

Intraoperative parathyroid hormone estimation: a valuable adjunct to parathyroid surgery

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Key words: Parathyroid gland surgery; Parathyroid hormone levels; Microtomy

Serial measurements of serum intact parathyroid hormone (PTH) and adjusted total calcium levels were performed on 10 patients during unilateral neck exploration for a solitary parathyroid adenoma localised preoperatively by ultrasound scan. Frozen section was performed preoperatively to establish the presence of parathyroid tissue. Levels of PTH were shown to be within the normal range within 15 min of adenoma removal (a mean of 13.4% of their preoperative values), allowing clear early distinction from unsuccessful surgery where no change occurred. Frozen section wrongly identified thyroid tissue as parathyroid in one case leading to a failure of the initial neck exploration.

Our findings show that intraoperative PTH measurements can accurately predict whether all hyperfunctioning parathyroid tissue has been removed. This is not always possible using frozen section techniques. The wider use of intraoperative PTH measurement, particularly in difficult cases, may avoid the need for prolonged explorations to identify all four glands and, perhaps, biopsy of normal glands, replacing the current standard use of frozen section as a more reliable indicator of the success of parathyroid surgery.

The advent of multichannel analysis for routine biochemical screening has increased the number of patients with apparently asymptomatic hypercalcaemia being identified (1) with a prevalence as high as 3.6% being found (2).

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Until recently the diagnosis of primary hyperparathyroidism in such patients was complicated by the fact that the rapid *in vivo* metabolism of the 84 amino acid PTH molecule resulted in multiple circulating immunoreactive fragments. Recently, new assays have been developed which specifically recognise intact PTH (3-7), allowing clear distinction between patients with primary hyperparathyroidism and other causes of hypercalcaemia. In the absence of any effective alternative (8), such patients are increasingly being offered surgery (9,10) in the expectation that the majority should be cured by the initial neck exploration.

Surgery used to routinely involve the identification of all four parathyroid glands and the removal of any pathological gland or glands, using frozen section to confirm their pathology. When this is done the morbidity following surgery is usually limited to transient hypocalcaemia, the incidence of which increases with the number of glands biopsied (11), but protracted hypoparathyroidism can occur in 2% of cases (10). Modern surgical practice, with preoperative identification of a single adenoma, allows a more limited approach to both the identification and biopsy of normal glands. Identification of all four parathyroid glands remains necessary in cases with multiple adenomas, unexpected hyperplasia or re-explorations, where failure to identify and remove all hyperfunctioning tissue results in a group of patients with persistent or recurrent hyperparathyroidism (12,13). Failure of frozen section also contributes to the need for reoperation (12) and disagrees with the definitive histology in 10% of cases (14), often to the extent of altering surgical management (15).

The short half-life of the intact PTH molecule (about 20 min) and the advent of rapid assays (16,17) appears to allow identification of these surgical failures at an intra-operative stage (17–19) and has implications for the extent of surgery necessary.

We report a series of 10 patients undergoing unilateral neck exploration for solitary parathyroid adenomas in whom the intra- and postoperative changes in PTH were determined. One patient required re-exploration for persisting hypercalcaemia.

Patients and methods

A series of 10 consecutive patients, three male and seven female, with biochemically proven primary hyperparathyroidism (persistently elevated adjusted serum calcium levels on at least three occasions with an inappropriate elevation of intact PTH levels) were studied. Their ages ranged from 21–74 years (median 55.2 years). Seven patients underwent surgery within a year of diagnosis, the other three had been under follow-up for 2, 4 and 8 years. Three presented with symptomatic renal stones, one with lethargy and the remaining six were identified on routine biochemical screening. On direct questioning, a further four complained of increased lethargy, one of polyuria and one was noted to have subperiosteal bone resorption of the terminal phalanges on hand radiographs.

Before surgery all patients had an ultrasound examination of the neck performed by a radiologist (AB) using a 7.5 and/or 5 MHz probe on an Aloka 650[®] ultrasound machine (Fig. 1). At midday on the day before surgery, fasting serum samples were taken for PTH levels and multichannel biochemical analysis including adjusted serum calcium levels. These and all subsequent samples were separated and the serum frozen to -40°C within 10 min for later assay. During surgery the same samples were taken from a peripheral vein at the time of adenoma removal (time 0) and then at 15, 30, 45, 60 and 120 min with further samples at 6, 12, 24 and 48 h.

In all cases surgery commenced with exploration of any ultrasonically localised abnormality. If a pathologically enlarged gland (consistent with a parathyroid adenoma on frozen section) was found at this site, together with an ipsilateral normal parathyroid, the other side of the neck was left undisturbed. This policy resulted in curative unilateral neck exploration in nine patients, in one patient (A), with previously undiagnosed Hashimoto's thyroiditis, a nodule of thyroid tissue was erroneously identified as parathyroid on frozen section and curative bilateral neck exploration was performed 3 days later.

The routine biochemistry was performed using a standard method on a SMAC II[®] analyser (Technica Ltd, Technicon). The PTH levels were performed within 3 months by the SAS laboratory, University Hospital Cardiff. An immunochemiluminometric assay (7), the Ciba Corning Magic Lite method (Ciba Corning Diagnostics, Halsted, Essex, UK) was used. This has a

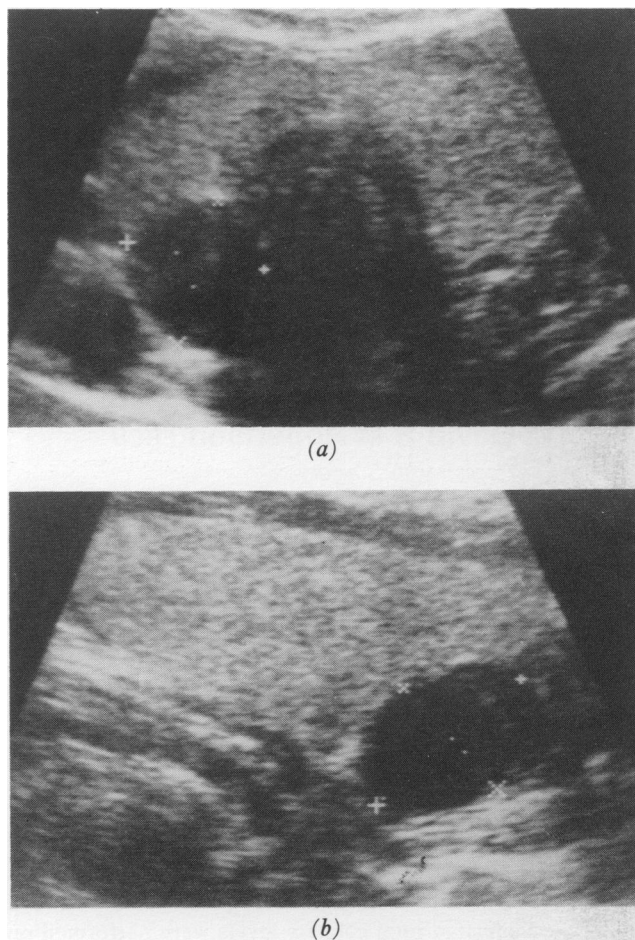


Figure 1. Ultrasound scan of a $2.0 \times 1.5 \times 1.6$ cm parathyroid adenoma in (a) transverse and (b) longitudinal section.

sensitivity of 0.2 pmol/l and a normal range of 0.9–5.4 pmol/l.

The results were compared with those from two patients who acted as controls. One male aged 53 years and one female aged 47 years who both underwent unilateral thyroid lobectomy with parathyroid preservation.

Results

All the patients studied were found to have normal hepatic and renal function throughout. Before surgery, all 10 patients were hypercalcaemic with a mean adjusted calcium of $3.2 \text{ SD} \pm 0.35$ mmol/l (normal range 2.10–2.60 mmol/l) and a mean PTH level of $20.8 \text{ SD} \pm 14.1$ pmol/l (normal range 0.9–5.4 pmol/l). There was a significant ($P < 0.001$) correlation between the two parameters.

All 10 patients remain normocalcaemic at 6 months, after removal of a single parathyroid adenoma. The average weight of the adenomas was 1.5 g (range 0.2–3.75 g). There was no significant correlation between the weight and either preoperative calcium or PTH levels ($0.5 > P > 0.1$).

Ultrasound accurately predicted the position of the adenoma in nine of the 10 patients, but incorrectly localised the smallest (0.2 g) gland in patient A. Six of the glands (including patient A's) were in the left inferior position, while on the right two were inferior, one superior and one intrathyroidal.

The changes which occurred in the levels of PTH during and after surgery are shown in Fig. 2. During the 10 successful operations (which include patient A's re-exploration) the level of PTH had fallen to within the normal range 15 min after removing the adenoma (with a mean level at this time of $2.36 \pm \text{SD } 1.5$ pmol/l—only 13.4% of that recorded preoperatively). In five patients the levels then fell below normal at 6 h, recovering by 24 h after surgery. During patient A's initial operation the level of PTH remained high and clearly indicated that

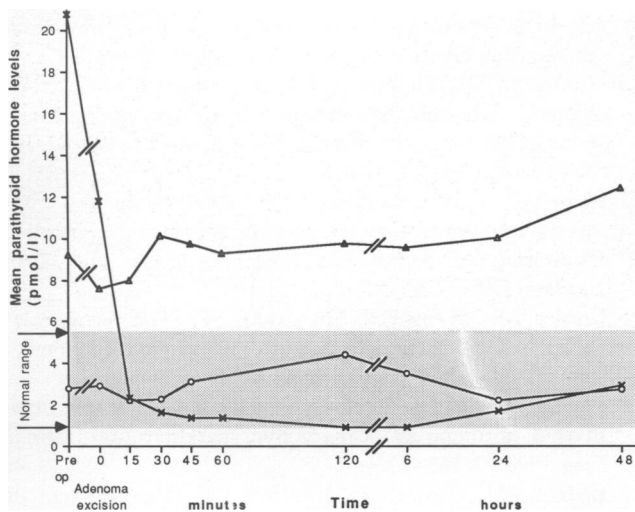


Figure 2. Changes in the mean parathyroid hormone levels (pmol/l) during and after surgery in the ten successful operations (x) compared with those in the control patients (o) and those for patient A's initial unsuccessful surgery (▲).

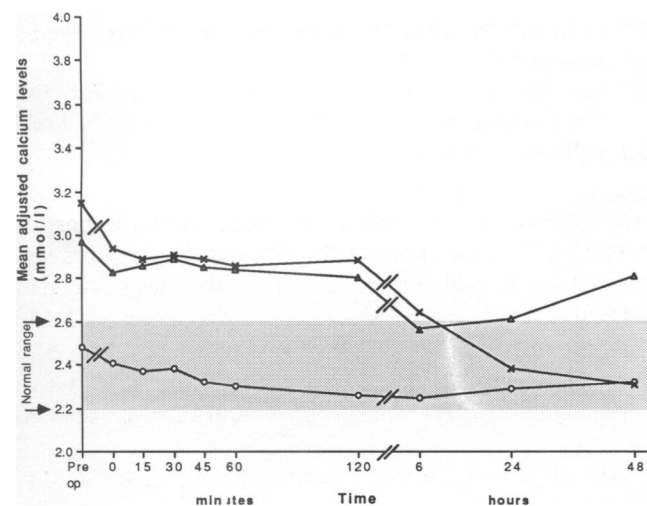


Figure 3. Changes in the mean adjusted calcium levels (mmol/l) during and after surgery in the ten successful operations (x) the control patients (o) and patient A's initial unsuccessful surgery (▲).

surgery had been unsuccessful within 15 min of adenoma removal. In the two control patients the PTH levels remained normal throughout.

Figure 3 shows the much slower decline in calcium levels after surgery and, more importantly, fell after both successful and unsuccessful neck exploration, failing to allow any decision on success to be made in the first 24 h. Transient hypocalcaemia did not occur in any of the nine patients undergoing unilateral neck exploration, and the lowest calcium level was recorded on either the first ($n=2$) or second ($n=7$) day. After patient A's bilateral neck surgery, a brief period of asymptomatic hypocalcaemia occurred.

Discussion

Our results fail to show the marked increase in PTH levels during surgery demonstrated by older assay methods (20), in which immunoreactive fragments of PTH, often with little bioactivity, were assayed (21). However, the rapid fall in levels of intact PTH after the removal of the adenoma and the lack of any fall during unsuccessful surgery, confirms the findings of others (17–19). The ability to measure intact PTH rapidly (in 15 min (16)) will allow confirmation of the success of surgery on an intraoperative basis, providing clear guidance on the need for further exploration. Measuring the level of PTH, as opposed to frozen section identification of the excised tissue as being parathyroid in origin has advantages, not only does it avoid the occasional error in tissue identification, but it measures the clinically relevant endpoint, that of complete excision of all hyperfunctioning tissue. Had the levels of serum PTH been available on an intraoperative basis for patient A, her initial surgery may have been successful.

Monitoring of PTH levels during difficult reoperations would avoid the possibility that a small parathyroid adenoma could be inadvertently removed resulting in unnecessarily protracted surgery and its attendant morbidity (22), and could allow a policy of tissue clearance in such cases until the level of PTH fell.

After surgery the parathyroid glands appear to recover their normal function extremely rapidly. This contrasts with the slow recovery after prolonged suppression of other endocrine tissues such as the thyroid or adrenal glands. Although our results show that a transient hypoparathyroid state does occur this is so brief that by the time the serum calcium is within normal limits the level of PTH has recovered. Indeed the subnormal PTH levels which occur between 2 and 6 h after removal of the adenoma may be appropriate to the elevated calcium levels which persist at the time. This suggests that in the absence of surgical damage to the normal parathyroid glands, they appear to be able to prevent even transient hypocalcaemia from occurring.

We suggest that the use of preoperative ultrasound to localise parathyroid adenomas, coupled with the use of intact PTH assays on an intraoperative basis have the potential to allow a highly successful policy of unilateral

neck exploration, decreasing the morbidity associated with parathyroid surgery (11,22) without adversely affecting cure rates. Leaving the contralateral field undisturbed allows relatively uncomplicated re-exploration of that side should the need arise in the future. Moreover, the need for frozen section, with the requirement for an available and experienced pathologist, its attendant problems with sampling in cases of small adenomas (23) and differences from the definitive histology in others could be avoided.

Our findings suggest that a prospective study comparing the value of intraoperative PTH measurement and frozen section in terms of cost, accuracy and operating time, should be undertaken.

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Received 28 March 1991