

Role of oral calcium supplementation alone or with vitamin D in preventing post-thyroidectomy hypocalcaemia

A meta-analysis

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Abstract

Background: Thyroidectomy is the main intervention for thyroid malignancies and some benign thyroid diseases. Its most common complication is hypocalcaemia, which requires oral or intravenous calcium therapy. The aim of this meta-analysis was to assess the efficacy of routine calcium supplementation with or without vitamin D in preventing hypocalcaemia post-thyroidectomy.

Methods: Systematic searches of the PubMed, EMBASE, and Cochrane Library databases were performed. The qualities of the included articles were assessed using the Cochrane risk of bias tool. The studies' qualities of outcomes and strengths of evidence were evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool. Data analysis was performed using Review Manager 5.3, and odds ratio (ORs) with their 95% confidence intervals (CIs) were computed for dichotomous data.

Results: Ten randomized controlled trials (RCTs) were included. The combined study recruited 1620 patients (343 men and 1277 women) who underwent total thyroidectomy alone or with neck dissection. Calcium supplementation decreased the risk of transient postoperative hypocalcaemia (OR 0.48 [95% CI, 0.31–0.74]; $P < .001$) but did not decrease the demand for intravenous supplementation or the rate of permanent hypocalcaemia compared to no treatment. Calcium and vitamin D supplementation significantly reduced the rate of transient hypocalcaemia and the demand for intravenous supplementation compared to either no treatment (OR 0.21 [95% CI, 0.11–0.40]; $P < .001$ and OR 0.26 [95% CI, 0.10–0.69]; $P = .007$, respectively) or calcium alone (OR 0.39 [95% CI, 0.18–0.84]; $P = .02$ and OR 0.18 [95% CI, 0.07–0.47]; $P < .001$, respectively), but did not decrease the rate of permanent hypocalcaemia. GRADE-based confidence was moderate.

Conclusion: Postoperative calcium supplementation is effective for preventing post-thyroidectomy hypocalcaemia. Calcium plus vitamin D was more effective than calcium alone in preventing postoperative hypocalcaemia and decreasing the demand for intravenous calcium supplementation. Further, well-designed RCTs with larger sample sizes are required to validate our findings.

Abbreviations: CI = confidence interval, OR = odds ratio, PTC = papillary thyroid cancer, RCT = randomized controlled trial, VD = vitamin D.

Keywords: calcium, hypocalcaemia, routine, thyroidectomy, vitamin D

1. Introduction

Hypocalcaemia is one of the most common complications of bilateral thyroid surgery.^[1–4] The reported incidence of post-thyroidectomy hypocalcaemia ranges widely from 13% to

49%.^[4,5] Transient hypocalcaemia can normalize spontaneously after the recovery of parathyroid function, while permanent hypocalcaemia can last for more than 1 year and often requires lifelong therapy or parathyroid transplantation.^[6]

Symptoms of mildly hypocalcaemia such as perioral or acral paraesthesia, tingling, and carpopedal tetany can impose different degrees of pressure on patients' emotions.^[7] Moreover, severe hypocalcaemia can cause life-threatening complications such as laryngospasm and cardiac arrhythmias.^[8,9] Many patients who experience symptoms of mild hypocalcaemia can be treated with oral calcium/vitamin D (VD).^[10] However, serious hypocalcaemic symptoms should be relieved by intravenous calcium supplementation as quickly as possible.^[11–16] Moreover, intravenous calcium administration to patients with refractory hypocalcaemia is a major reason for prolonged hospitalization after thyroid surgery.^[17]

Serum calcium levels reportedly drop to their lowest levels 24 to 48 hours after thyroid surgery, during which concomitant symptoms are also present. There are no reliable markers for identifying patients who are likely to develop symptomatic hypocalcaemia.^[18,19] Thus, patients who undergo thyroidectomy always require close observation in case they require calcium and VD supplementation. This results in prolonged in-hospital stay

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Table 1

Characteristics of included studies.

Study	Year	Country	Sample size (male/female)	Age (yrs ±SD)	Surgical procedure	Hypocalcemia		Intravenous supplementation		Permanent hypocalcemia		Controls	Definition of outcomes
						Treatment n (%)	No treatment n (%)	Treatment n (%)	No treatment n (%)	Treatment n (%)	No treatment n (%)		
Calcium vs no treatment													
Langner	2016	Brasil	3/44	52.1 ± 12.8	TT	6 (30)	17 (63)	12 (23)	14 (27)	1 (5)	8 (30)	No treatment	Hypocalcemia: ionized calcium <1.1 mmol/L (Langner), Ca <8.0 mmol/L (Ravikumar, Roh 2008, Bellantone, Tartaglia), Ca <2.1 mmol/L (Sun), Ca <8.0 mg/dl or ionized calcium <1.0 mmol/L (Roh 2006), hypocalcemia symptoms and signs (Choe).
Ravikumar	2017	India	30/178	39 ± 11	TT	26 (50)	30 (68)	2 (4)	7 (14)	2 (4)	1 (2)	No treatment	Permanent hypocalcemia: hypocalcemia duration >6 months (Langner, Ravikumar, Roh 2008, Aher, Roh 2006)
Roh	2008	Korea	28/120	48.5 ± 12.1	TT+ND	12 (24)	22 (44)	2 (4)	7 (14)	1 (2)	2 (4)	No treatment	
Bellantone	2002	Italy	18/61	49 ± 13	TT	9 (35)	11 (41)	0 (0)	2 (7)	0 (0)	2 (7)	No treatment	
Sun	2015	China	29/70	43.6 ± 14.1	TT+ND	15 (44)	22 (73)					No treatment	
Calcium and Vitamin D vs no treatment													
Aher	2016	Turkey	18/88	45.3 ± 12	TT+ND	1 (2)	18 (34)	1 (2)	0 (0)	4 (8)	5 (9)	No treatment	
Ravikumar	2017	India	30/178	39 ± 11	TT	16 (15)	30 (68)	5 (5)	14 (27)	2 (2)	1 (2)	No treatment	
Roh	2006	Korea	17/73	47 ± 2	TT+ND	6 (13)	16 (36)	0 (0)	5 (11)	1 (2)	2 (4)	No treatment	Indications for intravenous supplementation: symptoms persisted despite oral therapy (Ravikumar, Roh 2008, Bellantone, Aher, Roh 2006, Pisaniello), symptoms persisted despite oral therapy combined with Ca <7.5 mg/dl or ionized calcium <0.8 mmol/L (Choe)
Roh	2008	Korea	28/120	48.5 ± 12.1	TT+ND	4 (8)	22 (44)	0 (0)	7 (14)	1 (2)	2 (4)	No treatment	
Bellantone	2002	Italy	18/61	49 ± 13	TT	6 (23)	11 (41)	0 (0)	2 (7)			No treatment	
Choe	2010	Korea	76/230	49 ± 10	TT+ND	36 (23)	65 (43)	16 (10)	27 (18)			No treatment	
Calcium and Vitamin D vs calcium													
Ravikumar	2017	India	30/178	39 ± 11	TT	16 (15)	26 (50)	5 (5)	12 (23)	2 (2)	1 (2)	Ca 2.0 g/day	
Roh	2008	Korea	28/120	48.5 ± 12.1	TT+ND	4 (8)	12 (24)	0 (0)	2 (4)	1 (2)	2 (4)	Ca 3.0 g/day	
Bellantone	2002	Italy	18/61	49 ± 13	TT	6 (23)	9 (35)	0 (0)	0 (0)			Ca 3.0 g/day	
Tartaglia	2005	Italy	71/346	51.5 ± 2	TT	62 (29)	74 (37)					Ca 1.5 g/day	
Pisaniello	2005	Italy	53/67	NR	TT			1 (2)	4 (7)			Ca 0.3 g/day	

ND = neck dissection, NR = not report, SD = standard deviation, TT = total thyroidectomy, yrs = years.

and repeated biochemical testing.^[20,21] In order to reduce the risk of post-thyroidectomy hypocalcaemia and expedite early discharge, some centers have proposed routine calcium/VD supplementation.^[22,23] However, there is no solid evidence of any benefits provided by such management. To that end, the aim of this meta-analysis was to assess the effectiveness of administering routine oral calcium or calcium plus VD supplements in preventing postoperative hypocalcaemia.

2. Materials and methods

As this is a meta-analysis of previously published data, ethics committee approval was not required.

2.1. Search strategy and study selection

The search strategy was in accordance with a recent publication that described optimal literature search methods for surgical reviews.^[24] The PubMed, Embase, and Cochrane Library databases were searched without date constraints to identify studies that evaluated the effectiveness of calcium/VD supplementation in preventing postoperative hypocalcaemia; the final search was performed on June 1, 2018. The following free words and Medical Subject Headings terms were used in the search: “Vitamin D”, “Calcium”, “Calcitriol”, “calciferol”, “Caltrate”, “ergocalciferol”, “hypocalcemia”, “low calcium”, “thyroidectomy”, “thyroid surgery”, and “thyroidectomies”. The review was limited to published articles that were written in English. References within the extracted articles were explored for additional publications.

2.2. Population, interventions, and outcomes

Inclusion criteria: All randomized controlled trials that were designed to investigate the effectiveness of postoperative oral calcium/VD supplementation in preventing post-thyroidectomy hypocalcaemia were included.

Exclusion criteria: Studies designed for animals, and those that were in languages other than English or were non-randomized controlled trial (RCTs) were excluded. Studies that included patients with prior neck surgery, routine intravenous calcium supplementation, those that examined preoperative supplementation or those with underlying diseases or treatments like the use of corticosteroids, furosemide, or bisphosphates that could influence serum calcium levels were also excluded.

Interventions included calcium, calcium plus VD, or no treatment. Examined outcomes were the incidences of transient or permanent hypocalcaemia as well as the need for intravenous supplementation. Hypocalcaemia was defined as a calcium level below lower limit of normal or hypocalcaemic symptoms such as muscle spasms or cramps, numbness.^[25,26] Transient hypocalcaemia was usually defined as the need for replacement therapy for less than 6 months or 1 year after thyroidectomy; permanent hypocalcaemia was usually defined as the need for replacement therapy for more than 6 months or 1 year after thyroidectomy.^[27,28] Intravenous supplementation was most used when symptoms persisted despite oral therapy.^[13–15,29,30]

2.3. Data collection and analysis

Two investigators (Tengfei Xing and Yiyi Hu) extracted data independently. Any discrepancy was resolved through discussion. The extracted data included the name of the first author, year of publication, study location, number of cases and controls, number of patients with hypocalcaemia, and any intravenous supplementation requirements.

The Cochrane Collaboration’s risk of bias tool was used by 2 independent reviewers (Yiyi Hu and Bin Wang) to assess the quality of RCTs. The quality of key outcomes and the overall strength of the supporting evidence from the included studies were evaluated by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool.^[31]

The random effects model was used owing to heterogeneity across the included studies, as this can provide a more conservative result than a fixed effects model.^[32] Pooled odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated to evaluate the association between calcium with or without VD supplementation as well as the rate of post-thyroidectomy hypocalcaemia and the demand for intravenous supplementation. Cochrane’s *Q* test and *I*² test were used to evaluate heterogeneity and its magnitude across studies; a *P* value <.1 or *I*² >50% was defined as significant heterogeneity.^[33] Funnel plots were used to evaluate publication bias and identify

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Arer 2016	+	?	?	+	-	+	+
Bellantone 2002	+	?	?	+	+	+	+
Choe 2010	+	?	?	+	-	+	+
Langner 2016	-	?	?	+	+	+	+
Pisaniello 2005	+	?	?	+	-	+	+
Ravikummar 2017	+	?	?	?	+	+	+
Roh 2006	+	?	?	+	+	+	+
Roh 2008	+	+	+	+	+	+	+
Sun 2015	?	?	?	+	+	+	+
Tartaglia 2005	-	-	-	+	+	+	+

Figure 1. Risk of bias summary.

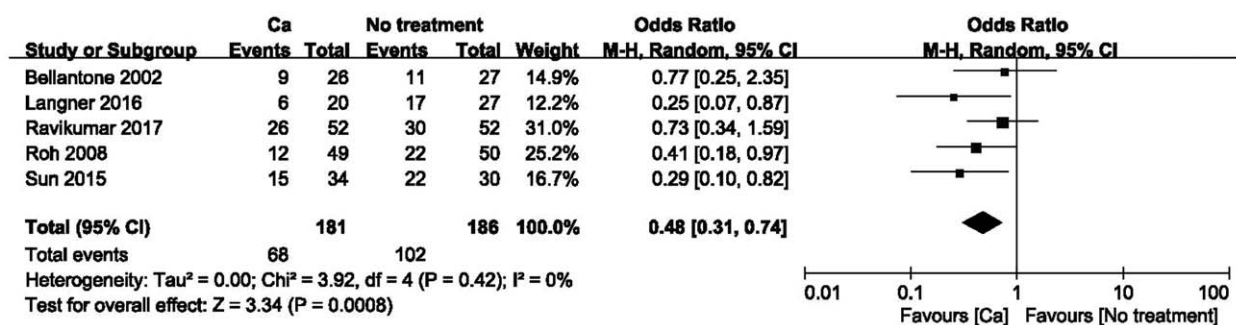


Figure 2. Forest plot of comparing calcium vs no treatment on the incidence of hypocalcemia. Ca = calcium, CI = confidence interval, OR = odds ratio.

the potential outlier studies that might cause heterogeneity.^[34] All analyses were performed using the Revman 5.3 software. This meta-analysis is reported in accordance with the Cochrane Collaboration guidelines and the PRISMA statement.^[35]

3. Results

3.1. Search results

Flow-chart from PRISMA shows the flow diagram of the selection process in which 260 references were retrieved by the electronic database. After screening and removal of duplicate publications, 15 references were considered to be potentially eligible. After further evaluation, 10 studies^[13-16,25,29,30,36-38]

finally met our inclusion criteria. Of the 5 excluded studies, 3 were omitted because the treatment groups were routinely administered preoperative VD supplements^[6,39] or hydrochlorothiazide.^[21] One article was excluded because patients in that study received prophylactic infusion of calcium,^[40] while another was excluded because the treatment group was compared to a historical control.^[23] All included studies were RCTs that were published in English.

The combined study comprised 1620 patients (343 men and 1277 women). The mean age was 49 ± 13 years and the overall incidence of post-thyroidectomy hypocalcaemia was 37.1%. Table 1 summarizes the key characteristics of the included studies. Patients in 5 studies^[13,16,30,36,38] underwent total thyroidectomy, while those in the remaining studies^[14,15,25,29,37]

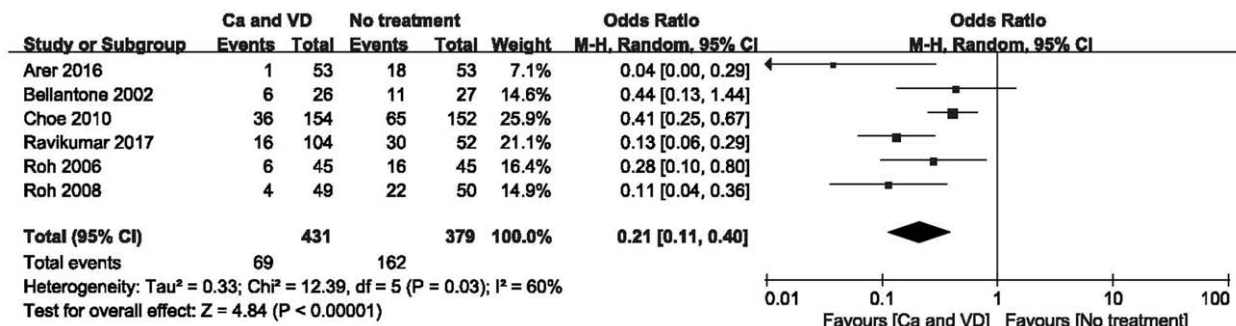


Figure 3. Forest plot of comparing calcium plus VD vs no treatment on the incidence of hypocalcemia. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

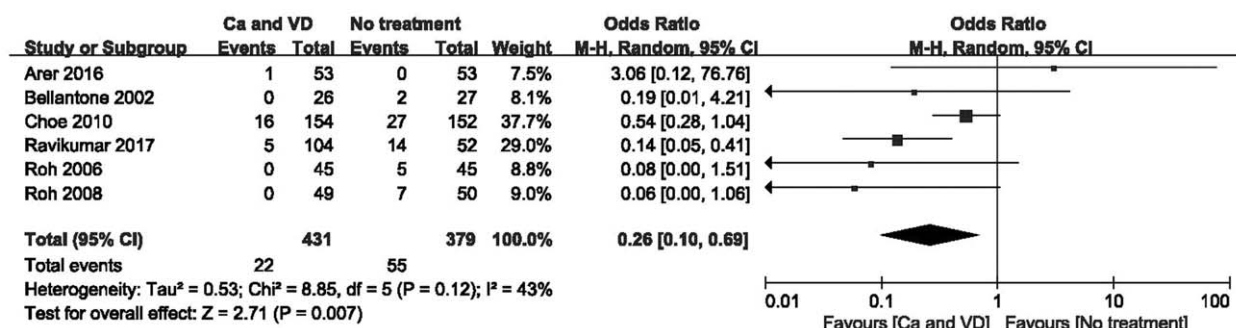


Figure 4. Forest plot of comparing calcium plus VD vs no treatment on the demand for intravenous supplementation. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

underwent total thyroidectomy and neck dissection. The calcium supplements prescribed in the studies included calcium carbonate,^[16,25,30,37] effervescent calcium,^[36] calcium,^[13,14,29] calcium salts,^[38] and Calcimax D3.^[15] The types of VD supplements were Calcitriol,^[13,16,25,38] Cholecalciferol,^[16,25,30] VD,^[14,29] and Calcimax D3.^[15] The most common biochemical cut-off value used to define hypocalcaemia was a total calcium <8.0 mg/dl or ionized calcium <1.0 mmol/L. Sun et al defined laboratory hypocalcaemia as serum calcium <2.1 mmol/L^[37] while Langner et al defined biochemical hypocalcaemia as ionized calcium <1.1 mmol/L.^[36] The most common indication for intravenous supplementation was the persistence of hypocalcaemic symptoms despite oral supplementation. Choe et al reported that intravenous supplementation was needed only when patients had severe or worsening hypocalcaemic symptoms combined with Ca <7.5 mg/dl or ionized calcium <0.8 mmol/L.^[25] Permanent hypocalcaemia was defined as that which lasted for 6 months or more. Risk of bias assessments are summarized in Figure 1. One study was rated as being at high risk of selection bias because the allocation was performed sequentially.^[38] Two studies did not interpret how allocation sequences were generated.^[36,37] Letters were sent to the corresponding authors, and only Langner^[38] replied that patients were allocated in a sequential form. Ten studies did not report whether allocation concealment was performed, while 8 did not offer any information on blinding procedures and 1 clearly indicated that it was not blinded. Nine studies explicitly reported the details of the hypocalcaemia assessment and indications for intravenous supplementation. One study^[16] did not specify the postoperative serum calcium detection method used for the diagnosis of hypocalcaemia. For the assessment of attrition bias, 3 studies were graded as high-risk because complete data of the incidence of biochemical hypocalcaemia was lacking. Therefore, we could only extract data on symptomatic hypocalcaemia, which may not be as objective as biochemical data. Reporting and other biases were low in all the studies.

3.2. Results of meta-analysis

Three comparisons were performed in our review: calcium vs no treatment, calcium plus VD vs no treatment, and calcium plus VD vs calcium alone.

3.2.1. Calcium vs no treatment. Routine supplementation of calcium significantly decreased the rate of postoperative hypocalcaemia but had no effect on the demand for intravenous supplementation or the rate of permanent hypocalcaemia compared with no prophylaxis (Fig. 2; OR 0.48 [95% CI, 0.31–0.74]; $P < .001$). Utilizing the GRADE tool, this evidence was considered of moderate quality (see Table S1, Supplemental Content, which illustrates the quality of this outcome and the strength of the evidence).

3.2.2. Calcium plus VD vs no treatment. The use of calcium plus VD or its metabolites significantly reduced the rate of transient hypocalcaemia (Fig. 3; OR 0.21 [95% CI, 0.11–0.40]; $P < .001$) and the demand for intravenous supplementation (Fig. 4; OR 0.26 [95% CI, 0.10–0.69]; $P = .007$), but did not affect the rate of permanent hypocalcaemia compared to no treatment. There was considerable heterogeneity in hypocalcaemia rates when comparing calcium plus VD vs no treatment ($P = .03$; $I^2 = 60\%$) based on the funnel plot constructed to determine the extent of heterogeneity (see Fig. S1, Supplemental Content, <http://links.lww.com/MD/C838>, which shows the

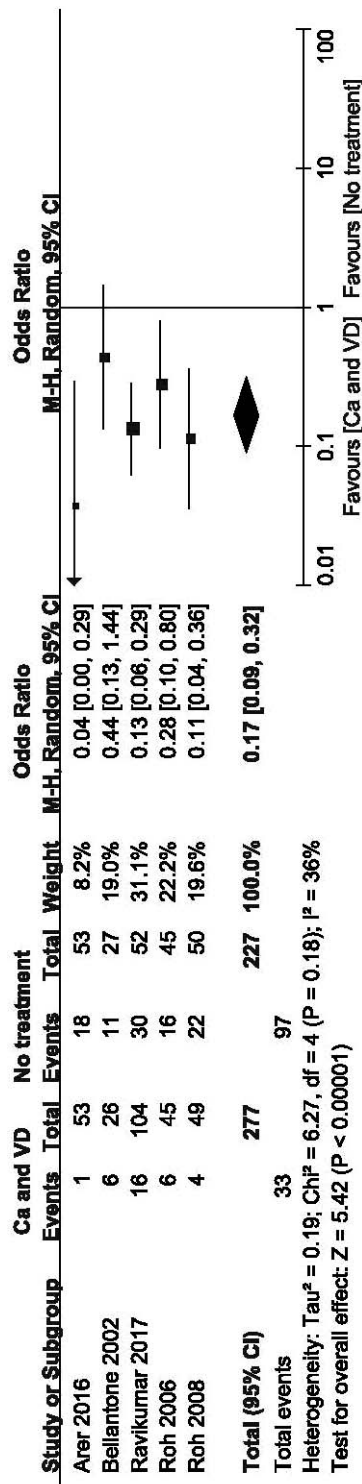


Figure 5. Forest plot of comparing calcium plus VD vs no treatment on the incidence of hypocalcaemia after the study with high heterogeneity was excluded. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

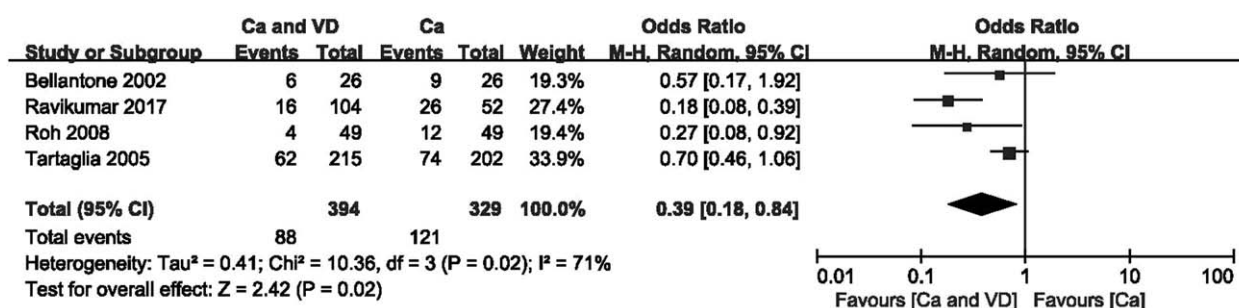


Figure 6. Forest plot of comparing calcium plus VD vs calcium alone on the incidence of hypocalcemia. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

studies that contributed to the heterogeneity). After 1 study that had extraordinary heterogeneity was excluded, the results were unchanged although the 95% CI was narrower (Fig. 5; OR 0.17 [95% CI, 0.09–0.32]; $P < .001$). Using the GRADE tool, the evidence for comparison between calcium plus VD vs no treatment was considered of moderate quality (see Table S2, Supplemental Content, which illustrates the quality of this outcome and the strength of the evidence, <http://links.lww.com/MD/C838>).

3.2.3. Calcium plus VD vs calcium alone. When compared with calcium supplementation alone, calcium plus VD supplementation significantly reduced the risk of transient hypocalcaemia (Fig. 6; OR 0.39 [95% CI, 0.18–0.84]; $P = .02$) and the demand for intravenous supplementation (Fig. 7; OR 0.18 [95% CI, 0.07–0.47]; $P < .001$) but did not decrease the rate of

permanent hypocalcaemia. The source of heterogeneity when comparing the demand for intravenous supplementation was determined by funnel plot (see Fig. S2, Supplemental Content, which shows the studies that caused heterogeneity, <http://links.lww.com/MD/C838>). After the study with extreme heterogeneity was excluded, the results remained significant (Fig. 8; OR 0.62 [95% CI, 0.41–0.93]; $P = .02$). Using the GRADE tool, this evidence was deemed to be of moderate quality (see Table S3, Supplemental Content, which illustrates the quality of this outcome and the strength of the evidence).

4. Discussion

Thyroid cancer, especially papillary thyroid cancer (PTC), is one of the most rapidly growing cancers in the world.^[41] One of the most common characteristics of PTC is susceptibility to central

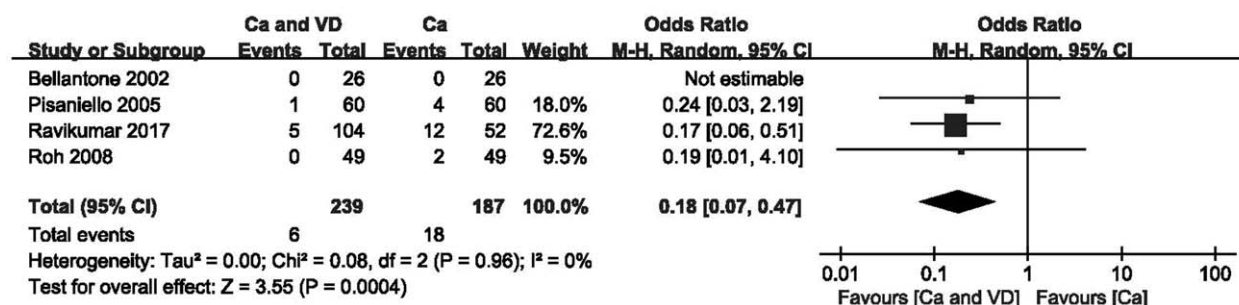


Figure 7. Forest plot of comparing calcium plus VD vs calcium alone on the demand for intravenous supplementation. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

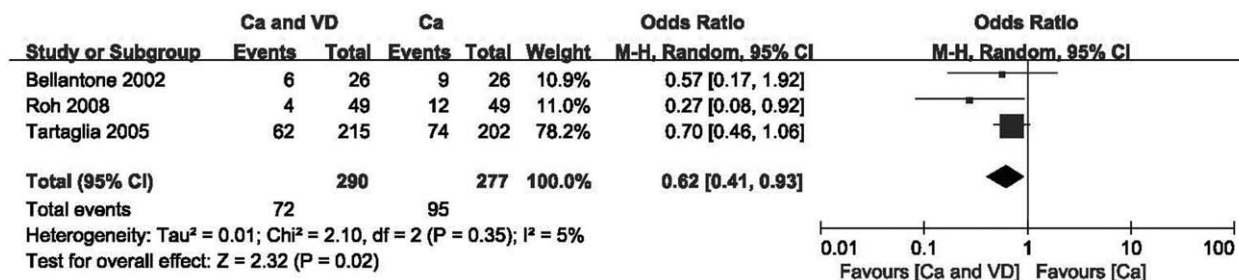


Figure 8. Forest plot of comparing calcium plus VD vs calcium alone on the incidence of hypocalcemia after the study with high heterogeneity was excluded. Ca = calcium, CI = confidence interval, OR = odds ratio, VD = vitamin D.

lymphoid node metastasis; therefore, thyroidectomy plus routine central neck dissection is recommended for the treatment of PTC in many countries.^[42,43] Although central neck dissection reduces the risk of locoregional recurrence, this procedure has been shown to significantly increase the rate of postoperative temporary hypocalcaemia.^[44]

Symptomatic hypocalcaemia exposes patients to physical and mental suffering, and several measures to reduce the risk of postoperative hypocalcaemia have been suggested. These mainly include modifying surgical procedures such as reducing the extent of thyroid surgery,^[45] application of alternative surgical instruments,^[46,47] and routine or selected calcium and VD supplementation after thyroidectomy.^[48] Various predictors of hypocalcaemia following thyroid surgery have been investigated to direct the use of calcium with or without VD supplementation; however, reproducible, reliable, and stable predictors have not yet been established.^[48–51] Therefore, routine supplementation of calcium and VD is advocated in many clinical centers.^[52–54] Our meta-analysis found that prophylactic calcium supplementation can significantly reduce the risk of postoperative hypocalcaemia, and that this effect is reinforced if calcium and VD are administered together. Moreover, our analysis is the first to reveal that combined calcium plus VD therapy can significantly decrease the demand for intravenous calcium supplementation. Thus, calcium can be administered routinely after thyroid surgery to reduce the risk of postoperative hypocalcaemia. Calcium plus VD administration should be reserved for patients who are more likely to develop hypocalcaemia, such as those who undergo parathyroid glands implantation, central lymph node dissection, or extensive thyroid surgery, for patients with recurrent neck surgery, patients who are known to have vitamin D deficiency, patients who have postoperative PTH below lower limit of normal, as calcium supplementation alone may not decrease the risk of requiring intravenous supplementation for such high-risk individuals. Routine calcium plus VD administration for high-risk patients may also reduce the incidence of readmission, especially as prolonged hospitalization increases medical costs. Results of your study support ACCE/ACE Disease State Clinical Review and American Thyroid Association Statement on Postoperative Hypoparathyroidism regarding the recommendations for an empirical prophylactic approach for managing potential post-thyroidectomy hypocalcaemia.^[55,56] However, the variability in cut-off values used to define hypocalcaemia, the dose and form of administered supplements, and the indications for intravenous supplementation limit the strength of evidence. Besides, this analysis had some limitations. First, inclusion criteria that only English articles were included might contribute to bias. Second, the number of patients that treated with intravenous supplementation and patients diagnosed as permanent hypocalcaemia were relatively small. Only 1 publication reported an adverse effect of supplementation in the form of mild gastric pyrosis, mostly in patients undergoing long-lasting therapies.^[30] Therefore, adverse effects were not considered in our analysis.

Our results are consistent with those of the meta-analysis conducted by Alhefdhi et al involving 2285 patients enrolled in 9 studies, although they only included a single cohort study.^[23] Another meta-analysis assessed various preventative and surgical measures performed to decrease the rate of post-thyroidectomy hypocalcaemia,^[57] in which combined calcium and VD supplements were found to decrease the rates of transient postoperative hypocalcaemia significantly more than either calcium alone or no supplements.

5. Conclusion

The results of our meta-analysis verified that the prophylactic administration of calcium is effective for reducing the risk of postoperative hypocalcaemia. Calcium plus VD was more effective than calcium alone in preventing immediate postoperative hypocalcaemia and in decreasing the demand for intravenous calcium supplementation. Routine supplementation may allow earlier and safer patient discharge, but could also lead to overtreatment in some patients with normal serum calcium. Therefore, further investigations should be considered to evaluate the applicability of this management strategy in actual clinical practice.

Author contributions

Data curation: Yiyi Hu.

Formal analysis: Yiyi Hu.

Methodology: Tengfei Xing.

Software: Yiyi Hu, Bin Wang.

Validation: Bin Wang.

Writing – original draft: Tengfei Xing.

Writing – review & editing: Jingqiang Zhu.

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