

Use of pre-operative calcium and vitamin D supplementation to prevent post-operative hypocalcaemia in patients undergoing thyroidectomy: a systematic review

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Review Article

Dr A S Khatiwada takes responsibility for the integrity of the content of the paper

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Abstract

Objective. This systematic review aimed to establish the evidence behind the use of pre-operative calcium, vitamin D or both calcium and vitamin D to prevent post-operative hypocalcaemia in patients undergoing thyroidectomy.

Method. This review included prospective clinical trials on adult human patients that were published in English and which studied the effects of pre-operative supplementation with calcium, vitamin D or both calcium and vitamin D on the rate of post-operative hypocalcaemia following total thyroidectomy.

Results. Seven out of the nine trials included reported statistically significantly reduced rates of post-operative laboratory hypocalcaemia (absolute risk reduction, 13–59 per cent) and symptomatic hypocalcaemia (absolute reduction, 11–40 per cent) following pre-operative supplementation.

Conclusion. Pre-operative treatment with calcium, vitamin D or both calcium and vitamin D reduces the risk of post-operative hypocalcaemia and should be considered in patients undergoing total thyroidectomy.

Introduction

Total thyroidectomy (removal of the entire thyroid gland) is the treatment of choice for a large proportion of thyroid malignancies and for benign thyroid pathologies such as Graves' disease and multinodular goitre.^{1–5} In the UK, around 9000 total thyroidectomies are performed every year, with benign disease accounting for a majority of the cases (Graves' disease: 31 per cent; toxic multinodular goitre: 29 per cent).⁶

Post-operative hypocalcaemia is a common complication following total thyroidectomy, with an incidence of around 30 per cent.^{3,7–9} Hypocalcaemia is variably defined by measured serum calcium levels, with or without the presence of symptoms and signs. It occurs as a result of inadvertent damage or removal of the parathyroid glands, either directly or indirectly through disruption of the blood supply. Most cases are transient, and calcium levels normalise over a period of months. However, around 2 per cent of patients develop permanent hypoparathyroidism, defined as low serum parathyroid levels or ongoing need for calcium supplementation at 12 months.^{9,10}

Although a majority of patients with post-operative hypocalcaemia are asymptomatic, up to 30 per cent may develop symptoms, and a small proportion develop severe hypocalcaemia requiring intravenous calcium supplementation. As well as prolonging hospital length of stay, hypocalcaemia necessitates repeated blood tests and may warrant intensive care unit admission for central line insertion and monitoring if intravenous calcium replacement is required.^{11,12}

Systematic reviews have shown that supplementation with calcium or vitamin D after thyroidectomy reduces the risk of hypocalcaemia.^{13,14} However, evidence around outcomes following pre-operative supplementation with hypercalcaemic agents remains ambiguous, and there are no systematic reviews or meta-analyses studying this.

This systematic review aimed to establish the evidence behind the use of pre-operative calcium or vitamin D supplementation to prevent post-operative hypocalcaemia in patients undergoing thyroidectomy. We hypothesised that pre-operative treatment with calcium or vitamin D would reduce the incidence of post-operative hypocalcaemia in total thyroidectomy patients. Our secondary aim was to assess whether pre-operative supplementation reduced the length of stay in hospital following total thyroidectomy.

Materials and methods

Inclusion criteria

This review included prospective clinical trials on adult human patients undergoing total thyroidectomy that were published in English and which assessed the effect of pre-

operative calcium or vitamin D and its derivatives on the rate of post-operative hypocalcaemia.

Method

PubMed, Embase and Cochrane databases were searched. Search terms used were 'thyroid', 'thyroid surgery', 'thyroid removal', 'thyroid resection', 'thyroidectomy', 'vitamin', 'vitamin D', 'vitamin D3', 'vitamin supplement', 'calcitriol', 'alfacalcidol', 'cholecalciferol', 'calcium carbonate' and 'calcium'. Limits used were 'English language' and 'human subjects'.

Results were initially screened by title and then by abstract. Finally, full papers were examined. Those that met the eligibility criteria were included in the review. Cochrane's risk of bias tool (version 2) was used for quality assessment of the trials included in this review.¹⁵

Results

The search identified 5501 articles on PubMed, 6784 articles on Embase and 778 articles on Cochrane. One hundred and twenty-six articles were selected following title screening. Of these, 25 articles selected following abstract screening were examined in full.

Nine trials met the inclusion criteria (Figure 1 and Table 1).^{16–24} They included a total of 912 patients. The trials were published between 2006 and 2019, spanning 14 years. All nine trials studied adult populations in surgical in-patient departments, with follow up in out-patient clinics. Two trials were based in Italy,^{18,24} two were in Pakistan^{17,22} and the others were in India,²⁰ the USA,²¹ Malaysia,²³ Australia¹⁶ and France.¹⁹

Six trials studied patients undergoing total thyroidectomy only: one included patients who had near total thyroidectomy,²⁰ where less than 1 ml of the thyroid gland is spared excision; one included patients who had completion thyroidectomy (removal of remnant thyroid tissue following less than total thyroidectomy);¹⁶ and one included patients undergoing near total and subtotal thyroidectomy (sparing 3–5 g of thyroid tissue).¹⁷

Indications for surgery included both malignant and benign thyroid disease in eight trials,^{16–20,22–24} whereas one trial exclusively studied patients with Graves' disease.²¹ Follow up ranged between 1 week to 6 months. None of the trials followed up patients for long enough to comment on permanent hypocalcaemia or hypoparathyroidism, defined as low parathyroid hormone levels or need for calcium supplementation at one-year post-surgery.

Rowe *et al.* treated 72 patients with a single dose of 300 000 IU cholecalciferol 7 days prior to surgery, while 78 patients received placebo.¹⁶ Post-operatively, both groups were treated with calcium, vitamin D or both, based on a standardised protocol. Calcium was measured at baseline, pre-operatively and post-operatively up to 180 days.

There were no statistically significant differences in the rates of hypocalcaemia between the treatment and control groups at 48 hours (22 vs 35 per cent; $p = 0.09$) or at any point within 180 days (29 vs 38 per cent; $p = 0.23$). Symptomatic hypocalcaemia rates were also not statistically significantly different (13 vs 15 per cent). There were no significant differences in hospital length of stay, nor on calcium requirement at 6 months.

Bhattani *et al.* studied 102 patients, 51 of whom were pre-treated with 200 000 IU of vitamin D one day before surgery.¹⁷ Both treatment and control groups were given 700 mg/day of

calcium carbonate for 2 days pre-operatively. Post-operatively, both groups received vitamin D and calcium for a month. Serum calcium was measured pre-operatively, post-operatively at 24 hours, on post-operative day 3 (if hypocalcaemic) and up to 4 weeks post-operatively.

Serum calcium levels were statistically significantly lower in the control group compared with the treatment group on post-operative days 1, 7 and 30. Symptomatic hypocalcaemia rate in the treatment group (11.7 per cent) was statistically significantly lower than in the control group (29.4 per cent; $p < 0.05$). Rates of hypocalcaemia in the treatment group were lower compared with the controls on post-operative day 1 (13.7 vs 23.5 per cent) and day 3 (2.9 vs 7.8 per cent), but the statistical significance was not reported.

Testa *et al.* studied 42 patients, of which 22 patients were treated with calcitriol of 1.5 mcg/day and hydrochlorothiazide of 25 mg/day for 7 days pre-operatively.¹⁸ In the control group, 20 patients were given placebo. Post-operatively, patients in both groups were given calcium and calcitriol. Serum calcium levels were measured at baseline, on the day before surgery and daily post-operatively.

Pre-treatment with calcitriol and hydrochlorothiazide led to a statistically significant increase in pre-operative serum calcium compared with baseline (2.44 vs 2.34 mmol/l; $p < 0.05$). No significant difference was seen in the control arm (2.30 vs 2.29 mmol/l). Laboratory hypocalcaemia (serum calcium less than 2.10 mmol/l) was seen in 4.5 per cent of patients in the treatment group compared with 50 per cent of controls ($p < 0.01$). None of the patients in the treatment group developed symptomatic hypocalcaemia compared with 20 per cent in the control arm. Hospital stay was longer in the control group (3.6 days) compared with the treatment group (2.4 days; $p < 0.05$).

Genser *et al.* studied 219 patients, of which 111 were treated with 2 ug of alfacalcidol per day from pre-operative day 1 to post-operative day 8.¹⁹ One-hundred and eight controls were not treated. Serum calcium levels were measured pre-operatively, on post-operative day 1 and daily thereafter in hypocalcaemic patients. Calcium supplementation was given to hypocalcaemic patients. Serum calcium was measured at 5 weeks and 6 months post-surgery.

Statistically significant lower calcium levels were seen in the control group (2.04 mmol/l) compared with the treatment group (2.12 mmol/l) on post-operative day 2 but not on post-operative day 1. Rates of hypocalcaemia (serum calcium less than 2 mmol/l) between the two groups on post-operative days 1 or 2 were not significantly different. However, rates of severe hypocalcaemia (serum calcium less than 1.90 mmol/l) (1 vs 6 per cent; $p = 0.04$) and symptomatic hypocalcaemia (11 vs 22 per cent; $p = 0.02$) were significantly lower in the treatment group compared with controls. Symptomatic hypocalcaemia was defined by the presence of one of the following: perioral or fingertip paraesthesia, muscle cramps, Chvostek and Trousseau signs, tetany, neuropsychiatric symptoms, and cardiovascular symptoms (not defined). Six months after surgery, hypocalcaemia persisted in four patients in the control arm compared with none in the treatment group ($p = 0.04$). Hospital length of stay between the two groups was not significantly different.

Jaan *et al.* studied 60 patients, 30 of whom were treated with 500 mg of oral calcium 4 times daily and 0.25 ug of calcitriol 4 times daily for 7 days prior to surgery and continued for 7 days post-operatively.²⁰ The control group of 30 patients received no treatment pre- or post-operatively unless they

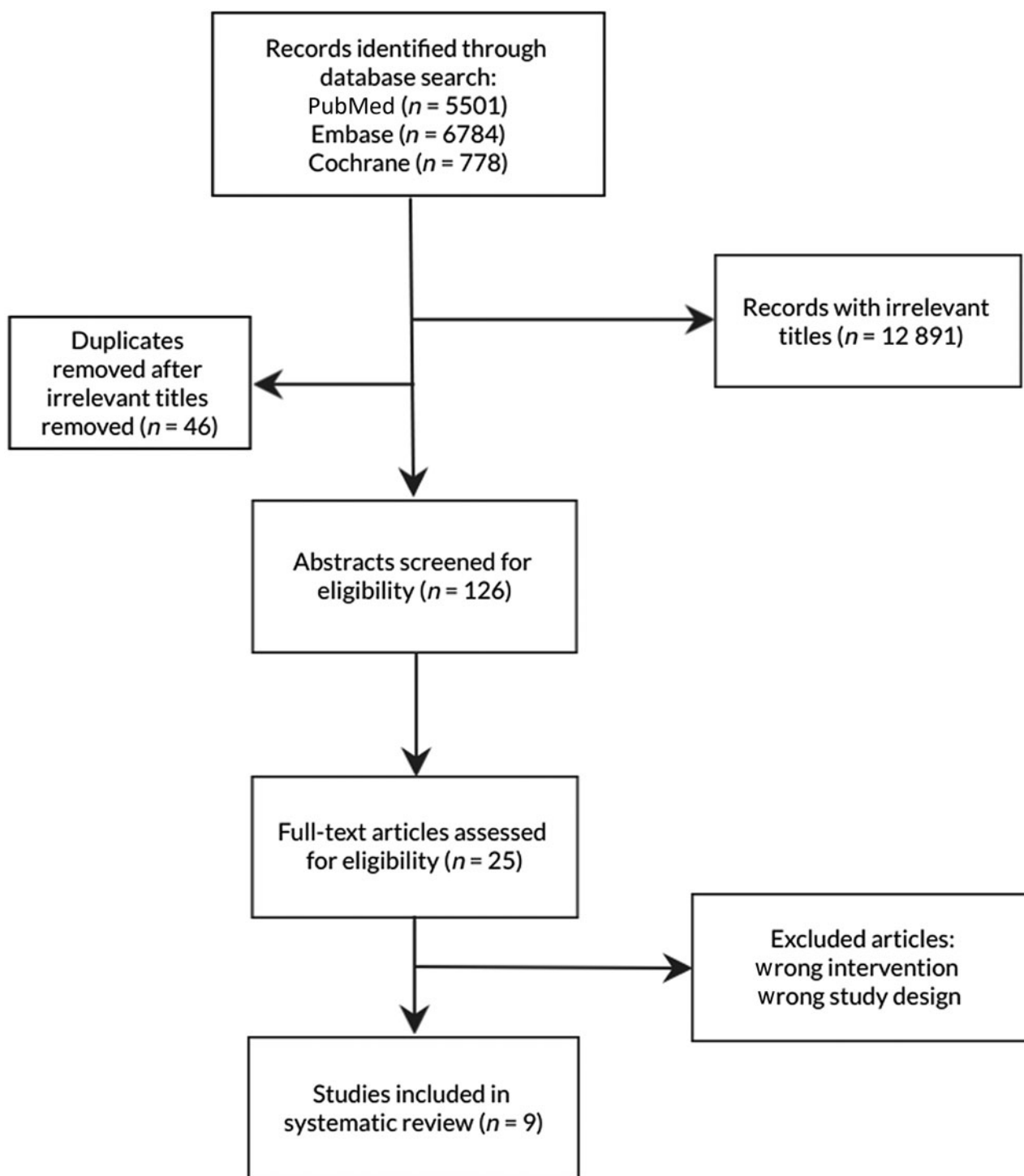


Fig. 1. Flowchart of search strategy.

developed symptomatic hypocalcaemia. Calcium levels were measured pre-operatively and post-operatively for up to 30 days.

Pre-treatment with oral calcium and calcitriol led to no statistically significant differences in post-operative calcium levels between the control and treatment arms. At 24 hours, the rates of hypocalcaemia (serum calcium less than 2.12 mmol/l) were not significantly different between the two groups. However, at 48 hours, hypocalcaemia rate in the treatment arm (20 per cent) was significantly lower compared with controls (43.3 per cent; $p = 0.04$). This statistically significant difference continued at 72 hours post-operatively, but after 30 days there was no significant difference in hypocalcaemia

rates between the two groups. The rate of symptomatic hypocalcaemia was significantly lower in the treatment arm (10 per cent) compared with controls (40 per cent; $p < 0.01$). Symptomatic hypocalcaemia was defined as the presence of one of the following: perioral or fingertip paraesthesia, neuropsychiatric manifestations, Chvostek and Trousseau signs, and prolonged QT interval on electrocardiogram.

Oltmann *et al.* studied 123 patients.²¹ Of these, 45 patients undergoing total thyroidectomy for Graves' disease were pre-treated with 1 g of calcium carbonate 3 times daily for 2 weeks prior to surgery. Thirty-eight historic controls undergoing total thyroidectomy for Graves' disease were not pre-treated. Forty patients undergoing total thyroidectomy for a

Table 1. Summary of included systematic reviews including rates of laboratory and symptomatic hypocalcaemia

| Trial | Patients (n) | Control | Treatment | Pre-operative treatment duration | Laboratory hypocalcaemia % (p-value) | Symptomatic hypocalcaemia % (p-value) |
|--------------------------------------|--------------|----------------------------|--|---|--|--|
| Rowe <i>et al.</i> ¹⁶ | 150 | Placebo | Cholecalciferol 300 000 IU | 7 days (single dose) | In-patient: 35 vs 22 (0.09); overall: 38 vs 29 (0.23) | 15 vs 13 (not statistically significant) |
| Bhattani <i>et al.</i> ¹⁷ | 102 | Calcium Carbonate 700 mg/d | Vitamin D 200 000 IU; calcium carbonate 700 mg/d | Vitamin D: 1 day (single dose); calcium: 2 days | Day 1: 23.5 vs 13.7*; Day 3: 7.8 vs 2.9* | 29.4 vs 11.7 [†] (0.05) |
| Lai <i>et al.</i> ²³ | 74 | None | Calcitriol 1.5 ug/d | 2 days | 75 vs 16 [†] (0.000) | 48.6 vs 8.3 [†] (0.001) |
| Docimo <i>et al.</i> ²⁴ | 50 | – | Vitamin D 880 IU/d; calcium 2 g/d | 3 days | 10 | 6 |
| Jaan <i>et al.</i> ²⁰ | 60 | None | Calcitriol 1 ug/day; calcium 2 g/d | 7 days | 48 hours: 43.3 vs 20 [†] (0.04); 72 hours: 46.7 vs 16.7 [†] (0.01) | 40 vs 10 [†] (0.01) |
| Malik <i>et al.</i> ²² | 92 | None | Vitamin D 200 000 IU; calcium 1 g | 1 day | 26.1 vs 6.5 [†] (0.011) | – |
| Oltmann <i>et al.</i> ²¹ | 123 | None | Calcium carbonate 3 g/day | 14 days | – | 26 vs 10 [†] (0.049) |
| Testa <i>et al.</i> ¹⁸ | 42 | Placebo | Calcitriol 1.5 ug/d; hydrochlorothiazide 25 mg/d | 7 days | 50 vs 4.5 [†] (0.01) | 20 vs 0 [†] (0.05) |
| Genser <i>et al.</i> ¹⁹ | 219 | None | Alfacalcidol 2 ug/d | 1 day | 24 hours: 37 vs 30 (0.25); 48 hours: 14 vs 6 (0.06) | 22 vs 11 [†] (0.02) |

*P-value not reported; [†]statistically significant data.

non-Graves' pathology, who were not pre-treated, acted as procedural controls. Post-operatively, all Graves' disease patients were routinely given calcium supplementation, whereas use of calcitriol was protocol driven. Calcium levels were measured pre-operatively. In patients staying in hospital overnight, calcium levels were also measured at 4 hours post-operatively. Calcium measurement on post-operative day 1 was at surgeon discretion.

Pre-treatment with calcium carbonate led to a symptomatic hypocalcaemia rate of 10 per cent, compared with 26 per cent in the control arm ($p = 0.049$). Symptomatic hypocalcaemia was defined as the presence of numbness, tingling, muscle cramping or tetany. Four-hour post-operative calcium levels were significantly higher in the pre-treated group (2.15 mmol/l) compared with controls (2.07 mmol/l; $p = 0.05$).

Malik *et al.* studied 92 patients.²² Forty-six were treated with 200 000 IU of vitamin D and 1 g of calcium for 24 hours prior to surgery. In the control group, patients were not given anything. Post-operative treatment was not reported. In the treatment arm, 6.5 per cent developed hypocalcaemia (serum calcium <2.12 mmol/l) compared with 26.1 per cent in the control arm ($p = 0.011$).

Lai *et al.* studied 74 patients, who received either 0.5 mcg of calcitriol 3 times daily for 2 days pre-operatively or no pre-operative supplement.²³ Post-operatively, patients in the treatment arm were given calcitriol and oral calcium for one week. In the control arm, patients were given neither unless they were symptomatic. Calcium was measured up to 48 hours post-operatively and patients were followed up at 2 weeks and 6 months.

Rate of hypocalcaemia (serum calcium less than 2.1 mmol/l) in the treatment group was 16.7 per cent compared with 75 per cent in the control group ($p = 0.000$). Symptomatic hypocalcaemia was also statistically significantly lower in the treatment group (8.3 per cent) compared with the control group (48.6 per cent). Serum calcium between the two groups was

significantly lower in the control group at 6 hours, 24 hours and 48 hours post-operatively. Post-operative hospital length of stay was shorter in the treatment group compared with the control group (3.92 vs 4.59 days; $p = 0.001$).

Docimo *et al.* studied 50 patients pre-treated with oral calcium of 2 g/day and vitamin D of 880 U/day for 3 days before surgery.²⁴ This trial did not have a control arm. Treatment was continued until post-operative day 14. Calcium levels were measured pre-operatively, on post-operative day 1 and then every 24 hours until discharge. Laboratory hypocalcaemia (serum calcium less than 2 mmol/l) occurred in 10 per cent of patients and symptomatic hypocalcaemia in 6 per cent of patients.

Using Cochrane's risk of bias tool (version 2), one trial had low risk,¹⁶ four were of some concern^{17–20} and four had a high risk of bias.^{21–24} Risk of bias was because of methodological issues around randomisation, concealment, blinding, analysis and reporting.

Discussion

This systematic review included nine trials studying the effect of pre-operative vitamin D, calcium or both vitamin D and calcium supplementation to reduce the rate of hypocalcaemia after total thyroidectomy.

Seven out of the nine trials showed a statistically significant reduction in the rates of laboratory hypocalcaemia, symptomatic hypocalcaemia or both in patients who were pre-treated.^{17–23} Absolute risk reduction in the rate of laboratory hypocalcaemia was 13–59 per cent and for symptomatic hypocalcaemia was 11–40 per cent. In the remaining two trials, one did not have a control arm for comparison.²⁴ Post-operative hypocalcaemia rates in pre-treated patients in this trial were comparable to those seen in the treatment arms of the other trials. Finally, Rowe *et al.* found no statistically significant differences in rates of laboratory or symptomatic hypocalcaemia,

although they reported a trend towards reduced hypocalcaemia rates with pre-treatment.¹⁶

Four out of nine trials reported on hospital length of stay.^{16,18,19,23} Two of these found statistically significant reduced length of stay in the treatment group,^{18,23} and two found no difference.^{16,19} A longer length of stay in hospital would be explained by the need for calcium infusion in patients in the control arm who developed symptomatic or severe hypocalcaemia. Hospital length of stay should be measured as an outcome in more trials, given that this is rightly cited as being a significant consequence of hypocalcaemia.

The treatments used in the intervention arms of the trials were not identical. However, all trials used a variant of oral vitamin D (calcitriol, alfalcidol, cholecalciferol or vitamin D, unspecified) or oral calcium or both. Testa *et al.* used hydrochlorothiazide, a calcium sparing diuretic, in addition to calcitriol.¹⁸ Three trials used oral vitamin D only,^{16,19,23} four trials used vitamin D and calcium^{17,20,22,24} and one trial used calcium only.²¹ Doses of the hypercalcaemic agents were comparable across the trials.

The duration of pre-operative supplementation varied significantly between the trials, which is one of the limitations of this review. Two trials used pre-operative supplementation for one day,^{19,22} two trials used it for two days^{17,23} and one trial used it for three days.²⁴ Four trials had supplementation durations of seven days or longer: two for seven days,^{18,20} one for two weeks²¹ and one which gave a single loading dose of cholecalciferol seven days before surgery.¹⁶ Two out of these four reported statistically significant increased peri-operative serum calcium levels, which led to reduced hypocalcaemia rates.^{18,21} One reported no significant difference in serum calcium levels but found statistically significant reduced rates of hypocalcaemia in the treatment arm.²⁰ In the fourth trial, post-operative serum calcium levels were not reported, and no significant decrease in post-operative hypocalcaemia rates was found.¹⁶

Genser *et al.* also reported statistically significant increased calcium levels in pre-treated patients compared with controls.¹⁹ Of note, they started supplementation on pre-operative day 1 and only noted a statistically significant increase in serum calcium on day 2 post-operatively.

These findings suggest that the reduction in rate of post-operative hypocalcaemia is likely mediated through direct effects on serum calcium levels.

Only two out of nine trials measured vitamin D levels.^{16,19} Rowe *et al.* studied a predominantly Caucasian Australian cohort replete in vitamin D, with a mean pre-supplementation level of 72 nmol/l and no patients with severe vitamin D deficiency (less than 25 nmol/l). There was no correlation between baseline vitamin D levels and post-operative hypocalcaemia rates. Loading with 300 000 IU cholecalciferol raised the vitamin D levels in the treatment group from 77 nmol/l to 119 nmol/l but did not lead to a significant pre-operative rise in serum calcium. There was a trend towards reduced hypocalcaemia rate in the treatment group, but this did not reach statistical significance ($p = 0.09$). Post-operative serum calcium levels were not reported.

Genser *et al.* reported a mean baseline vitamin D level of 54 nmol/l.¹⁹ Alfalcidol of 2 µg, given from pre-operative day one to post-operative day eight, led to statistically significant higher calcium levels (2.12 vs 2.04; $p = 0.04$). Hypocalcaemia rate was reduced in the pre-treated group (6 vs 14 per cent), but this was not statistically significant ($p = 0.06$). However, symptomatic hypocalcaemia rate was significantly lower in

the treatment group (11 vs 22 per cent; $p = 0.02$). Vitamin D levels five weeks post-operatively were unchanged from baseline.

Jaan *et al.* and Bhattani *et al.* did not measure vitamin D levels in their studies but cited high vitamin D deficiency rates of 83 to 92 per cent within their respective populations.^{17,20} They reported post-operative hypocalcaemia rates of 43 and 23.5 per cent, respectively, in their control groups, comparable to the 38 per cent found by Rowe *et al.* in their vitamin D replete population.¹⁶

These findings suggest that post-operative hypocalcaemia rates are not related to pre-operative vitamin D levels. However, vitamin D supplementation may be more beneficial in deficient populations compared with populations replete in vitamin D. This needs further investigation.

Post-operative treatment in the two arms varied between the trials. Four trials used uniform post-operative treatment in both arms.^{16–18,21} Testa *et al.* gave all patients calcium and calcitriol post-operatively.¹⁸ They reported an absolute risk reduction of laboratory hypocalcaemia of 45 per cent and symptomatic hypocalcaemia of 20 per cent. Bhattani *et al.* gave all patients calcium and vitamin D post-operatively.¹⁷ They found an absolute risk reduction in symptomatic hypocalcaemia of 18 per cent. They also found a 10 per cent absolute risk reduction in laboratory hypocalcaemia, but the statistical significance was not reported. Oltmann *et al.* routinely gave all patients calcium post-operatively.²¹ They reported a 16 per cent absolute risk reduction in symptomatic hypocalcaemia. These changes may be attributed to the differential pre-operative supplementation given in these trials.

Where differential pre-operative supplementation was continued into the post-operative period, it is difficult to ascertain how much of the treatment effect is attributable to pre-operative supplementation rather than differential post-operative treatment. This is especially true of the trial conducted by Genser *et al.*, which only started supplementation one day before surgery.¹⁹

Two trials reported hypercalcaemia associated with treatment.^{16,18} Testa *et al.* reported hypercalcaemia in 3 of 22 pre-treated patients.¹⁸ However, all were asymptomatic and did not require treatment. Rowe *et al.* reported hypercalcaemia in three patients pre-treated with vitamin D, which was not statistically significantly different compared with the control group.¹⁶ Again, none of the patients required intervention.

The effect of pre-operative vitamin D or calcium on post-operative hypocalcaemia reported in these trials is likely to be applicable to the UK population. The mean post-operative calcium levels in the control arms of the trials ranged from 2.03 to 2.19 mmol/l, comparable to post-thyroidectomy calcium levels reported in the UK population (2.07–2.17 mmol/l).^{25,26} Furthermore, the majority of patients included in this review underwent either total thyroidectomy or near-total thyroidectomy, which represents a large proportion of thyroid surgery undertaken in the UK.⁶

Of the nine trials, seven were reportedly randomised.^{16–20,22,23} Three of these adequately described their randomisation process.^{16,19,22} Three trials used a placebo for the control arm and were double-blinded.^{16–18}

Oltmann *et al.* used historic controls.²¹ This trial was neither randomised, nor blinded. Baseline differences between the treatment and control groups included the rate of auto-transplantation required during surgery (significantly higher in the study population). Docimo *et al.* had no control arm, so randomisation and blinding were not applicable.²⁴ This

rendered their findings difficult to interpret, and highly susceptible to bias.

Conclusion

Seven out of nine trials identified in this systematic review have shown that pre-operative supplementation with hypercalcaemic drugs (calcium, vitamin D and derivatives or calcium sparing diuretics) reduces the rate of hypocalcaemia. Randomised controlled trials of more robust design and improved standardisation of peri-operative treatment are required before the evidence base can support standardised guidelines in this area. However, the current available evidence suggests that the use of hypercalcaemic drugs in the pre-operative period reduces the number and severity of cases of post-operative hypocalcaemia. Furthermore, none of the trials reported significant side effects from the use of hypercalcaemic drugs, indicating that pre-operative supplementation may provide benefit without conferring increased risk.

Competing interests. None declared

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