Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults (Protocol)

Kreidieh OI, Ahmadieh H, Akl EA, El-Hajj Fuleihan G

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*Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults (Protocol)*

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Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of minimally invasive parathyroidectomy guided by preoperative imaging and intraoperative parathyroid hormone monitoring (IOPTH) versus bilateral neck exploration for the surgical management of primary hyperparathyroidism.

BACKGROUND

Description of the condition

Primary hyperparathyroidism (PHP) is a common disorder of bone metabolism and hypercalcemia, occurring in 28 per 100,000 individuals yearly in the United States (Ning 2009), and in up to 2% of postmenopausal women. The most common etiology for the disease is a single gland adenoma in 80% to 85% of cases, with the rest of the cases constituting multiple gland hyperplasia (10% to 15%), double adenomas (2% to 5%) and carcinoma (1%). The molecular basis for sporadic hyperparathyroidism remains largely unknown. In some cases, it includes mutations in several proto-oncogenes and tumor suppressor genes, such as cyclin D1 and MEN1, that stimulate parathyroid gland growth, and as a result increase parathyroid hormone (PTH) secretion (Pyram 2011). Since the development of adequate screening techniques, the disorder has evolved in developed countries into a mostly asymptomatic disease, often picked up as a laboratory abnormality, hypercalcemia, incidentally discovered via routine examinations.
Conversely, in developing countries, classical presentations prevail including bone pain, nephrolithiasis, nephrocalcinosis, bone loss, increased fractures, and osteitis fibrosa cystica (Bilezikian 2000; Parfitt 1991). Skeletal effects seen through changes in bone mineral density (BMD) and histomorphometric analysis were originally thought to be most prominent at cortical bony sites. However, newer studies have noted volumetric BMD loss at both sites (Chen 2003) and an increased fracture risk in both traditional cortical bony areas, such as the distal radius, as well as trabecular bony areas like the vertebral bodies (Khosla 2002). Renal calcification or stones appear to be increased up to four-fold in patients with PHP compared to controls (Starup-Linde 2012; Suh 2008). Non-classical manifestations of PHP include impaired concentration, decreased non-verbal learning process, difficulties in using direct memory, verbal fluency and visual constructive abilities (Babinska 2012).

**Description of the intervention**

In general, while surgery for hyperparathyroidism in the setting of chronic kidney disease often involves subtotal parathyroidectomy or total parathyroidectomy with autotransplantation (Al-Rawashdeh 2012), surgery for primary hyperparathyroidism aims to resect the diseased gland(s) and, therefore, remove the source for excess PTH production; the ultimate goal is to thus decrease the incidence of nephrolithiasis, improve bone mineral density, decrease fractures, and improve quality of life. Even in asymptomatic individuals, there is evidence that surgery improves BMD, functional capacity and quality of life (Ramakant 2012). Therefore, surgery is indicated for all patients with symptomatic PHP, and some patients with asymptomatic PHP presenting with either a serum calcium concentration of 1.0 mg/dl or more above the upper limit of normal, creatinine clearance equal to or less than 60 ml/min, a bone density at any site with a T-score less than -2.5, or age less than 50 years (Bilezikian 2009). The T-score is a person’s bone density compared with what is normally expected in a healthy young adult of the same sex. The T-score is the number of units (standard deviations) that this person’s bone density is above or below the average.

**Bilateral neck exploration**

Bilateral neck exploration is the traditional approach to primary sporadic hyperparathyroidism. While minimally invasive parathyroidectomy has largely replaced such an approach, bilateral neck exploration remains the mainstay treatment for patients with un-localized pathology, familial or hereditary cases, or concomitant thyroid disease. The exploration is done via direct visualization of all parathyroid glands, and may be performed under local or general anesthesia, through an open traditional incision, minimally invasive incision, or even via a videoscopic approach (Alesina 2011; Allendorf 2007; Lo 1999; Lowney 2000).

**Minimally invasive parathyroidectomy (MIP)**

We will use the 2002 summary statement on asymptomatic hyperparathyroidism definition for MIP, mainly that it is a set of techniques employing preoperative imaging and intraoperative parathyroid hormone assays (IOPTH) to limit surgical visualization only to the suspected gland (Bilezikian 2002). There are currently several variations for techniques satisfying these criteria. In general, focused parathyroidectomy aims towards visualization of just the suspected gland, whereas unilateral exploration visualizes the entire side suspected to have a pathology. Exploration is either open or endoscopic. Two common endoscopic techniques are described in the literature, and offer advantages of magnified vision and tactile control over the procedure (Gracie 2012; Henry 1999; Miccoli 1999). The technique suggested by Henry et al uses a more lateral approach avoiding dissection of the strap muscles and allowing possible direct visualization of the adenoma but compromises through the frequent requirement of carbon dioxide insufflation in order to maintain an adequate working space. The technique suggested by Miccoli et al on the other hand suggests a more medial approach wherein gas insufflation is only maintained for a few minutes in order to allow for dissection of the strap muscles, after which a working space is maintained simply by the use of external retraction. This ‘gasless approach’ promised to avoid emphysema, pneumomediastinum, and neck swelling (Henry 1999; Miccoli 1999). Despite the nuances of slight differences in technique, the fundamental methods of all MIP are the same. Single gland disease is identified and localized by use of either preoperative ultrasound, Sestamibi scan (technetium (99m-Tc) nuclear medicine imaging), or both. A limited exploration then targets the suspicious side or gland in an attempt to avoid a cumbersome full neck exploration (Irvin 1991; Irvin 1994; Udelsman 2004). Intraoperative PTH (IOPTH) monitoring is carried out generally through peripheral venous measurements, with pre-incision, pre-gland ligation, and 5,10, and 20 minutes post-gland ligation measurements being drawn. Criteria used for evidence of adequate incision, and thus termination of surgery, vary widely. The most accepted, the Miami criterion, considers a decrease in PTH measurement by more than 50% from the highest baseline to the 10 minutes value post-gland ligation as evidence for adequate gland excision (Barczynski 2009; Carneiro-pla 2009; Irvin 1993). In the event of inadequate decline using this criterion, surgery is then converted to a bilateral conventional technique, possibly due to location of abnormal gland on the opposite side or due to suspicion of multiglandular disease. MIP techniques are usually offered to patients with preoperative localization studies suggestive of single gland disease, in the absence of thyroid pathology, familial or hereditary hyperparathyroidism, and of lithium intake.

**Adverse effects of the intervention**

Apart from a theoretical concern for possibilities of subcutaneous emphysema following gas insufflation in the endoscopic technique
described by Henry et al (Henry 1999), both bilateral neck exploration and MIP have essentially similar adverse events, which are rare for both. These include anesthesia-related or postoperative complications, or both, such as hypocalcemia, vocal cord paralysis, hematomas, and infections. A retrospective review of 656 parathyroid operations showed a 3% complication rate for bilateral neck exploration and a 1.2% complication rate for MIP (Udelsman 2002). Hematomas are potentially life threatening complications arising in 0.3% of surgeries, and may present with a variety of symptoms including neck pain, respiratory distress, dysphagia and wound drainage (Burkey 2001; Carty 2004). Hypoparathyroidism is commonly transient and presents with decreased calcium concentration in association with either mild symptoms of tingling or numbness, or more severe symptoms like profound fatigue or carpopedal spasm. Severe hypocalcemia is rare unless after subtotal parathyroidectomy (Carty 2004). Such presentations are only transient and permanent hypoparathyroidism occurred in only 0.3% of 380 operations reviewed by Carty et al (Carty 2002). Similarly, permanent recurrent laryngeal nerve injury is very rare. In recent reports, 0.2% of 1112 patients, and 3 of 401 bilaterally explored patients had permanent recurrent laryngeal nerve injury (Allendorf 2007; Udelsman 2002) whereas 0.3% of 380 patients and 1 of 255 patients receiving a minimally invasive surgery had similar injury (Carty 2002; Udelsman 2002). Differences in the incidence of adverse effects between MIP and bilateral neck exploration are controversial and randomized controlled trials (RCT) have differing findings. Apart from scar length differences, Slepavicius et al did not report any significant differences in adverse events between intervention groups, Miccoli et al noted insignificant differences in one study and did not have any adverse events in either group in another, while Bergenfelz et al noted a greater incidence of severe hypocalcemia in the bilateral group (10% versus 0%) (Bergenfelz 2005; Miccoli 1999; Miccoli 2008; Rulli 2007; Slepavicius 2008).

**How the intervention might work**

The theoretical basis behind MIP is that most cases are caused by single gland pathology, and that modern tools can identify such pathology with acceptable accuracy, rendering the need for complete visualization of both sides of the neck almost obsolete. This may also decrease operative time and cost, although this has been debatable (Bergenfelz 2002; Miccoli 1999). Indeed, more than 80% of spontaneous primary hyperparathyroidism is caused by a single solitary adenoma (Kunstman 2012). Improvements in imaging techniques have reached sensitivities between 71% to 80% for ultrasound imaging and a sensitivity greater than 90% for Sestamibi scanning (Dijkstra 2002). The advent of intraoperative PTH monitoring assays have optimized the accuracy of adequate resection, reaching accuracy greater than 96% for the Miami criterion (Barczynski 2009; Carneiro 2003), and ensured the success of MIP for most surgeons. Indeed, by 2008, 68% of American surgeons were found to be practicing limited exploration techniques and only 10% practiced bilateral neck exploration exclusively (Greene 2009).

**Why it is important to do this review**

The importance of our review stems from the large number of patients undergoing these procedures yearly, without a definitive answer about the long-term success of MIP. The greatest uncertainty in this subject stems from concerns about increased long-term recurrence or missed multi-glandular disease in patients undergoing MIP. We are aware of only one RCT that had an extended follow-up for five years postoperatively. The investigators noted 4/47 recurrent cases in the MIP group compared to 2/44 in the conventional exploration group, with these results being statistically nonsignificant (Westerdahl 2007). Notably, 75% of patients in the MIP group who recur had converted from MIP to bilateral neck exploration. A recent retrospective analysis by a high volume group found that the long-term failure rate of the unilateral approach was 11 times higher than that of conventional bilateral surgery. However, that group is known for not using IOPTH monitoring (Norman 2012). Another group noted a higher than 8% recurrence rate after eight years of follow-up in patients undergoing MIP as opposed to 0% in the open parathyroidectomy group (Schneider 2012). The differences were not significant because of the small number of patients followed up for this duration. Identifying further publications with long-term follow-up may either quell concerns, re-ignite them, or highlight the urgent need for long-term outcome studies.

The review will help characterize the respective risks and benefits of each type of surgery more clearly, both in the short term and longer term. Few RCTs have been published on this topic, often with differing conclusions, as was demonstrated in the adverse events section. A properly conducted systematic review and meta-analysis will provide an objective risk-benefit assessment for both techniques, on prespecified patient outcomes, in the short term as well as at long-term follow-up. This will serve to empower patients and doctors alike in making better educated choices.

Furthermore, we only identified one recent systematic review comparing both approaches on the topic (Gracie 2012). The above mentioned review had several limitations: amongst other things it excluded unilateral exploration. We also find the above-mentioned review to be deficient in key criteria reflecting methodological quality. On AMSTAR (Shea 2007), a validated tool used for assessing methodological quality of systematic reviews, the previous review scored only two out of a possible 11 queries positively. Inclusion and exclusion criteria were provided in a table format but the type of studies, languages, and publication status (grey literature) were not discussed. The methods of study selection and data abstraction were also not entirely clear and there was no indication of whether these processes occurred in duplicate. While the search study was presented in the paper, the initial results, excluded...
studies, and reasons for exclusions were not presented. There was no meta-analysis done for any of the outcomes of interest. There was also no attempt made to assess risk of bias in included studies. The review also did not address what we feel is the greatest source of uncertainty in the topic, that is, long-term success rate. We believe that inclusion of this outcome is extremely important in order to truly gauge the long-term impact of potentially leaving residual enlarged tissue in patients who undergo minimally invasive techniques relying on localization studies and IOPTH monitoring. Our discussion will aim to highlight such long-term studies for specific analysis and discussion of the level of evidence we have about long-term outcomes.

OBJECTIVES

To assess the effects of minimally invasive parathyroidectomy guided by preoperative imaging and intraoperative parathyroid hormone monitoring (IOPTH) versus bilateral neck exploration for the surgical management of primary hyperparathyroidism.

METHODS

Criteria for considering studies for this review

Types of studies
Randomized controlled clinical trials (RCTs).

Types of participants
We will limit participants of interest to adults with primary hyperparathyroidism and without renal failure presenting for first time parathyroidectomy. We will exclude studies of the following patients.
- Those undergoing repeat surgeries.
- Those with secondary hyperparathyroidism.
- Those with tertiary hyperparathyroidism.
- Those with parathyroid carcinoma.
- Those with increased risk of multi-glandular disease (i.e. pediatric patients or those with genetic predispositions to have hyperparathyroidism like multiple endocrine neoplasia patients).
- Those with different types of hyperparathyroidism with no separate reporting of results by type.
- Those with elevated mean creatinine at entry into study.

Types of interventions

Intervention
- Minimally invasive parathyroidectomy (open unilateral parathyroidectomy) guided by intraoperative PTH hormone monitoring (IOPTH) and preoperative imaging.
- Minimally invasive parathyroidectomy (open focused parathyroidectomy) guided by IOPTH and preoperative imaging.
- Minimally invasive parathyroidectomy (endoscopic unilateral parathyroidectomy) guided by IOPTH and preoperative imaging.
- Minimally invasive parathyroidectomy (endoscopic focused parathyroidectomy) guided by IOPTH and preoperative imaging.

Comparator
- Bilateral neck exploration regardless of use of and results of any operative adjuncts.

Preoperative imaging
Localization may be done prior to or after randomization. We will accept either case, but will downgrade studies with localization procedures done prior to randomization due to indirectness because patients receiving bilateral neck exploration in the general population do not routinely receive preoperative imaging. We will accept imaging results as suggestive of single gland disease, suggestive of multiple gland disease, and inconclusive as determined by an expert radiologist or the surgeon and reported in the paper. Accepted procedures include at least one or more of the following during the localization protocol.

Diagnostic criteria for considered conditions

Hyperparathyroidism (Bilezikian 2002)
- Elevated or inappropriately normal parathyroid hormone (PTH) with serum calcium above normal reference levels.
- Elevated serum PTH with normal calcium levels and exclusion of secondary causes for elevation of PTH (mainly decreased calcium intake, vitamin D deficiency, renal insufficiency, hypercalciuria of renal origin).

Sporadic primary hyperparathyroidism
- Primary hyperparathyroidism.
- Exclusion of secondary causes like renal insufficiency, vitamin D deficiency, and familial hyperparathyroidism.
• Ultrasound imaging using a 5 MHz, 7.5 MHz or 10 MHz transducer.
• Technetium 99m Sestamibi scanning using single isotope dual phase scan, dual isotope subtraction scan, and three dimensional SPECT imaging scan.
• Thallium technetium scanning.

Intraoperative parathyroid hormone monitoring
We will accept use of a second or third generation rapid PTH assay intraoperatively for confirmation of adequate gland resection, per a commonly accepted criterion, such as the Miami criterion, of a fall in serum PTH of 50% at 10 minutes post-gland excision from the higher of either a pre-skin incision baseline or a pre-gland excision baseline.

Types of outcome measures

Primary outcomes
• Success rate.
• Total incidence of perioperative adverse events.

Secondary outcomes
• Specific adverse events.
• Conversion rate from minimally invasive to open procedure.
• Postoperative increase in PTH with eucalcemia.
• All-cause mortality.
• Health-related quality of life.
• Cosmetic satisfaction.
• Bone fracture rate.
• Nephrolithiasis rate.
• Absence from work.
• Duration of surgery.
• Length of hospital stay.
• Economic costs.

Method and timing of outcome measurement
• Success rate: defined as eucalcemia; we define short-term success rate as within six months of surgery, medium-term success rate as between more than six months and five years, and long-term success rate as at five years or more after surgery.
• Total incidence of perioperative adverse events: defined as adverse events occurring within 48 hours of surgery.
• Specific adverse events:
  o bleeding events (identified as such in the included study or one requiring transfer to an intensive care unit or requiring blood transfusion within 48 hours of surgery);
  o infection within one month of surgery;
  o hypocalcemia within 48 hours, one month, and six months of surgery (including transient, permanent, severe and mild hypocalcemia as defined in the adverse events section of our protocol). We will differentiate symptomatic hypocalcemia, in which patients exhibit typical symptoms of hypocalcemia, from biochemical hypocalcemia, referring to any patient with calcium levels below the lower limit of normal for the laboratory in which the measurements were made. Transient hypocalcemia will be defined as hypocalcemia resolving within six months of surgery, while permanent hypocalcemia will refer to hypocalcemia persisting longer than six months postoperatively (Mehrabi 2012).
  o postoperative pain using a validated pain score such as the visual analogue scale at 48 hours postoperatively.
  o vocal cord paralysis identified as such in the study in the postoperative period (usually being 48 hours).
  o anesthesia-related complications identified as such in the study occurring intraoperatively.
• Conversion rate from minimally invasive to a bilateral procedure: Defined as the proportion of patients who were planned to have a minimally invasive procedure but were converted to a bilateral exploration intraoperatively. Timing is not applicable here.
• Postoperative increase in PTH with eucalcemia: defined as a within normal serum level of calcium for the local laboratory, with an above normal level of PTH at short term (within six months of surgery), medium term (between six months and five years after surgery), and long term (at five years or more after surgery).
• Health-related quality of life: measured by a validated instrument such as the medical outcomes study 36 item Short Form Health Survey (SF-36) at one month and six months postoperatively.
• Cosmetic satisfaction: measured using a validated instrument such as a Holander Scale within 48 hours of surgery and at six months postoperatively.
• Bone fracture rate: we will consider bone loss as evidenced by a decrease in bone mineral density (BMD) as a surrogate for fracture rate in case data on the former are not readily available. The minimal important difference in each center will be defined by the center-specific quality assurance protocol, if defined in the study. If it is not available, we will consider as significant any decrease in BMD that exceeds 5% at any skeletal site, considering the recommended precision of up to 2.5%, as recommended by the International Society of Clinical Densitometry (ISCD) (Baim 2008). However, this could still result from random error in centers that do not abide by the ISCD quality assurance measures. For the pooled estimate we will consider the minimally important difference as the highest obtained from all studies. Both outcomes will be considered within one year and after five years of surgery.
• Absence from work: defined as the number of days of work...
missed and determined by study authors to have been caused by the surgery. Timing is not applicable to this item.

- Nephrolithiasis rate: defined as percentage of patients having an incidence of nephrolithiasis within five years of surgery.
- Duration of surgery: defined as time from skin incision to skin closure during surgery. Timing not applicable.
- Length of hospital stay: defined as the number of days of hospitalization prior to and following first admission for surgery. Timing is not applicable to this item.

'Summary of findings' table

We will present a 'Summary of findings' table reporting the following outcomes listed according to priority.

- Success rate.
- Adverse events.
- All-cause mortality.
- Health-related quality of life.
- Cosmetic satisfaction.
- Duration of surgery.
- Length of hospital stay.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception to the present.

- The Cochrane Library.
- MEDLINE.
- EMBASE.

We will also search databases of ongoing trials (ClinicalTrials.gov (www.clinicaltrials.gov/), Current Controlled Trials metaRegister (www.controlled-trials.com/), the EU Clinical Trials register (www.clinicaltrialsregister.eu/) and the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/)). We will provide information, including trial identifier, about potentially relevant ongoing studies in the table 'Characteristics of ongoing studies' and in the appendix 'Matrix of study endpoints (protocol/trial documents)'. We will try to find the protocol of each included study, either in databases of ongoing trials, in publications of study designs, or both, and specify data in the appendix 'Matrix of study endpoints (protocol/trial documents)'.

For detailed search strategies please see under Appendix 1. We will continuously apply PubMed’s 'My NCBI' (National Center for Biotechnology Information) email alert service for identification of newly published studies using a basic search strategy (see Appendix 1). We will perform a complete update search on all specified databases four weeks before we submit the final review draft to the Cochrane Metabolic and Endocrine Disorders Group (CMED) for editorial approval. Should we detect new studies for inclusion we will evaluate these and incorporate findings in our review before submission of the final review draft.

If we detect additional relevant key words during any of the electronic or other searches we will modify the electronic search strategies to incorporate these terms and document the changes. We will place no restrictions on the language of publication when searching the electronic databases or reviewing reference lists in identified studies.

We will send results of electronic searches to Cochrane Metabolic and Endocrine Disorders Group for databases which are not available at the editorial office.

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, systematic or other reviews, meta-analyses and health-technology assessment reports.

Data collection and analysis

Selection of studies

To determine the studies to be assessed further, two review authors (OK, HA) will independently scan the abstract, title, or both sections of every record retrieved by the searches. We will investigate all potentially relevant articles as full text. The two review authors will then assess the full texts for eligibility, in duplicate and independently, using a standardized and pilot-tested screening form. They will then compare their results and resolve any disagreements by consensus and, when unsuccessful, with the help of a third reviewer. Before starting the selection process, OK and HA will conduct calibration exercises to ensure the validity of the selection process. We will present an adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of study selection (Figure 1 (Liberati 2009)).

We will obtain full text articles from the database searches available at the American University of Beirut. We will translate studies available in languages other than English, Arabic, or French.
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Data extraction and management

For studies that fulfil inclusion criteria, two review authors (OK, HA) will independently abstract relevant population and intervention characteristics using standard data extraction templates (for details see Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6; Appendix 7; Appendix 8; Appendix 9; Appendix 10; Appendix 11; Appendix 12) with any disagreements to be resolved by discussion, or if required, by a third party. We will send an email to all study authors of included studies to enquire whether they are willing to answer questions regarding their trials. We will present the results of this survey in Appendix 13. Furthermore, we will seek relevant missing information on the trial from the primary author(s) of the article, if required.

Dealing with duplicate publications and companion papers

In the event of duplicate publications, companion documents or multiple reports of a primary study, we will maximize yield of information by collating all available data. We will attempt to resolve any remaining uncertainties by contacting the authors whenever possible.

Assessment of risk of bias in included studies

Two review authors (HA, OK) will assess the risk of bias of each included study independently. We will resolve disagreements by consensus, or by consultation with a third party. For randomized trials, we will assess risk of bias using The Cochrane Collaboration’s tool (Higgins 2011a; Higgins 2011b).

We will use the following criteria.
- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants, providers, data collectors, outcome adjudicators, and data analysts (performance bias and detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other bias.

We will assess outcome reporting bias (Kirkham 2010) by integrating the results of ‘Examination of outcome reporting bias’ (Appendix 7), ‘Matrix of study endpoints (protocol/trial documents)’ (Appendix 6) and section ‘Outcomes (outcomes reported in abstract of publication)’ of the ‘Characteristics of included studies’ table. This analysis will form the basis for the judgement of selective reporting (reporting bias).

We will judge risk of bias criteria as ‘low risk’, ‘high risk’ or ‘unclear risk’ and evaluate individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a).

We will present a ‘Risk of bias’ figure and a ‘Risk of bias summary’ figure. For blinding of participants and personnel (performance bias), detection bias (blinding of outcome assessors) and attrition bias (incomplete outcome data) we intend to evaluate risk of bias separately for subjective and objective outcomes (Hróbjartsson 2013). We will consider the implications of missing outcome data from individual participants.

We define the following endpoints as subjective outcomes.
- Total incidence of perioperative adverse events.
- Health-related quality of life.
- Postoperative pain.
- Cosmetic satisfaction.

We define the following outcomes as objective outcomes.
- Success rate.
- All-cause mortality.
- Economic costs.
- Bone loss/fracture rate.
- Nephrolithiasis rate.
- Absence from work.
- Increased PTH with eucalcemia postoperatively.
- Duration of surgery.
- Length of hospitalization.
- Conversion from minimally invasive to open procedure.
- Anesthetic complications.
- Perioperative bleeding rate.
- Perioperative infection.
- Postoperative hypocalcemia.
- Vocal cord paralysis rate.

We will provide an overview of this evaluation per study as an appendix. We will grade the overall quality of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The approach classifies the quality of evidence into four categories: high, moderate, low and very low. It takes into account the study design as well as the following factors: risk of bias, imprecision, inconsistency, indirectness, publication bias, large effect size, dose-response effect, and confounding (Guyatt 2011).

Measures of treatment effect

We will express dichotomous data as risk ratio (RR) or hazard ratio (HR) with 95% confidence intervals (CIs). We will express continuous data as mean differences (MDs) with 95% CI.
Unit of analysis issues
The unit of analysis will be the individual patient. We will take into account the level at which randomizations occurred, such as cluster-randomized trials and multiple observations for the same outcome.

Dealing with missing data
We will attempt to obtain relevant missing data from authors. If unsuccessful, we will use a complete case approach in the main analysis. We will then conduct sensitivity analyses using plausible assumptions about the outcomes of participants with missing outcome data to test the robustness of statistically significant results. For both continuous and dichotomous data, we will impute plausible treatment effects using progressively stringent criteria, as outlined by Ebrahim et al and Akl et al (Akl 2013; Ebrahim 2013).

Assessment of heterogeneity
In the event of substantial clinical, methodological, or statistical heterogeneity, we will not report study results as meta-analytically pooled effect estimates. We will identify heterogeneity (inconsistency) by visual inspection of the forest plots and by using a standard Chi² test with a significance level of α = 0.1. In view of the low power of this test, we will also consider the I² statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003); where an I² statistic of 75% or more indicates a considerable level of heterogeneity (Higgins 2011a).

We expect the following characteristics to introduce clinical heterogeneity.
- Surgeon specialty.
- Academic versus non-academic setting.
- High volume versus low volume groups.
- IOPTH criteria use.

Assessment of reporting biases
If we include 10 studies or more for a given outcome, we will use funnel plots to assess small study effects. Due to several explanations for funnel plot asymmetry we will interpret results carefully (Sterne 2011).

Data synthesis
We will conduct meta-analyses using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration of the whole distribution of effects, ideally by presenting a prediction interval (Higgins 2009). A prediction interval specifies a predicted range for the true treatment effect in an individual study (Riley 2011). In addition, we will perform statistical analyses according to the statistical guidelines referenced in the latest version of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011a).

Subgroup analysis and investigation of heterogeneity
If we find heterogeneity, we will attempt to determine potential reasons by conducting subgroup analyses. We plan to conduct subgroup analyses and investigate interaction based on the following characteristics.
- Surgeon specialty.
- Academic versus non-academic setting.
- High volume versus low volume groups.
- IOPTH criteria used.

Sensitivity analysis
We will perform sensitivity analyses in order to explore the influence of the following factors (when applicable) on effect sizes.
- Restricting the analysis to published studies.
- Restricting the analysis taking into account risk of bias, as specified above.
- Making plausible assumptions about the outcome of participants with missing data.
- Restricting the analysis to very long or large studies to establish how much they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We will also test the robustness of the results by repeating the analysis using different measures of effect size (RR, OR etc.).

Acknowledgements
We wish to thank the staff of the Cochrane Metabolic and Endocrine Disorders group for their comments and feedback.
Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults (Protocol)

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REFERENCES

Additional references

Akl 2013

Al-Rawashdeh 2012

Alesina 2011

Allendorf 2007

Babinska 2012

Baim 2008

Barczynski 2009

Bergenfelz 2002

Bergenfelz 2005

Bilezikian 2000

Bilezikian 2002

Bilezikian 2009

Burkey 2001

Carneiro 2003

Carneiro-pla 2009

Carty 2002

Carty 2004

Chen 2003

Dijkstra 2002
Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults (Protocol)

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Ning 2009

Ning 2009

Norman 2012

Parfitt 1991

Pyram 2011

Parfitt 1991

Ramakant 2012

Riley 2011

Rulli 2007

Schneider 2012
Schneider DF, Mazeh H, Sippel RS, Chen H. Is minimally invasive parathyroidectomy associated with greater recurrence compared to bilateral exploration? Analysis of more than 1,000 cases. \textit{Surgery} 2012;152(6):1008–15.

Shea 2007

Slepavicius 2008

Starup-Linde 2012

Sterne 2011

Suh 2008

Udelsman 2002

Udelsman 2004

Westerdahl 2007

Wood 2008

* Indicates the major publication for the study
# Additional Tables

Table 1. Overview of study populations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Sample size(^a)</th>
<th>[N] Screened/eligible</th>
<th>[N] Randomized</th>
<th>[N] Safety</th>
<th>[N] ITT</th>
<th>[N] Finishing study</th>
<th>[%] Randomized finishing study</th>
<th>Follow-up (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Study ID</td>
<td>Intervention 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Comparator 2</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grand total</td>
<td>All interventions</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All comparators</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td></td>
<td>All interventions and comparators</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)According to power calculation in study publication or report

\(^b\)Duration of intervention and/or follow-up under randomized conditions until end of study

“-” denotes not reported

ITT: intention-to-treat; N/A: not applicable

---

Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults (Protocol)

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Appendix 1. Search strategies

Search terms and databases

Unless otherwise stated, search terms are free text terms.
Abbreviations:
'S': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word

The Cochrane Library

#1 MeSH descriptor Hyperparathyroidism, Primary explode all trees
#2 (primary adj3 hyperparathyroidis* in All Text)
#3 (parathyroid* in All Text near/6 adenoma* in All Text) or (parathyroid* in All Text near/6 hyperplasia* in All Text) or (parathyroid* in All Text near/6 neoplasm* in All Text)
#4 MeSH descriptor parathyroid neoplasms explode all trees
#5 (#1 or #2 or #3 or #4)
#6 MeSH descriptor parathyroidectomy explode all trees
#7 (neck in All Text near/3 exploration* in All Text)
#8 (surg* in All Text near/6 bilateral in All Text) or (surg* in All Text near/6 unilateral in All Text) or (surg* in All Text near/6 minimal in All Text) or (surg* in All Text near/6 conventional in All Text) or (surg* in All Text near/6 limit* in All Text)
#9 (resection* in All Text near/6 bilateral in All Text) or (resection* in All Text near/6 unilateral in All Text) or (resection* in All Text near/6 minimal in All Text) or (resection* in All Text near/6 conventional in All Text) or (resection* in All Text near/6 limit* in All Text)
#10 (excision* in All Text near/6 bilateral in All Text) or (excision* in All Text near/6 unilateral in All Text) or (excision* in All Text near/6 minimal in All Text) or (excision* in All Text near/6 conventional in All Text) or (excision* in All Text near/6 limit* in All Text)
#11 (surg* in All Text near/6 focus* in All Text) or (resection* in All Text near/6 focus* in All Text) or (excision* in All Text near/6 focus* in All Text)
#12 (#6 or #7 or #8 or #9 or #10 or #11)
#13 (#5 and #12)

MEDLINE

1 exp Hyperparathyroidism, Primary/
2 (primary adj3 hyperparathyroidis*).tw,ot.
3 (parathyroid* adj6 (adenoma* or hyperplasia* or neoplasm*)).tw,ot.
4 exp Parathyroid Neoplasms/
5 1 or 2 or 3 or 4
6 exp Parathyroidectomy/
7 parathyroidectomy*.tw,ot.
8 (neck adj3 exploration*).tw,ot.
9 ((surg* or resection* or excision*) adj6 (bilateral or unilateral or minimal invasiv or conventional* or limit* or focus*)).tw,ot.
10 or/6-9
11 5 and 10
12 randomized controlled trial.pt.
13 controlled clinical trial.pt.
14 randomi?ed.ab.
15 placebo.ab.
16 drug therapy.fs.
17 randomly.ab.
18 trial.ab.
19 groups.ab.
20 exp Cohort Studies/
21 or/12-20
22 Meta-analysis.pt.
23 exp Technology Assessment, Biomedical/
24 exp Meta-analysis/
25 exp Meta-analysis as topic/
26 hta.tw.ot.
27 (health technology adj6 assessment$).tw.ot.
28 (meta analy$ or metaanaly$ or meta?analy$).tw.ot.
29 (search$ adj10 (medical databas* or medline or pubmed or embase or cochrane or cinahl or psycinfo or psyclit or healthstar or biosis or current content*)).tw.ot.
30 (systematic adj3 review*).tw.ot.
31 or/22-30
32 21 or 31
33 (comment or editorial or historical-article).pt.
34 32 not 33
35 11 and 34
36 limit 35 to human

EMBASE

1 exp primary hyperparathyroidism/
2 exp parathyroid tumor/
3 (primary adj3 hyperparathyroidis*).tw.ot.
4 (parathyroid* adj6 (adenoma* or hyperplasia* or neoplasm*)).tw.ot.
5 1 or 2 or 3 or 4
6 exp parathyroidectomy/
7 parathyroidectomy.tw.ot.
8 (neck adj3 exploration*).tw.ot.
9 ((surg* or resection* or excision*) adj6 (bilateral or unilateral or minimal invasiv or conventional*)).tw.ot.
10 6 or 7 or 8 or 9
11 5 and 10
12 exp Randomized Controlled Trial/
13 exp Controlled Clinical Trial/
14 exp Clinical Trial/
15 exp Comparative Study/
16 exp Drug comparison/
17 exp Randomization/
18 exp Crossover procedure/
19 exp Double blind procedure/
20 exp Single blind procedure/
21 exp Placebo/
22 exp Prospective Study/

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Appendix 2. Description of interventions

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
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<tbody>
<tr>
<td>Study 1</td>
<td>Intervention 1</td>
<td>Comparator 1</td>
</tr>
<tr>
<td></td>
<td>Intervention 2</td>
<td>Comparator 2</td>
</tr>
</tbody>
</table>

Footnotes

“Anesthesia” denotes type of anesthesia (e.g. local or general)
**Appendix 3. Baseline characteristics (I)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Duration of intervention (duration of follow-up)</th>
<th>Participating population</th>
<th>Study period [year to year]</th>
<th>Country</th>
<th>Setting</th>
<th>Ethnic groups [%]</th>
<th>Duration of disease [mean/range years (SD), or as reported]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>Intervention 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention 2</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Footnotes*

"-" denotes not reported
SD: standard deviation

**Appendix 4. Baseline characteristics (II)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Sex [female %]</th>
<th>Age [mean/ range years (SD), or as reported]</th>
<th>Preoperative serum calcium [mean% (SD)]</th>
<th>Preoperative serum PTH concentration [pg/ml]</th>
<th>Preoperative serum vitamin D concentration [ng/ml]</th>
<th>Preoperative imaging results [% single gland disease]</th>
<th>Co-medications/ Co-interventions</th>
<th>Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>Intervention 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comparator 1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Comparator 2</td>
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<td></td>
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<td></td>
<td></td>
</tr>
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</table>
Appendix 5. Matrix of study endpoints (publications)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Characteristic</th>
<th>Endpoint reported in publication</th>
<th>Endpoint reported in publication</th>
<th>Endpoint not reported in publication</th>
<th>Time of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Review’s primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total incidence of perioperative adverse events</td>
<td>x</td>
<td></td>
<td></td>
<td>24 mo</td>
</tr>
<tr>
<td></td>
<td>Success rate</td>
<td>x</td>
<td></td>
<td></td>
<td>6 mo, 12 mo, 24 mo</td>
</tr>
<tr>
<td></td>
<td>Review’s secondary outcomes reported in publication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific adverse events</td>
<td>x</td>
<td></td>
<td></td>
<td>6 mo, 12 mo, 24 mo</td>
</tr>
<tr>
<td></td>
<td>Conversion rate from minimally invasive to open procedure</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Postoperative increase in PTH with eucalcemia</td>
<td>x</td>
<td></td>
<td></td>
<td>1 mo</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Health-related quality of life</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Cosmetic satisfaction</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Bone fracture rate</td>
<td>x</td>
<td></td>
<td></td>
<td>6 mo, 12 mo, 24 mo</td>
</tr>
<tr>
<td></td>
<td>Nephrolithiasis rate</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Absence from work</td>
<td></td>
<td>x</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>
Duration of surgery  x  1 mo

Length of hospital stay  x  1 mo

Economic costs  x  N/A

Other than review’s primary/secondary outcomes reported in publication (classification: P/S/O)\(^b\)

Change in voice (P); satisfaction with surgery (S)

Subgroups reported in publication

Surgeon speciality; academic versus non-academic center; high-volume versus low-volume group

Footnotes
\(^a\) Underlined data denote times of measurement for primary and secondary review outcomes, if measured and reported in the results section of the publication (other times represent planned but not reported points in time)

\(^b\) (P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes which were not specified as ‘primary’ or ‘secondary’ outcomes in the publication

mo: months; N/A: not applicable; PTH: parathyroid hormone

Appendix 6. Matrix of study endpoints (trial documents)

<table>
<thead>
<tr>
<th>Characteristic / Study ID (trial identifier)</th>
<th>Endpoint(^a)</th>
<th>Review’s primary outcome</th>
<th>Review’s secondary outcome</th>
<th>Time of measurement</th>
<th>Source (FDA document / EMA document / manufacturer’s website / design paper / trial protocol document)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example</td>
<td>Success rate (P)</td>
<td>x</td>
<td></td>
<td>12, 24 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Length of hospital stay (S)</td>
<td>x</td>
<td>x</td>
<td>1 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Size of glands excised (O)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

Footnotes
\(^a\) “-” denotes not reported

\(^a\) (P) Primary or (S) secondary endpoint(s) refer to verbatim statements in the publication, (O) other endpoints relate to outcomes which were not specified as ‘primary’ or ‘secondary’ outcomes in the report

mo: months; N/A: not acknowledged

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## Appendix 7. Examination of outcome reporting bias

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study ID</th>
<th>Clear that outcome was measured and analyzed [trial report states that outcome was analyzed but only reports that result was not significant]</th>
<th>Clear that outcome was measured and analyzed [trial report states that outcome was analyzed but no results reported]</th>
<th>Clear that outcome was measured [clear that outcome was measured but not necessarily analyzed (judgement says likely to have been analyzed but not reported because of non-significant results)]</th>
<th>Unclear whether the outcome was measured [not mentioned but clinical judgement says likely to have been measured and analyzed but not reported on the basis of non-significant results]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Footnotes*

'High risk of bias' categories for outcome reporting bias according to the Outcome Reporting Bias In Trials (ORBIT) study classification system for missing or incomplete outcome reporting in reports of randomized trials (Kirkham 2010).

- Classification 'A' (table 2, Kirkham 2010)
- Classification 'D' (table 2, Kirkham 2010)
- Classification 'E' (table 2, Kirkham 2010)
- Classification 'G' (table 2, Kirkham 2010)

## Appendix 8. Definition of endpoint measurement (I)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Success rate</th>
<th>Total incidence of perioperative adverse events</th>
<th>Bone fracture rate</th>
<th>Nephrolithiasis rate</th>
<th>Absence from work</th>
<th>Postoperative increase in PTH with eucalcemia</th>
<th>Duration of surgery</th>
<th>Length of hospital stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

*Footnotes*

ND: not defined; PTH: parathyroid hormone
### Appendix 9. Definition of endpoint measurement (II)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cosmetic satisfaction</td>
<td></td>
</tr>
<tr>
<td>Conversion rate from minimally invasive to open procedure</td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
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</tr>
<tr>
<td>Bleeding events</td>
<td></td>
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<tr>
<td>Infection</td>
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<tr>
<td>Hypocalcemia</td>
<td></td>
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<tr>
<td>Postoperative pain</td>
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<tr>
<td>Vocal cord paralysis</td>
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<tr>
<td>Anesthetic related complications</td>
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#### Footnotes

ND: not defined

### Appendix 10. Adverse events (I)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Randomized / Safety [N]</th>
<th>Deaths [N]</th>
<th>Deaths [%]</th>
<th>All adverse events [N]</th>
<th>All adverse events [%]</th>
<th>Severe/serious adverse events [N]</th>
<th>Severe/serious adverse events [%]</th>
</tr>
</thead>
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<td>Intervention 2</td>
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<td>Comparator 1</td>
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<td>Comparator 2</td>
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#### Footnotes

“-” denotes not reported
### Appendix 11. Adverse events (II)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Randomized / Safety [N]</th>
<th>Severe hypocalcemia [N]</th>
<th>Severe hypocalcemia [%]</th>
<th>Mild to moderate hypocalcemia [N]</th>
<th>Mild to moderate hypocalcemia [%]</th>
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</thead>
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<td><strong>Study 1</strong></td>
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<td>Intervention 2</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Comparator 1</td>
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</tbody>
</table>

*Footnotes*

“-” denotes not reported

### Appendix 12. Adverse events (III)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention(s) and comparator(s)</th>
<th>Randomized / Safety [N]</th>
<th>Laryngeal nerve injury [N]</th>
<th>Laryngeal nerve injury [%]</th>
<th>Hematoma [N]</th>
<th>Hematoma [%]</th>
<th>Infection [N]</th>
<th>Infection [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>Intervention 1</td>
<td></td>
<td></td>
<td></td>
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*Footnotes*

“-” denotes not reported
Appendix 13. Survey of authors providing information on trials

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Footnotes
N: no; Y: yes

Contributions of Authors
Ghada El-Hajj Fuleihan (GEHF): protocol draft, search strategy development, oversight of trial selection, data extraction and data analysis, data interpretation, review draft and future review update.
Omar I Kreidieh (OIK): Protocol draft, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation and future review update.
Elie A Akl (EAA): protocol draft, search strategy development, data analysis, data interpretation, review draft and future review update.
Hala Ahmadieh (HA): Trial selection, data extraction, data analysis, data interpretation, review draft and future review update.

Declarations of Interest
None known.

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Internal sources
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Medical Resource Package Plan

External sources
• No sources of support supplied