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EDITORIAL

Iatrogenic/post-surgical hypoparathyroidism: where do we go from here?

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Hypoparathyroidism and hypocalcaemia have been described as postoperative complications since the early descriptions of thyroid surgery from the days of Kocher and Bilroth [1]. In addition, surgical hypoparathyroidism also occurs in a significant proportion of patients undergoing other surgical procedures such as parathyroidectomy [2] and laryngectomy [3]. The steady stream of publications on post-surgical hypoparathyroidism suggests that the problem is still of major significance to patients and surgeons.

Two recent papers in the 'Endocrine' journal have highlighted the problem in different cohorts of patients. The first paper by Pelizzo et al. [4] reported complication rates in 233 patients undergoing re-operative thyroid surgery over a 5-year period. Their detailed description of the operation is a good educational resource for trainee surgeons. Their low complication rates (transient and definitive hypoparathyroidism rates of 36.4 and 3.3 %, respectively; transient and definitive recurrent laryngeal nerve injury rates of 7 and 1.7 %, respectively; reoperation for bleeding in 2.5 %) provides reassurance on the safety of re-operative surgery and encourages surgeons to adopt hemi-thyroidectomy for unilateral benign disease (if they have not already done so). Hemi-thyroidectomy (or lobectomy) is widely practised in the UK and represents around 50 % of all thyroid procedures registered in the National British Association of Endocrine and Thyroid Surgeons (BAETS) registry [5]. The limited nature of this procedure reduces the risk of nerve damage and postoperative hypocalcaemia; reduces the requirement for postoperative thyroxine replacement therapy; and is effective, given that the indication is benign disease in the majority of instances.

The second paper [6] is a large prospective study of the incidence and risk factors for post-thyroidectomy hypocalcaemia in 2,631 patients from 39 Italian centres undergoing thyroidectomy (excluding Graves' disease) in a 7-month period. The study demonstrated a risk of 28.8 and 0.9 % for temporary and long-term hypocalcaemia, respectively. Variables found to be associated with risk were thyroid cancer, female gender and concomitant neck dissection. Limitations of this study include a lack of clarity on the definition of long-term hypocalcaemia and on the reasons underlying the exclusion of patients with Graves' disease from the cohort.

Outside published series from selected (and probably high volume) centres, the risk of long-term hypocalcaemia seems higher than the often quoted 1 % rate. The Scandinavian multicentre audit demonstrated that 4.4 % of patients required treatment with vitamin D at 6 months following surgery [7]. Data from the UK BAETS registry suggest a much higher 'late hypocalcaemia' rate of 12.1 % following total thyroidectomy [5]. Given that there is a significant proportion of missing data and that the BAETS dataset only accounts for around a quarter of all thyroid surgery in the UK, there is concern that these figures may be an underestimate of the true magnitude of the problem in the community.

A common problem in the reporting of the risk of this problem is the significant influence of the definition of hypocalcaemia on the reported incidence rate. Mehanna and colleagues demonstrated how the rate of hypocalcaemia in their cohort ranged from 0 to 46 % depending on

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the definition used [8]. The definition of hypocalcaemia should consider the biochemical threshold for the level of calcium, the presence of clinical features of hypocalcaemia and the need for treatment. The timing of measurement (after thyroid surgery), the nature of measurement (total calcium, adjusted calcium, ionized calcium) and the specific assay used will also have an impact on the perceived risk of hypocalcaemia. Hypocalcaemia may be due to factors other than hypoparathyroidism, such as hungry bone syndrome following thyroidectomy for Graves' disease [9]; this needs to be taken into consideration. In defining long-term hypocalcaemia, the duration of the condition (what is long term?) and ongoing treatment with calcium and/or vitamin D supplements will significantly influence the apparent frequency of the condition. Although other factors such as eligibility criteria for inclusion of patients, underlying disease, extent of surgery, surgical volume and experience of the surgeon may explain the variation in incidence, it is clear that the surgical community should move towards a consensus in defining immediate and persistent (long-term) hypocalcaemia.

The problem of early and accurate prediction of post-operative hypocalcaemia has also been discussed in great detail and has recently been a subject of a detailed review [10]. While prediction may help in targeting 'at risk' patients with prophylactic calcium and/or vitamin D supplementation and facilitate early discharge, it does not (yet) have an impact on the long-term consequences of the disease. Several preventative measures have been studied for their impact on reducing the risk of the problem. Although, prophylactic supplementation may reduce the risk of transient hypocalcaemia, they do not appear to have an impact on long-term hypocalcaemia. Surgeons and researchers have to look elsewhere for solutions—perhaps technologies that facilitate accurate identification and preservation of parathyroid glands at surgery should be explored. These may include the use of intraoperative fluorescent imaging [11, 12], confocal imaging [13] and optical coherence tomography [14].

Only a minority of patients with transient hypoparathyroidism end up with long-term or persistent disease. Resolution of hypoparathyroidism is likely to be related to recovery of the parathyroid glands from the surgical insult. Not only is it currently difficult to predict which patients will recover, but it is also unclear as to whether any specific intervention will facilitate recovery. Surgeons have traditionally called for 'under treating' patients with calcium and/or active vitamin D supplements (such as Alfacalcidol or Calcitriol) in the hope that the resultant mild hypocalcaemia will stimulate parathyroid recovery. This 'under treatment' where the aim is to maintain mild but asymptomatic hypocalcaemia is referred to as the 'stimulating' strategy; this will also reduce the risk of hypercalcaemia resulting from over treatment. However, more recently, Sitges-Serra et al. have argued in favour of an alternative 'splinting strategy' which refers to adequate treatment with calcium and/or active vitamin D to ensure that the calcium remains well in the normal range during the period of transient hypoparathyroidism. Observational evidence suggests that this may reduce the metabolic stress on already injured and ischaemic glands, allowing these glands to 'rest and recover'; thus reducing the risk of long-term hypoparathyroidism [15]. The debate over 'splinting' versus 'stimulating' strategies continues!

In comparison to long-term laryngeal nerve damage, the impact and morbidity associated with long-term hypoparathyroidism has been relatively unrecognised. Anecdotally, surgeons have traditionally held the view that this problem is easily treated (with supplements)! This is illustrated by a report demonstrating a distinct discordance between surgeons' perceptions of the impact of this problem on quality of life and patients' self-reported quality of life (QoL) [16]. Surgeons also tend to underestimate the impact of treatment-related morbidity in comparison to physicians [17]. In addition to a detrimental impact of QoL, patients with long-term hypoparathyroidism have an increased risk of renal and basal ganglia calcifications [18] and chronic kidney disease [19]; the latter made worse by the need for calcium supplements and resulting hypercalciuria in the presence of a low serum PTH. Recent epidemiological data has also shown that these patients are more likely to be predisposed to neuropsychiatric diseases (including depression) and infections [20]. Despite the low incidence of the problem, the prevalence of post-surgical hypoparathyroidism in the Western world is estimated to be around 22 per 100,000 population [19]. This combined with the need for active and close monitoring and the effects on kidney, brain and other organ function makes post-surgical hypoparathyroidism an iatrogenic disease with significant healthcare costs.

The current management of long-term hypoparathyroidism involves close monitoring of calcium levels and treatment with calcium and active vitamin D; the aim of treatment being to keep the level of adjusted calcium at the lower end of the normal range. This will reduce the risk of hypercalcaemia [21, 22] and hypercalciuria [23], which have potential for renal impairment. There now reports that synthetic human PTH in the form of PTH(1–34) [23] or PTH(1–84) [24] may be used as PTH replacement therapy and that this may be superior to calcium and vitamin D supplements; this is however not advocated for routine clinical practice at the current time.

In summary, I believe that a concerted effort is required to address the problem of post-surgical hypoparathyroidism. The efforts need to focus on achieving a consensus on definitions and reporting standards; encouraging research

on intraoperative techniques and technologies aimed at parathyroid preservation; evaluation of the comparative effectiveness of 'splinting' vs 'stimulating' strategies for patients with temporary hypoparathyroidism; and determination of an optimum treatment strategy in patients with established long-term hypoparathyroidism. Perhaps, the time is right for the establishment of an international study group to address these objectives?

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