Abstract
Hypocalcemia is the most common complication following total thyroidectomy and could be due to direct injury or ischemic damage to parathyroid glands during surgery. Hypocalcemia adds significantly to hospital stay and cost of hospitalisation. While there are numerous proposed treatment algorithms for post-thyroidectomy hypocalcemia, there are no universally accepted standard guidelines or treatment algorithms available. We present a case of prolonged recalcitrant hypocalcemia post-total thyroidectomy, requiring hospitalisation for more than a month, to illustrate the practical problems we faced during management of this patient.

Keywords
Hypocalcemia, thyroidectomy, calcium, parathormone.

Introduction
While hypocalcemia is the most common documented complication post-total thyroidectomy, hypocalcemia requiring prolonged hospitalisation and intravenous (IV) calcium supplementation is relatively rare. Hypocalcemia occurs due to manipulation of parathyroids during surgery, devascularisation, venous engorgement or accidental removal. The incidence of temporary and permanent hypocalcemia is reported to be around 27% and 1% respectively. Since the risk of reactionary/secondary haemorrhage after 24 hours of thyroidectomy is very rare, symptomatic hypocalcemia is the main reason for prolonged hospitalisation post-thyroidectomy.

The pre-operative factors associated with post-thyroidectomy hypocalcemia are still unclear and various scoring systems have been proposed to identify patients likely to develop post-operative hypocalcemia. Identification of at-risk patients allows earlier and more aggressive calcium correction regimens allowing for shorter hospital stays and invasive investigations in low-risk patients.

Feeling of ‘heat waves’ are a documented adverse effect of IV calcium gluconate, especially when given rapidly. We could not find any literature linking either severe thrombophlebitis or high-grade fever with IV calcium injections. However, this is the second patient in our institute to develop high spiking fever coinciding with IV calcium injections.

Case report
A 39-year-old woman presented with thyromegaly and features suggestive of hyperthyroidism. She was worked up for the same
and diagnosed to have a multinodular goiter (MNG) with secondary thyrotoxicosis. Hyperthyroidism was controlled with carbimazole, thyroid status was optimised and patient was posted for total thyroidectomy. Intra-operatively, parathyroid glands were not identified and inferior thyroid artery branches were ligated and divided after crossing the recurrent laryngeal nerve (subcapsular vascular ligation). Intra-operative period was uneventful, patient was extubated and shifted to post-operative ward.

In the evening following thyroidectomy, patient complained of tingling in the fingers. On examination, Trousseau’s sign was present (Figure).

**Figure 1: Bilateral carpal spasm**

Blood calcium levels were low, hence IV calcium gluconate bolus (10ml of 10% calcium gluconate in 100 ml 0.9% Saline) was given. Symptoms subsided but reappeared the next morning. Patient was started on thrice daily IV calcium boluses, however symptoms persisted and additional calcium boluses had to be given as needed. Patient also developed high spiking fever, for which she was worked up, and no evident source could be identified. Fever spikes coincided with IV calcium injections and patient developed pain and swelling around IV lines. A diagnosis of thrombophlebitis was made and IV lines were changed. Fever abated temporally but reappeared. Patient developed episodes of symptomatic hypocalcemia whenever an attempt to taper calcium infusion was made. Hence treatment was altered: oral calcium reduced to 4g/day, oral calcitriol increased to 1.50 mcg (0.75mcg BD) daily, low dose hydrochlorthiazide (12.5 mg) added and salt restriction was advised. Calcium infusion was gradually tapered and stopped, and replaced with IV calcium boluses that were also gradually tapered and stopped. Patient did not have any further episodes of symptomatic hypocalcemia or fever.

Patient was started on oral Vitamin D (60,000 IU once fortnightly), urine calcium and serum phosphate were assessed and calcitriol was reduced to 1.00 mcg/day and was discharged from the hospital after 46 days post-thyroidectomy.

Patient has since come for 5 follow-up visits. Serum calcium has stabilized and hence oral calcium supplementation was reduced. Calcitriol was gradually tapered and stopped. Oral Vitamin D was reduced to 60,000 IU monthly. Patient is currently doing well, with no constipation, fever or any symptoms suggestive of hypocalcemia.

**Discussion**

Severe hypocalcemia is one of the life-threatening complications post-thyroidectomy. The initial features of perioral numbness and tingling of fingers which often go unnoticed, can prove fatal due to cardiac arrest if prompt action is not taken at the appropriate moment.

Post-op hypocalcemia can be transient (lasting <12 months) or permanent, in which medical supplementation is required for more than 12 months. Post-thyroidectomy hypocalcemia may be asymptomatic, termed ‘lab hypocalcemia’ or symptomatic. Symptomatic hypocalcemia, severe hypocalcemia (corrected calcium <7.5mg/dl, <1.87
mmol/L) or hypocalcemia associated with ECG QT prolongation warrants hospitalisation and immediate IV calcium supplementation. Initial correction by bolus of 10 ml of 10% calcium gluconate in 50-100 ml 0.9% Saline/5% dextrose should be urgently administered in all cases of symptomatic hypocalcemia over 20 minutes, as more rapid infusion can cause lethal cardiac dysfunction.\textsuperscript{3,5} It is recommended that this be followed by IV calcium infusion regimen, as this bolus will only correct the calcium levels for 2-3 hours.\textsuperscript{6}

Accurate prediction of which patients will develop this complication is difficult, leading to unnecessary long hospitalisation to monitor for this rather rare complication. A meta-analysis published by Edafe et al\textsuperscript{1} identifies these factors as independent predictors of post-thyroidectomy hypocalcemia: (a) identification of <2 parathyroids during surgery; (b) reoperation for bleeding; (c) corrected calcium <7.5mg/dl or <1.87 mmol/L 24 hours post-surgery; (d) Graves’ disease; (e) heavier thyroid specimens. An accurate risk stratification would allow for earlier and more aggressive institution of calcium correction regimens, possibly reducing hospital stay. This would also reduce unnecessary supplementation and investigations in the majority of patients who would not develop hypocalcemia. Albuja-Cruz et al\textsuperscript{4} have proposed a risk stratification protocol (Table 1). In this prospective study, the above-mentioned protocol was applied to 120 patients, demonstrating a significant reduction in calcium supplementation (\textit{P}≤0.001) and hypocalcemic events (\textit{P}=0.008). However, this protocol requires routine measurement of pre-and post-operative PTH levels, an expensive test that may not be justified given the low incidence of persistent, severe hypocalcemia. Another prospective study by Arer et al\textsuperscript{5} on 106 patients demonstrated that routine calcium supplementation can prevent early hypocalcemia post-thyroidectomy. A retrospective study by Maxwell et al\textsuperscript{6} confirms that routine supplementation of calcium and Vitamin D were associated with reduced cost and duration of hospitalisation with fewer episodes of hypocalcemia.

Recalcitrant hypocalcemia patients not responding to conventional doses of active vitamin D analogues (calcitriol or 1-alpha calcidol) and oral calcium, and requiring prolonged IV calcium are exceptionally rare. Treatment options for such patients include addition of thiazide diuretic and use of recombinant PTH. Thiazide diuretics also serve to offset the dose limiting side effect of Vitamin D and calcium supplementation: nephrocalcinosis due to increased renal calcium loss in the absence of the resorbptive effects of PTH on the renal tubules.\textsuperscript{7}

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<tr>
<th>Risk group</th>
<th>Recommended treatment</th>
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<tr>
<td><strong>High risk:</strong> Post-op PTH &lt;10 and/or fall in PTH more than 60% from pre-op value</td>
<td>Calcitriol 0.5 mcg BD + 6 g calcium daily</td>
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<tr>
<td><strong>Intermediate risk:</strong> PTH 10-19 and/or corrected calcium &lt;8</td>
<td>3 g calcium daily</td>
</tr>
<tr>
<td><strong>Low risk:</strong> PTH &gt;20 and/or corrected calcium &gt;8</td>
<td>Nil</td>
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Recombinant PTH (rPTH) is expensive, and there are no controlled trials demonstrating its effectiveness or safety in the setting of post-thyroidectomy hypocalcemia. However, it has a lower incidence of hypercalciiuria, significantly reduces calcium and calcitriol requirement. A prospective phase 2 randomised trial by McLeod et al\textsuperscript{8} on 26 patients demonstrated that rPTH may prevent post-thyroidectomy hypocalcemia, shorten duration of hospitalisation and reduce the need for calcium and Vitamin D on discharge. The drug label carries a warning for osteosarcoma although this has only been observed in rats, at a dose much higher than what is generally used in humans\textsuperscript{9}. The cost of this injectable drug limits its use in clinical practice and it is only recommended for use in patients who cannot attain normocalcemia on oral calcium and Vitamin D supplements alone.\textsuperscript{9}

All patients receiving active vitamin D analogues and calcium supplementation should have regular monitoring of serum calcium and phosphate levels, until values stabilise. The lowest dose required to achieve a low-normal serum calcium while avoiding hyperphosphatemia should be administered. Shorter acting calcitriol should be replaced with longer acting vitamin D analogues.
such as cholecalciferol to simplify dosing. Also, urine calcium should be maintained less than 300 mg/24 hours to prevent nephrocalcinosis that can result in chronic kidney disease. This case highlights the significant morbidity and difficulty faced in managing a relatively simple complication. Accurate prediction and early institution of treatment could possibly reduce length of hospitalisation.

References