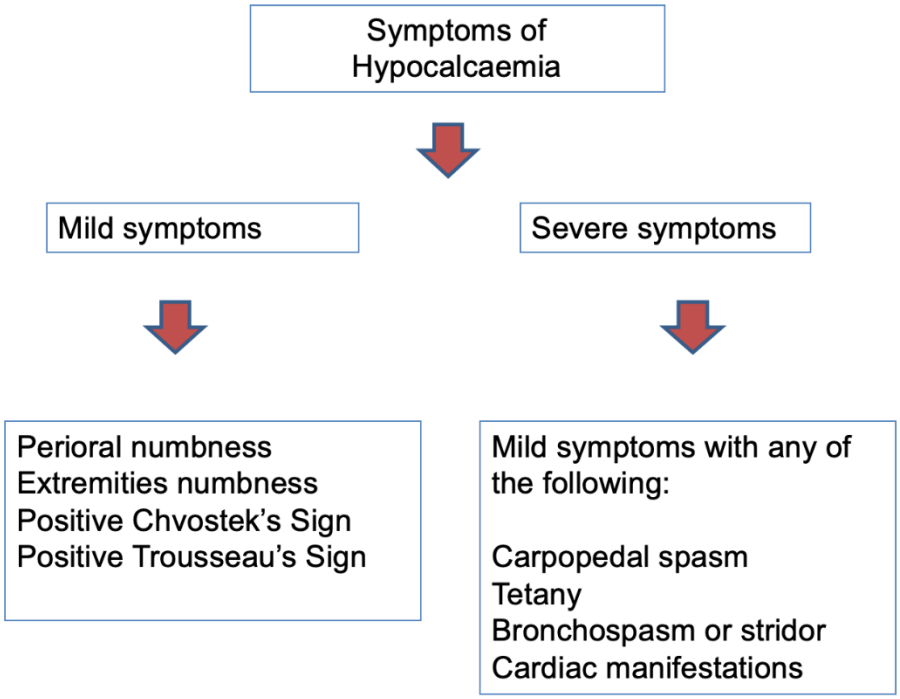
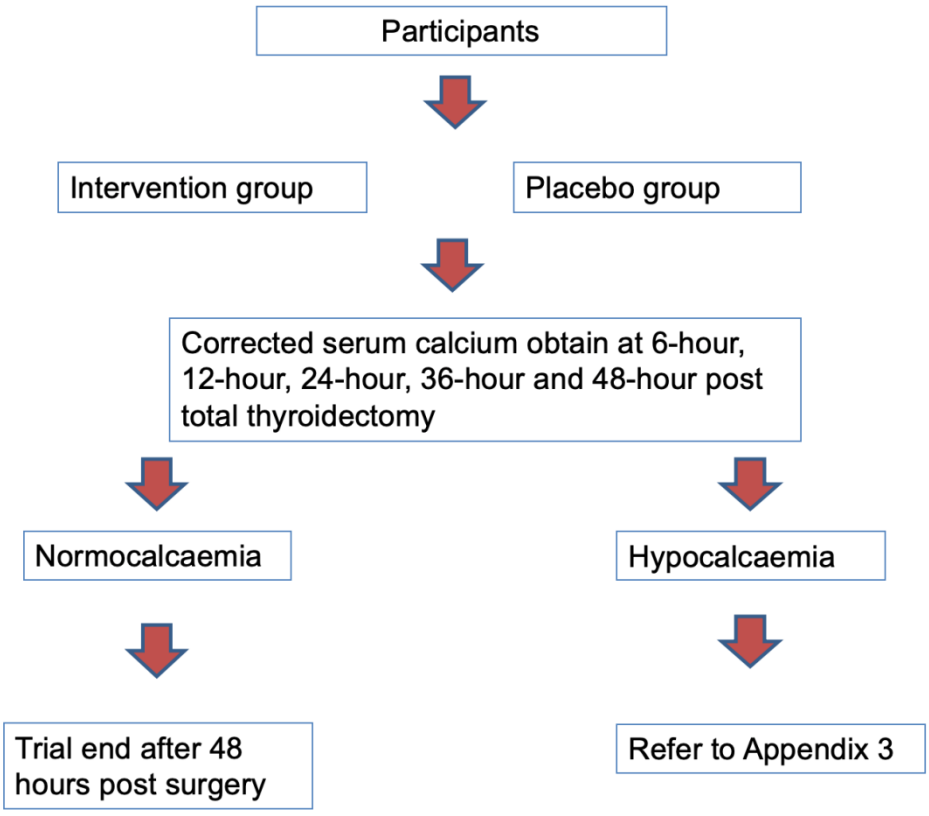
Appendix

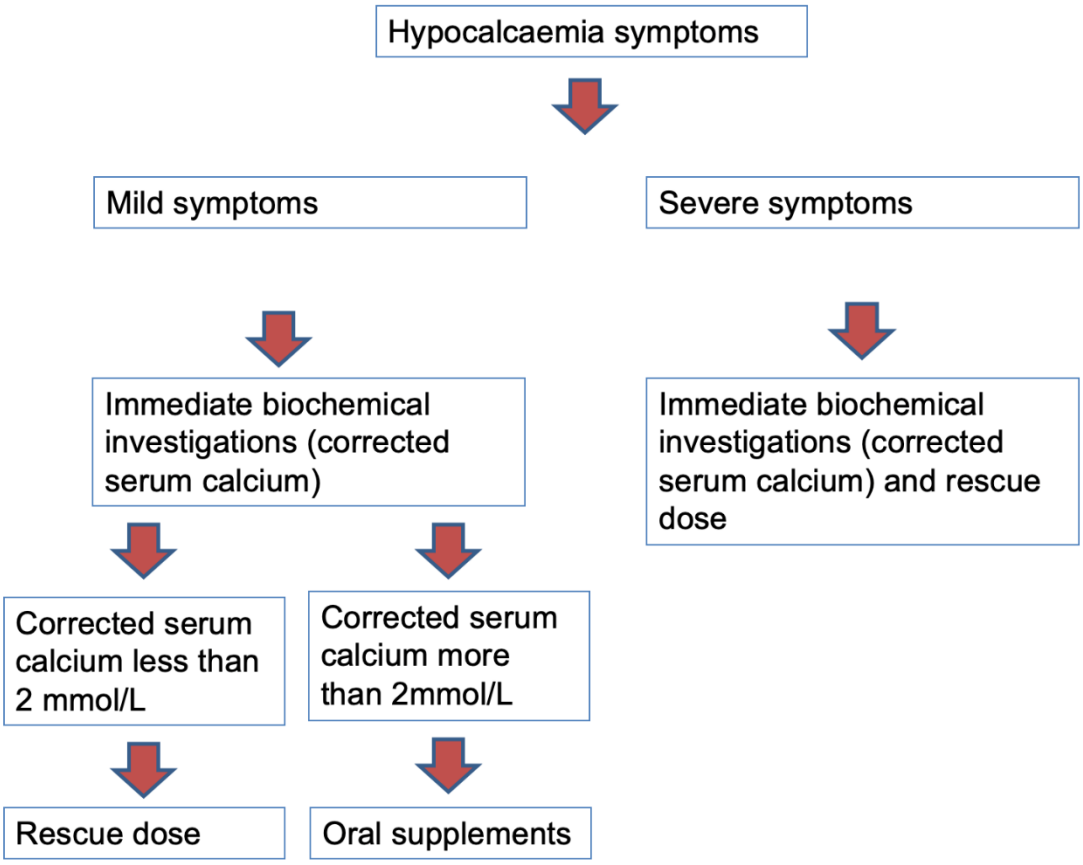
Appendix 1


Symptoms of Hypocalcaemia
Mild symptoms
Severe symptoms
Perioral numbness
Extremities numbness
Positive Chvostek's Sign
Positive Trousseau's Sign
Mild symptoms with any of the following:
Carpopedal spasm
Tetany
Bronchospasm or stridor
Cardiac manifestations

Appendix 2


Participants
Intervention group
Placebo group
Corrected serum calcium obtain at 6-hour, 12-hour, 24-hour, 36-hour and 48-hour post total thyroidectomy
Normocalcaemia
Hypocalcaemia
Trial end after 48 hours post surgery
Refer to Appendix 3

Appendix 3


Hypocalcaemia symptoms
Mild symptoms
Severe symptoms
Immediate biochemical investigations (corrected serum calcium)
Immediate biochemical investigations (corrected serum calcium) and rescue dose
Corrected serum calcium less than 2 mmol/L
Corrected serum calcium more than 2mmol/L
Rescue dose
Oral supplements