The influence of prophylactic Calcium- and Magnesium supplementation on postoperative hypocalcemia after total thyroidectomy: study protocol for a randomized controlled trial

Navid Tabriz
Carl von Ossietzky Universitat Oldenburg
Dennis Fried
Carl von Ossietzky Universitat Oldenburg
Verena Nicole Uslar (verena.uslar@uol.de)
Carl von Ossietzky Universitat Oldenburg https://orcid.org/0000-0003-3252-2076
Dirk Weyhe
Carl von Ossietzky Universitat Oldenburg

Study protocol

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Abstract

• **Background**

We want to investigate if a routine preoperative dietary supplementation of calcium and magnesium prior to thyroidectomy for nodular goiter and grave´s disease can influence patients' outcome with regards to hypocalcemia associated symptoms and quality of life in order to reduce the risk of post-thyroidectomy hypocalcemia and to improve patient`s quality of life.

• **Methods**

The study will be conducted as a two-armed randomized controlled trial with patients scheduled for total thyroidectomy. The patients assigned to the intervention group will receive calcium carbonate and magnesium oxide, and will begin the intake 2 weeks preoperatively. Primary outcome is the postoperative quality of life measured by using the ThyPRO-39 and EQ-5D questionnaires. Secondary outcome is the assessment of postoperative biochemical (calcium and PTH levels) and clinical hypocalcemia (symptoms as reported by the patient).

• **Discussion**

A prophylactic dietary substitution with calcium and magnesium, which could easily be done in the preoperative setting, could potentially help to avoid or reduce hypocalcemia-associated symptoms and improve quality of life. In the event of a positive outcome, this preoperative procedure can be an inexpensive way to prepare patients scheduled for thyroidectomy and can possibly reduce disease-specific costs by reducing the postoperative complication rate.

• **Trial registration**: DRKS00017195 in the German clinical trials register (Deutsches Register Klinischer Studien, DRKS) on the 22.05.2019.

Administrative Information

Note

the numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	**The influence of prophylactic Calcium- and Magnesium supplementation on postoperative hypocalcemia after total thyroidectomy - A monocenter prospective randomized controlled trial**
Trial registration {2a and 2b}.	DRKS00017195 in the German clinical trials register (Deutsches Register Klinischer Studien, DRKS)
Protocol version {3}	Version 3.0, 05.06.2018
Funding {4}	For laboratory examinations, financial support without further conditions was received from: handke medizintechnik gmbh Gottlieb-Daimler-Straße 11 30974 Wennigsen (Deister) Germany
Author details {5a}	Navid Tabriz, Dennis Fried, Verena Uslar, Dirk Weyhe All: University Hospital for Visceral Surgery, Carl von Ossietzky University Oldenburg
Name and contact information for the trial sponsor {5b}	Prof. Dr. Dirk Weyhe Universitätsklinik für Viszeralchirurgie, Pius-Hospital Oldenburg Georgstr. 12 26121 Oldenburg Deutschland Telephone: +49 (0)441 2291470 Email: dirk.weyhe at pius-hospital.de
Role of sponsor {5c}	This is a scientifically initiated study. As such, Dirk Weyhe initiated the study and provided infrastructure and was involved in study design. Also, he will be involved in the interpretation of data; writing of the report, and the decision to submit the report for publication. Funding was received from a third party (handke medizintechnik gmbh) in the form of financial support for additional laboratory examinations, without any further conditions.

Introduction

Background and rationale {6a}

Thyroid surgery is one of the most common surgeries worldwide [1]. Although the total number of thyroid surgeries has decreased in Germany in the last years, the proportion of total thyroidectomies is increasing [2]. Total thyroidectomy is performed, i.e., in case of malignancy, suspected bilobular or symptomatic goiter or grave
*sdisease. Hypocalcemiaiso ≠ ofthemostcommoncomplicationsofbilateralthyroe*sec*tionswithan ∈ cncewhichwlyran ≥ so*m0.3 → 49 % [3]. *S*

s quality of life [5, 6]. Therefore, serum calcium level is monitored in the early postoperative course. Despite this clinically accepted postoperative procedure, there is no generally accepted recommendation for the treatment of postoperative hypoparathyroidism. Recently, a meta-analysis has verified the effectiveness of calcium and vitamin D in the postoperative course of preventing hypocalcemia-associated symptoms but a routine supplementation could also lead to overtreatment in patients with normal serum calcium [7]. In a prospective study for thyroidectomy in grave´s disease a preoperative supplementation of 3 grams of calcium carbonate could reduce postoperative biochemical and symptomatic hypocalcemia [8]. This is the only study, which deals with a preventive preoperative calcium supplementation prior to total thyroidectomy.

Retrospective studies on the role of preoperative vitamin D level on early postoperative hypocalcemia reveal contradictory results. On the one hand, low preoperative vitamin D and low postoperative parathyroid hormone levels were seen as predictors for the development of hypocalcemia [9, 10]. On the other hand, these biochemical parameters could not be detected as a risk factor in other studies [11, 12].

There is evidence that thyroidectomy can cause significant hypomagnesaemia, which may correlate with the development of hypocalcemia [13-15]. Therefore, in the postoperative monitoring after thyroidectomy, the control of both, serum calcium and magnesium are recommended.

Objectives {7}

We want to investigate if a routine preoperative dietary supplementation of calcium and magnesium prior to surgery can influence patients' outcome with regard to hypocalcemia associated symptoms and quality of life in order to reduce the risk of post-thyroidectomy hypocalcemia and to improve patient`s quality of life. This could potentially reduce hospital stay and medical expenses. Therefore, the primary aim of this study is the assessment of the role of preoperative calcium and magnesium substitution on postoperative quality of life measured by the ThyPRO-39 and EQ-5D questionnaire.

The secondary aim is the assessment of the mentioned supplementation on postoperative biochemical and clinical hypocalcemia.

Trial design {8}

We propose a prospective randomized controlled intervention study with a postoperative follow up of 6 weeks (see Figure 1).

Methods: Participants, Interventions And Outcomes

Study setting {9}

The study is conducted in a monocentric setting at a DGAV certified center for thyroid and parathyroid surgery in a German university hospital for visceral surgery.

Eligibility criteria {10}

The study population will consist of adult patients (> 18 years) scheduled for total thyroidectomy due to symptomatic bilobular goiter, grave`s disease or suspected or proven malignancy.

Exclusion criteria are lack of written consent, inability to communicate in the German language, medication with thiazide diuretics, digitalis or lithium therapy, previous neck operation or radiation, preexisting hyperparathyroidism, or chronic kidney failure.

Individual criteria for discontinuation include withdrawal of patient´s consent, and necessity of following central or lateral neck dissection due to malignancy.

Who will take informed consent? {26a}

Informed consent will be obtained and validated using both the physician*s*$(De \cap isFried \text{ or } \in |e|nceNavabriz)$ and *patient*s signatures.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Participation is voluntary, and patients can quit the trail at any time without disclosure of their motives for withdrawal and without fear of subsequently receiving poor medical care. In the case of withdrawal, relevant data will be deleted if desired by the patient. Patient names and all other confidential information are subject of medical confidentiality under the German Data Protection Act. Transmission of data will be done in an encrypted format. Others not involved in the trial will have no access to original documents. This study will be carried out in accordance with the Helsinki Declaration in its current version. The Commission for Impact Assessment Research and Ethics, Carl von Ossietzky University, Oldenburg, Germany has approved its protocol (No. 2017-105).

Interventions

Explanation for the choice of comparators {6b}

A group of patients will receive nutritional supplementation in the form of calcium carbonate and magnesium oxide, and will begin the intake 2 weeks
[illegible] group without nutritional supplements. This should allow for enough time to build up a significantly higher

calcium and magnesium level in patients receiving the supplement as compared to the group without supplements.

Intervention description {11a}
The patients assigned to the intervention group will receive calcium carbonate 3 x 500mg/d (Calcium Sandoz® 500mg, Hexal) and magnesium oxide 1 x 375mg/d (Magnetrans® 375mg, StadaVital), and will begin the intake 2 weeks preoperatively.

Criteria for discontinuing or modifying allocated interventions {11b}

One week after the start of the supplementation the patients will be contacted by phone to evaluate their well-being and exclude any side effects. If patients report any side effects to the intervention (e.g., diarrhea), patients may reduce or stop the intake.

Strategies to improve adherence to interventions {11c}

The planned phone call should improve adherence.

Relevant concomitant care permitted or prohibited during the trial {11d}

Not applicable.

Provisions for post-trial care {30}

Since the amount of supplementation is within the range for recommended uptake of calcium and magnesium, no harm from trial participation is expected. However, at any time patients may contact the involved physicians.

Outcomes {12}

Primary outcome is the postoperative quality of life measured using the ThyPRO-39 and EQ-5D questionnaires.

Secondary outcome is the assessment of postoperative biochemical (calcium and parathormone (PTH) levels) and clinical hypocalcemia (symptoms as reported by the patient).

Participant timeline {13}

After checking the necessity for total thyroidectomy and obtaining informed consent, the patient`s quality of life will be assessed by the health-related EQ-5D-5L and the disease-specific questionnaire ThyPRO-39 (see Figure 1). Laboratory tests for thyrotropin (TSH), free triiodothyronine (fT3), free tetraiodothyronine (fT4), calcium, magnesium, phosphate, albumin, 25-OH vitamin D3, PTH, alkaline phosphatase (AP) will be performed. Biometric patients´ data (age, weight, size, body mass index) and the results of the ultrasound thyroid exam will be recorded.

Patients assigned to the intervention group will be supplemented with calcium carbonate 3 x 500mg/d (Calcium Sandoz® 500mg, Hexal) and magnesium oxide 1 x 375mg/d (Magnetrans® 375mg, StadaVital), and will begin the intake 2 weeks preoperatively. One week after the start of the supplementation the patients will be contacted by phone to evaluate their well-being and exclude any side effects.

One day before the scheduled operation both questionnaires will be filled out again and PTH, calcium and magnesium will be determined.

Thyroidectomy is by default performed under intraoperative neuromonitoring of the recurrent laryngeal nerves. Intraoperatively, the macroscopic view of the parathyroid glands and description of structure and blood flow are required. If the lower parathyroid glands are not in loco typico, an explicit representation is not necessary.

4-6h after the operation the PTH level will be checked and all patients will be routinely monitored on the intermediate care unit overnight. Dependent on the measured PTH level (norm 15-65pg/ml) calcium with or without Alfacalcidol (Einsalpha®, LEO) will be substituted regardless of group affiliation (table 1) and serum calcium will be determined on first or second postoperative day.

Table 1: Postoperative procedure dependent on 4-6h PTH levels

	PTH<15pg/ml	PTH 15-30pg/ml	PTH 30-65pg/ml	PTH>65pg/ml
Alphacalcidol	0,5µg 2xd	-	-	-
Calcium carbonate	2x1g	2x1g	as required 1g	as required 1g
Magnesium oxide	2x375mg	375mg	-	-

Before patient's discharge EQ-5D-5L and ThyPRO-39 will be completed for a third time.

Six weeks postoperatively laboratory examinations for TSH, fT3, fT4, calcium, magnesium, phosphate, albumin, 25-OH vitamin D3, PTH, AP and both questionnaires will be carried out during a clinical visit 6 weeks after surgery. In case of PTH<15pg/ml the laboratory exams will be repeated after 6 months to determine a potential persistent hypoparathyroidism.

Sample size {14}

We aim for a patient population of 80 male and female adults. This corresponds to a usually meaningful order of magnitude for studies on quality of life. Due to the exploratory nature of the study and the lack of comparative data, no prospective study power calculation is possible. The power calculation takes place retrospectively. The p-value by Fisher is used as a measure of the quality of the evidence.

Recruitment {15}

All patients scheduled for thyroidectomy at our hospital will be asked to participate in this trial. Since about 100 patients are surgically treated by thyroidectomy in our hospital per year, we expect to recruit the 80 patients in about 18-24 months.

Assignment of interventions: allocation

Sequence generation {16a}

A block randomization with a block length of 6 will be applied. The randomization script is written in Matlab by an uninvolved researcher.

Concealment mechanism {16b}

Numbered envelopes containing the assigned group will be prepared and opened by the investigator or an assigned study nurse in front of the patient.

Implementation {16c}

The allocation sequence will be generated by Verena Uslar. Patients will be enrolled by Dennis Fried, or Navid Tabriz in his absence. They will also assign participants to interventions as described above.

Assignment of interventions: Blinding

Who will be blinded {17a}

Blinding is not possible, since the physicians and or study nurses responsible for data collection need to be aware of the treatment arm in order to assess any side effects.

Procedure for unblinding if needed {17b}

Not applicable.

Data collection and management

Plans for assessment and collection of outcomes {18a}

The physicians and study assistants responsible for data collection will collect all data on paper and in an Excel spreadsheet.

Plans to promote participant retention and complete follow-up {18b}

As all important outcome variables are collected during the hospital stay, it is expected that there will be an almost complete follow-up. This will be additionally ensured by the study team informing themselves daily about discharge of study patients and contacting the patients to be discharged in time to obtain any missing data. In case of patients wish to terminate their participation in the study before the end of the last follow-up appointment, they will be asked whether we may at least use all data relevant to the study from the hospital information system.

Data management {19}

All data will be entered into an excel spreadsheet by only two different persons (Dennis Fried and the responsible study nurse). A codebook is available to ensure correct data entry. The data will be checked for plausibility and completeness by an independent third person.

Confidentiality {27}

All documents (both paper and electronic) are accessible only to study staff. Electronic documents are password protected. A coding list is created in which patients are entered as soon as they agree to participate. This coding list contains the patients' real names and contact details, as well as a unique random study number. The Excel spreadsheet in which the study data is entered only contains the corresponding study number. After the evaluation is completed, the coding list is deleted, so that only the Excel spreadsheet with the anonymous data is available. This Excel spreadsheet will be stored for 10 years with a password in accordance with the recommendations for good clinical and scientific practice. After this period, this list will also be deleted.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical evaluation will be performed by means of analysis of variance for repeated measures and chi-square test for categorical variables. In the case of non-parametric distribution of the variables, a comparison will be performed according to Kruskal-Wallis. EQ-5D-5L- and ThyPRO-39 will be analyzed according to the recommendations. Due to the exploratory nature of the study and the lack of comparative data, no prospective study power calculation is possible. The number of participants therefore depends on the number of subjects normally used for validation studies of questionnaires. The power calculation will be performed retrospectively. The p- by Fisher value is used as a measure of the quality of the evidence.

Interim analyses {21b}

No interim analysis is planned.

Methods for additional analyses (e.g. subgroup analyses) {20b}

As the patho-mechanism of nodular goiter and grave´s disease differ, a subgroup analyses for these two diseases will be performed.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Patients in the intervention group who for some reason did not undergo the intervention are excluded from the analysis. Missing values will be handled using multiple imputation.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

All data will be made available upon reasonable request to the corresponding author.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The trial steering committee will be comprised of Navid Tabriz, Verena Uslar, and Dirk Weyhe. Navid Tabriz will be the coordinating physician, Verena Uslar will be the scientific member, responsible for data completeness and plausibility, and Dirk Weyhe functions as the sponsor of this study. In addition. Dennis Fried is responsible for data collection and entry. He will receive support from a study nurse of our hospital.

Composition of the data monitoring committee, its role and reporting structure {21a}

The study is initiated by the involved scientist, with Dirk Weyhe as the sponsor. There are no competing interests, although an amount of 3000€ was provided by handke medizintechnik gmbh for additional laboratory examinations in the follow-up period

Adverse event reporting and harms {22}

If any adverse event occurs, it will be reported to the medical ethic committee of the Carl von Ossietzky University Oldenburg.

Frequency and plans for auditing trial conduct {23}

The auditing will take place on a monthly basis in the form of discussions with the entire study team. Further meetings will be held if necessary.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

If the audits reveal that changes to the study protocol are necessary, these will be submitted to the Ethics Committee. Also, changes in protocol will be entered in the DRKS trial registration system. Participants will be informed if necessary.

Dissemination plans {31a}

Results will be published in a medical journal.

Discussion

Postoperative hypocalcemia as a potential signal for disturbed blood flow of the parathyroid glands can influence patients´ outcome, prolong hospital stay and increase treatment cost. Currently, in case of total thyroidectomy serum calcium concentration and PTH levels are monitored postoperatively followed by needs-based calcium and vitamin D substitution. Through this regime, transient hypocalcemia can be adequately treated in most cases. In grave´s disease, it is well known that patients have much higher rates of symptomatic hypocalcemia after total thyroidectomy than in other diagnosis due to, i.e., “hungry bone syndrome” or increased inflammation of the gland making the operation technically more demanding with increased risk of disturbance of blood supply of the parathyroid glands [16–18]. Therefore, different thyroid disease entities such as grave´s disease or nodular goiter, that all can be treated by total thyroidectomy, should be analyzed separately.

Nevertheless, a prophylactic dietary substitution with calcium and magnesium, which could easily be done in the preoperative setting, could potentially help to avoid or reduce hypocalcemia-associated symptoms and improve quality of life. We have no data concerning the duration of the preoperative substitution, so we have pragmatically used the data of Oltmann et al. [8]. Even the amount of calcium and magnesium to be administered can be discussed. We decide to

prescribe 1500 mg calcium and 375 mg magnesium that can be given to the patients safely, as potential side effects are rare and associated with much higher doses, according to the EFSA-recommendations [19, 20].

This preoperative procedure can be a potential way to prepare patients scheduled for thyroidectomy and can possibly reduce disease-specific costs and improve patient's quality of life.

Trial Status

This study protocol corresponds to version 3.0, which has been positively reviewed by the Medical Ethics Committee (No. 2017 – 105). Recruitment started on 19.03.2019 and will be probably completed in July of 2021. Currently 35 of the targeted 80 patients are recruited. The trial was registered with the DRKS (Deutsches Register Klinischer Studien; German Clinical Trials Registry) on 22.05.2019.

Abbreviations

AP	alkaline phosphatase
DGAV	Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie
DRKS	Deutsches Register Klinischer Studien (German Clinical Trial Register)
EFSA	European Food Safety Authority
EQ-5D-5L	health-related quality of life questionnaire
fT3	free triiodothyronine
fT4	free tetraiodothyronine
PTH	parathormone
ThyPRO-39	disease-specific quality of life questionnaire.
TSH	thyrotropin

Declarations

Acknowledgements

We thank handke medizintechnik gmbh for financial support.

Authors' contributions {31b}

NT is the principal investigator and developed the study design and wrote the first draft of the manuscript

DF will be mainly responsible for data collection and contributed to the study design, the ethics proposal, and revision of this manuscript.

VU was responsible for the scientific evaluation of the study design, development of the statistic analysis plan, and wrote the respective parts of this manuscript.

DW is sponsor of this study and contributed to the study design and revised the manuscript.

Funding {4}

Funding was received in the form of financial support (3000€) from handke medizintechnik gmbh. Handke medizintechnik gmbh was in no way involved in the design of the study and writing of this manuscript, and will not be involved in collection, analysis, and interpretation of data and in writing the publication after finalization of this study.

Availability of data and materials {29}

The final, anonymized trial dataset will be available upon reasonable request to the corresponding author.

Ethics approval and consent to participate {24}

This study is approved by the Medical Ethic Committee of the Carl von Ossietzky University Oldenburg (No.: 2017-105). Informed consent will be obtained from all study participants.

Consent for publication {32}

Not applicable

Competing interests {28}

The authors declare that they have no competing interests.

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Figures

	STUDY PERIOD						
	Enrolment	Post-allocation					Close-out
TIMEPOINT	*Indication for surgery*	*2w prior to surg*	*1w prior to surg*	*1d prior to surg*	*4-6h after surg*	*Before dis-charge*	*6w after surg*
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation	X						
INTERVENTIONS:							
Mg and Ca supplementation*		X ←	X	X →	X	X	X
No supplementation		X	X	X	X	X	X
ASSESSMENTS:							
TSH, fT3, fT4, 25-OHVit. D, AP, Mg, Ph, Albumin	X			X			X
PTH	X			X	X		X
ThyPRO-39 & EQ-5D-5L questionnaires & Ca	X			X		X	X
Age, weight, size and results of the ultrasound thyroid exam	X						X
Phonecall about well-being and side effects			X				

* 500 mg Calcium 3x daily & 375 mg Magnesium 1x daily

Figure 1

Schedule of enrolment, interventions, and assessments according to SPIRIT statement