

Peer Review File

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

Reviewer A

The authors report about the interesting question of postoperative prophylactic intravenous calcium administration in patients undergoing total thyroidectomy.

However, concerns are as following:

1. As mentioned in the reference section, Uruno et al already reported in about 500 patients in 2006 that prophylactic intravenous calcium increased serum Calcium levels and reduced symptoms of hypocalcaemia.

Reply: The study performed by Uruno et al was prospective cohort study instead of randomized controlled trial. There was neither fix dose of calcium nor timing of infusion being standardized in the study. All the patients underwent total thyroidectomy were included in the study (including malignancy, neck dissection and etc). All these factors mentioned lead to several biases.

2. even if this study was conducted as a randomized trial, the sample size is relatively small to draw any solid conclusions for the clinical management of intravenous prophylactic calcium administration.

Reply: The sample size calculation was based on a pilot study performed at my center prior to the actual RCT (minimum of 28 participants). I agreed with the sample size is relatively small in order to draw solid conclusions but these results can contribute some basic knowledge that low-risk total thyroidectomy with oral prophylactic supplements were adequate.

3. it seems that after standardization of post-operative oral calcium and vitamin D supplementation the authors could already reduce the postoperative need of rescue calcium shots to only 1 patient of the included patients compared to up to 40% in 2018/19 which is already known in the literature. Hence, the rationale to investigate the effectiveness of prophylactic intravenous calcium is questionable or needs at least a greater sample size.

Reply: This study was initiated based on an audit performed in our center (year 2018 & 2019) that postoperative hypocalcemia up to 40% despite majority of them given various dose prophylactic oral calcium and/or vitamin D supplementation. Hence, this result brought our concern whether any role of prophylactic intravenous calcium infusion despite oral calcium and vitamin D supplementation.

4. the authors should clarify the number of preserved or identified parathyroid glands

and if there was any difference between the groups.

Reply: The number of parathyroid glands preserved or identified was not recorded in this study. As based on literature, only one parathyroid gland preserved is needed to prevent permanent hypocalcemia. But not much of evidence on identifying parathyroid gland in early hypocalcaemia as disruption of vascular supply to parathyroid gland (despite preserved) during surgery also can lead to early hypocalcaemia.

Reviewer B

This is a single-center, double-blinded randomized controlled trial of 34 patients undergoing total thyroidectomy. Patients were randomized 1:1 to either routine calcium and Rocaltrol supplementations (Placebo group) or prophylactic calcium infusions perioperatively in addition to routine calcium and Rocaltrol supplementations (Intervention group). The aim was to evaluate the impact of prophylactic perioperative calcium infusions on postoperative hypocalcemia.

The authors found no difference in the occurrence of early hypocalcemia postoperatively when comparing the two groups. The only difference found, was that median serum calcium levels 24 hours postoperatively were significantly higher in the intervention group than in the placebo group.

Some important points need to be addressed:

1. Did the authors use total calcium or albumin-corrected calcium concentrations? This needs to be elaborated as total calcium is less representative of the biologically active calcium (than e.g. ionized calcium or albumin-corrected calcium).

Reply: Albumin-corrected calcium concentrations was used in this study instead of total calcium level.

2. Why were patients with 4 accidentally removed parathyroid glands excluded? How do these patients differ (in the short term) from patients with i-PTH <0.5 pmol/L at the 12 postoperative hour mark (these patients were not excluded)?

Reply: Patients with 4 accidentally removed parathyroid glands will be suffered from hypocalcaemia (temporary and permanent). However, not all patients with i-PTH <0.5 pmol/L postoperatively will develop hypocalcaemia as i-PTH is just a predictor, and it is not 100% specific. Hence, both groups mentioned above was not the same and cannot be group together.

3. Why was there such a substantial difference in the specimen weight among the two groups if patients were properly randomized? This needs to be elaborated.

Reply: Despite patients were properly randomized, unfortunately 2 of the patient's specimen weight were >200g in intervention arm and hence leading to higher median specimen weight in the intervention arm compared to placebo. However, specimen weight didn't appear to affect the postoperative hypocalcaemia based on the result of this study.

4. It seems strange that the median postoperative i-PTH in the placebo group was as low as 0.5 pmol/L, when the corresponding median postoperative calcium levels were high (2.37mmol/L; 2.22 mmol/L; 2.23 mmol/L respectively). How do the authors explain this discrepancy?

Reply: Firstly, i-PTH is a marker to predict hypoparathyroidism postoperatively and is not 100% specific. Based on the result, placebo group have lower median i-PTH level and correspondingly lower median serum calcium at 24H and 48H compared to intervention group. However, I believe with the usage of prophylactic oral calcium and vitamin D supplementation in low-risk total thyroidectomy, it reduces the incidence of early hypocalcaemia.