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Hypocalcaemia and Parathyroid Hormone Assay Following Total Thyroidectomy: Predicting the Future

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Abstract

Background: Ambulatory surgery (23:59-hour hospital stay) is gaining popularity in endocrine surgery. Hypocalcaemia is common following total thyroidectomy. Identifying patients with low risk of hypocalcaemia may facilitate early discharge (24-hour stay).

Methods: We conducted a prospective study including all patients undergoing total thyroidectomy. Blood samples were taken immediately following skin closure and the following morning for parathyroid hormone (PTH) and calcium measurement. Calcium supplements were routinely given when serum calcium was below 2.0 mmol/l.

Results: Thirty patients (27 females, 3 males) underwent total thyroidectomy (including 4 nodal dissection) for multinodular goitre (14), Graves' disease (11), papillary (4) and follicular (1) thyroid carcinoma. Twelve patients developed symptomatic transient hypocalcaemia. Based on morning calcium of <2.0 mmol/l as trigger for calcium supplementation, 8 patients received calcium supplement with 4 false negatives, resulting in a specificity of 94.4%, sensitivity of 66.7%, positive predictive value (PPV) of 88.9% and negative predictive value (NPV) of 81%. Based on PTH levels (<1.5 pmol/l) immediately following skin closure, 11 patients would receive calcium supplement, with 1 false negative resulting in a specificity of 83.3%, sensitivity of 91.7%, PPV of 78.6% and NPV of 93.8%. If supplementation is based on PTH levels (<1.5 pmol/l) immediately following skin closure and morning calcium level (<2.0 mmol/l), all 12 symptomatic patients will be correctly treated, with 4 false positives resulting in a combined specificity of 77.8%, sensitivity of 100%, PPV of 75% and NPV of 100%.

Conclusions: Combining the immediate postoperation PTH levels (<1.5 pmol/l) and morning serum calcium (<2.0 mmol/l) can accurately identify patients at risk of hypocalcaemia following total thyroidectomy, allowing safe, early discharge.

In the UK, the number of patients being treated in hospitals as ambulatory surgery (23:59-hour hospital stay) has increased dramatically in recent years.[1] The benefits of ambulatory care surgery include reduced disruption to patients' lives, reduced morbidity (*e.g.,* deep venous thrombosis, nosocomial infections), reduce demand on in-patient waiting lists/in-patients beds and reduce operational costs. Ambulatory care surgery is gaining popularity in endocrine surgery (thyroid lobectomy and parathyroidectomy). Postoperative transient hypocalcaemia (27.7%) is common following total thyroidectomy (BAES, National Thyroid/parathyroid database report 2003). At our institute, total thyroidectomy is carried out on an in-patient basis, with an average 60- to 84-hour hospital stay (including presurgery stay). Most of

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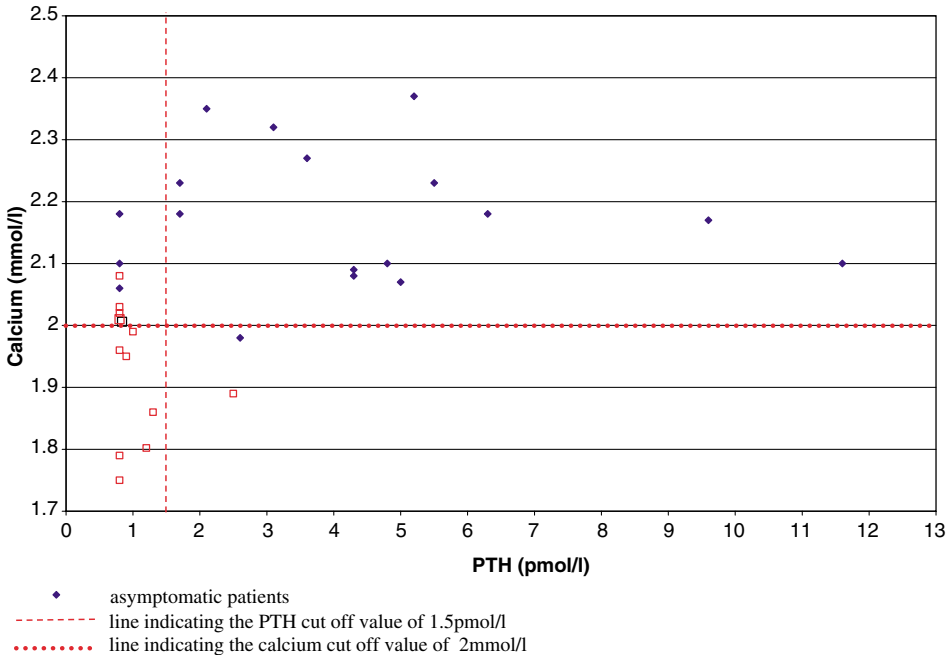

Figure 1. Distribution of parathyroid hormone (PTH) levels measured immediate following skin closure and corresponding serum calcium from next morning:□ denotes symptomatic hypocalcaemic patients; asymptomatic patients; ····· line indicating PTH cut-off value of 1.5 pmol/l; • • • • • • • • • • •line indicating calcium cut-off value of 2 mmol/l

these patients are otherwise suitable for early discharge but for the 24- to 48-h postoperative serum calcium monitoring.

Several groups have reported the significance of low perioperative parathyroid hormone (PTH) levels (1–6 hours postoperation) as predictors of hypocalcaemia following total thyroidectomy.[2–5] Lo *et al.*,[6] using the intraoperative PTH assay, reported an intraoperative PTH fall >75% to be associated with postoperative hypocalcaemia. We carried out a prospective study of all patients undergoing total thyroidectomy to determine the usefulness of perioperative (<23:59-hour) PTH levels to predict transient hypocalcaemia in a mock ambulatory care setting.

METHODS

This was a prospective study carried out between April and October 2004 for all patients undergoing total thyroidectomy for benign and malignant disease as in-patients. Venous blood samples were taken immediately following skin closure and the following morning for parathyroid hormone measurement (results not available for >72 hour) in addition to routine blood samples for serum calcium measurement (next mané and daily until discharge). The number of parathyroid glands identified and preserved during the operation was also recorded. At our institute, calcium supplements were routinely given when serum calcium was below 2.0 mmol/l.

RESULTS

During the study period, 30 patients (27 females, 3 males) aged between 15 and 76 years (mean: 42 years 4 months) underwent total thyroidectomy (including 4 nodal dissection) for multinodular goitre (MNG) (13), Plummer's disease (1), Graves' disease (11) and papillary (4) and follicular (1) thyroid carcinoma. All 4 parathyroid glands were identified and preserved in 7 (23.3%), 3 parathyroid glands in 16 (53.4%) and 2 parathyroid glands in 7 (23.3%) patients. Parathyroid tissue was reported in the histology report in 4 (13.3%) patients. The mean PTH measured immediately following skin closure and the following morning were 2.88 pmol/l (<0.8–11.6 pmol/l; reference range: 0.4–5.9 pmol/l) (Fig. 1) and 2.37 pmol/l (<0.8–10.8 pmol/l) (Fig. 2). The mean postoperative serum calcium was 2.07 mmol/l (1.75–2.37 mmol/l) (Fig. 1). Twelve patients (40%) developed postoperative symptomatic transient hypocalcaemia (3 patients had Ca^{2+} <2.0 mmol/l in first 24 hours postoperation, 1 presented 7 days postoperation with severe hypocalcaemia) (Table 1). Of the 4 patients who had parathyroid tissue

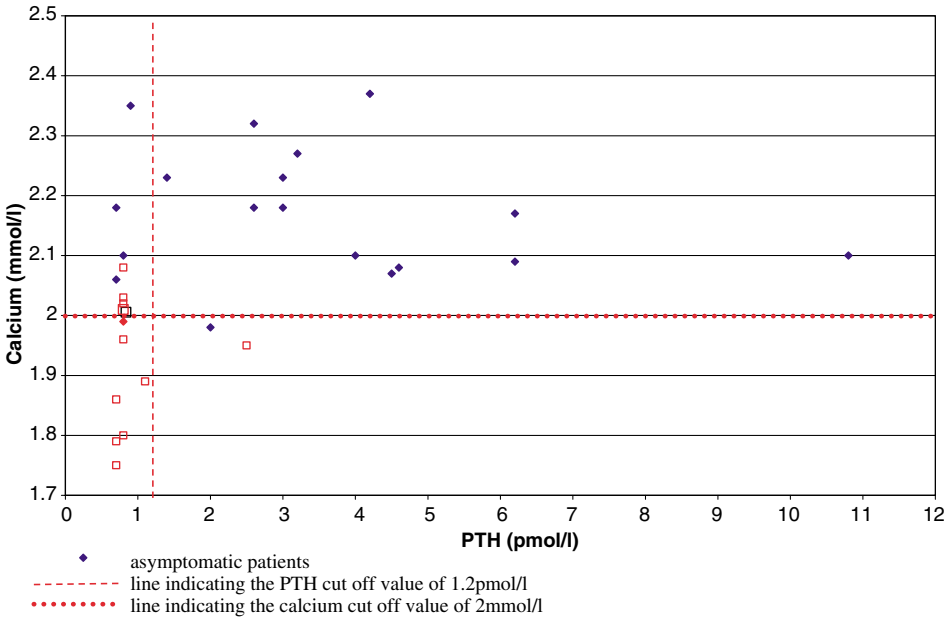

Figure 2. Distribution of parathyroid hormone (PTH) levels measured next morning and corresponding serum calcium from next morning:□ denotes symptomatic hypocalcaemic patients; asymptomatic patients; ····· line indicating PTH cut-off value of 1.2 pmol/l; • • • • • • • • • • line indicating the calcium cut off value of 2 mmol/l

reported in the histology report, only 2 experienced transient hypocalcaemia. At 3 months follow-up, all patients were normocalcaemic without calcium supplementation.

When comparing hypoparathyroidism and hypocalcaemia with the number of parathyroid glands preserved and indications for surgery, patients who had 3 parathyroid glands identified at operation accounted for the majority of hypoparathyroidism [immediate following skin closure, PTH <1.5 pmol/l (n=11); next morning PTH <1.2 pmol/l (n=11)] and hypocalcaemia [Ca^{2+} <2.0 mmol/l (n=5)] (Table 2 Fig 3a–c). Hypocalcaemia was observed in 41.7% (5/12) patients with thyrotoxicosis (Graves'), 23.1% (3/13) of MNG and 25% (1/4) of papillary thyroid carcinoma (Table 1).

Based on postoperative calcium of <2.0 mmol/l as trigger for calcium supplementation, 8 patients will receive correct treatment with one unnecessary treatment. Four patients would have been missed (Table 3), resulting in a specificity of 94.4%, sensitivity of 66.7%, PPV of 88.9% and NPV of 81% (Table 4). Using an arbitrary PTH cut off at <1.5 pmol/l (Fig. 1) immediately following skin closure as trigger, 11 patients would have been correctly treated, 3 patients would have had unnecessary calcium supplement and 1 patient would have missed treatment (Table 3), resulting in a specificity of 83.3%, sensitivity of 91.7%, PPV of 78.6% and NPV of 93.8% (Table 4). Based on an arbitrary cut-off level of <1.2 pmol/l (Fig. 2) for PTH measurements taken from the following morning, 11 patients would have received calcium supplement, 4 patients would have received unnecessary supplement and 1 patient would have missed treatment (Table 3) giving a specificity of 77.8%, sensitivity of 91.7%, PPV of 73.3% and NPV of 93.3% (Table 4). Using a protocol amenable to ambulatory care (23:59 hours) setting, based on PTH levels (<1.5 pmol/l) immediately following skin closure and morning calcium level (<2 mmol/l), all 12 symptomatic patients would be correctly treated, with only 4 (22.2%) of the remaining 18 receiving unnecessary supplement (Table 3). This results in a combined specificity of 77.8%, sensitivity of 100%, PPV of 75% and NPV of 100% (Table 4).

DISCUSSION

Ambulatory surgery has many advantages and is gaining momentum in the UK. The concept of ambulatory surgery is particularly suited to parathyroidectomy and thyroid lobectomy. Both these procedures have low inherent morbidity rate (<2%) and low analgesic requirement (BAES, National Thyroid/Parathyroid Database Report 2003). The incidence of hypocalcaemia following total thyroidectomy has been reported to be between 12.5% and 37.6%.[7–11] Consequently, few centres offer ambulatory surgery for total thyroidectomy.[12,13]

Table 1.
Distribution of perioperative parathyroid hormone (PTH) levels and serum calcium according to indications for surgery

Indications for surgery (n)	PTH immediate following skin closure (pmol/l)	Number of patients with PTH <1.5 pmol/l	PTH next morning (pmol/l)	Number of patients with PTH <1.2 pmol/l	Calcium next morning (mmol/l)	Number of patients with Ca^{2+} <2 mmol/l	Number of patients needed calcium supplements
Thyrotoxicosis Graves' (11)	4.17	4	3.25	5	2.02	5	5
Plummer's (1)	(<0.8–11.6)		(<0.8–10.8)		(1.75–2.35)		
MNG (11)	2.35	7	2.05	7	2.11	3	5
MNG -retrosternal (2)	(<0.8–5.5)		(<0.8–6.2)		(1.8–2.37)		
Papillary thyroid	1.25	2	1.4	2	2.11	1	2
Carcinoma (4)	(<0.8–1.7)		(<0.8–2.6)		(1.96–2.23)		
(nodal dissection)							
Follicular thyroid carcinoma (1)	<0.8	1	<0.8	1	2.01	0	0

MNG: multinodular goitre

It is generally accepted that identification and preservation of parathyroid glands during operation is crucial to avoid postoperative permanent hypocalcaemia, accepting that it may increase the incidence of transient hypoparathyroidism.[14,15] Against expectation, in this series, hypocalcaemia and transient hypoparathyroidism occurred largely in those patients who had 3 glands preserved as opposed to the subgroup with only two parathyroid glands identified (Table 1). The reason for this is unlikely to be a result of less manipulation/devascularisation during the dissection [15] in those who only had two glands identified, as the incidence of hypoparathyroidism in the subgroup where all four glands were identified was equally low.[3,16]

The main hurdle for total thyroidectomy to be successful in ambulatory surgery is symptomatic hypocalcaemia. Several groups have advocated routine postoperative calcium supplements to avoid this complication to allow for early discharge.[17–19] Oral calcium supplements are unpleasant to take; it seems unjust and a blunt approach to subject 62.4%–87.5% of patients to taking oral calcium supplement unnecessarily to avoid hypocalcaemia.

Our results (Tables 3, 4) show that using serum calcium from the next morning alone, whilst effective (specificity: 94.4%; sensitivity: 66.7%), would have failed to identify 25% (false negative) of patients who required calcium supplementation.[2,20–22] One of these 4 patients required re-admission, having developed delayed onset (5–7 days) hypocalcaemia in spite of having normal calcium for 48 hours postoperation. Similar specificity and sensitivity for hypocalcaemia were achieved using an arbitrary PTH cut-off level of 1.5 pmol/l (immediate skin closure) and 1.2 pmol/l (next mané) with only one false negative in a thyrotoxic patient (Table 1). The predictive power can be enhanced by utilising both hypocalcaemia (Ca^{2+} <2 mmol/l) and perioperative PTH levels. We adopted measuring the PTH immediately following skin closure, as it was more suited to the ambulatory care setting. This strategy achieved 100% sensitivity with zero false negative whilst accepting a false positive of 22.2% of patients (specificity: 77.8%). It is by far safer to overtreat a few than to under treat patients when they are discharged early to minimise the risk of untreated hypocalcaemia and unplanned re-admission.

The cause for hypocalcaemia is multifactorial. It is thought to be due to hypoparathyroidism (transient or permanent) as a result of iatrogenic injury to the parathyroid glands from physical handling, ischaemia or inadvertent removal during surgery (risk proportionate to extent/type of surgery) and avidity of the skeleton

Table 2.
Number of patients below parathyroid hormone (PTH) and calcium cut-off levels according to number of parathyroid glands preserved

Parathyroid glands preserved(n)	PTH immediate following skin closure <1.5 pmol/l	PTH next morning < 1.2 pmol/l	Hypocalcaemia Ca^{2+} <2 mmol/l
2 (7)	3	3	2
3 (16)	11	11	5
4 (7)	1	1	2

Table 3.
Hypothetical distribution of patients who would be treated or missed according to parathyroid hormone (PTH) and calcium levels

	Hypocalcaemia Ca^{2+} <2 mmol/l	PTH immediate following skin closure <1.5 pmol/l	PTH next morning <1.2 pmol/l	PTH <1.5 pmol/l ± Ca <2 mmol/l
Correctly treated	8	11	11	12
Overtreated (false positive)	1	3	4	4
Missed treatment (false negative)	4	1	1	0
Correctly withheld treatment	17	15	14	14

Table 4.
Sensitivity and specificity of using calcium and parathyroid hormone (PTH) as indicator of hypocalcaemia

	Specificity (%)	Sensitivity (%)	Positive predictive value (%)	Negative predictve value (%)
Ca^{2+} <2 mmol/l	94.4	66.7	88.9	81
PTH <1.5 pmmol	83.3	91.7	78.6	93.8
PTH <1.2 pmol/l	77.8	91.7	73.3	93.3
PTH <1.5 pmol/l & Ca^{2+} <2 mmol/l	77.8	100	75	100

(thyrotoxic osteodystrophy or hungry bone syndrome) for calcium in thyrotoxic patients.[15,23–28] Whilst hypoparathyroidism will reflect hypocalcaemia caused by non-functioning parathyroid glands, it will not detect hypocalcaemia caused by thyrotoxic osteodystrophy where PTH will be present (low/normal/elevated).[10,25,29–31] It is therefore important to combine PTH and serum calcium monitoring to accurately predict hypocalcaemia.

Several investigators have reported measuring serial serum calcium (total or ionised) in the early postoperative period (6 hours postoperation) to predict hypocalcaemia.[3,22] Our experiences with serial calcium measurements (total and ionised Ca^{2+} at 6 hours) have failed to support this, as the serum calcium of hypocalcaemic patients did not separate from normocalcaemic patients till 12–18 hurs postoperation.[2,32] The arrival of quick intraoperative PTH assays have revived the interest of using biochemical markers as predictor for postoperative hypocalcaemia.[3–6,33] Several groups have reported hypocalcaemia being associated with an intraoperative PTH fall of >75% or a postresection intraoperative PTH level less than the reference range.[2,6,34] Others advocated measurement of PTH in the early postoperative period, together with serum calcium 6 hours postoperation as standard.[3,5] The short half-life (3.43–5 minutes) of PTH [35,36] is the basis of intraoperative PTH assays for hyperparathyroidism. The results of our PTH levels at the conclusion of the operation and the following morning, consistent with reported series, suggest little recovery of parathyroid function in the immediate postoperative period (up to 96 hours).[8,34] Therefore, measuring PTH at the conclusion of the operation (average: 15–20 minutes after removal of specimen), 6 hours following operation or next morning are equally representative of the perioperative functional status of the parathyroid glands. Furthermore, measuring PTH at the conclusion of the operation lessens the demand on manpower and allows incorporation of intraoperative PTH assay or use of the laboratory PTH assay (depending on resource availability).

This study has demonstrated the feasibility to accurately predict hypocalcaemia (specificity: 77.8%, sensitivity: 100%) following total thyroidectomy based on

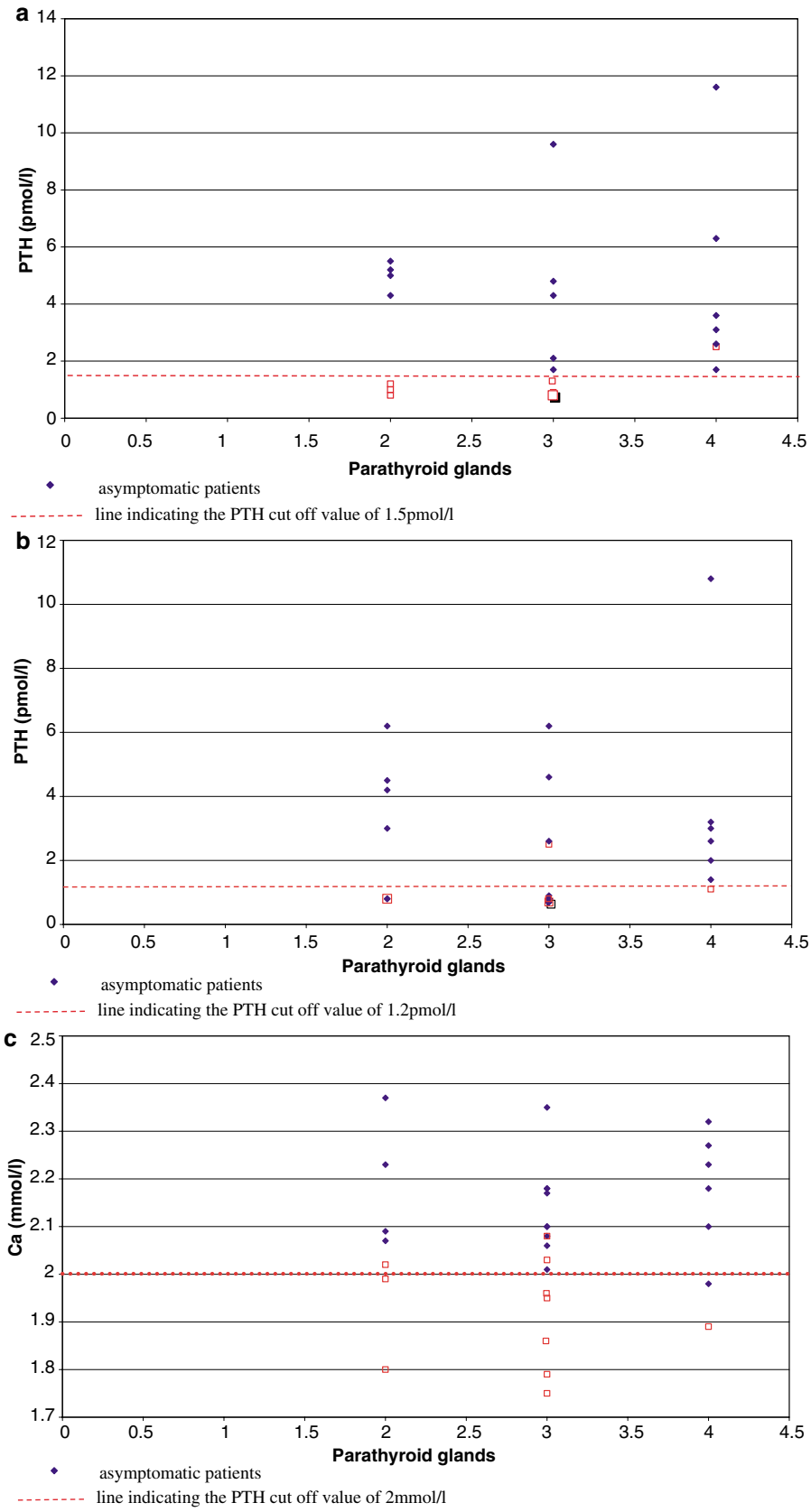

Figure 3. **a** Distribution of parathyroid hormone (PTH) levels measured immediately following skin closure and number of parathyroid glands identified:□ denotes symptomatic hypocalcaemic patients; asymptomatic patients; ····· line indicating PTH cut-off value of 1.5 pmol/l. **b** Distribution of PTH levels measured next morning and number of parathyroid glands identified:□ denotes symptomatic hypocalcaemic patients; asymptomatic patients; ····· line indicating PTH cut-off value of 1.2 pmol/l. **c** Distribution of serum calcium levels measured next morning and number of parathyroid glands identified:□ denotes symptomatic hypocalcaemic patients; asymptomatic patients; • • • • • • • • • • line indicating calcium cut-off value of 2 mmol/l

biochemical indicators within an ambulatory care setting (<23:59 hours) by combining PTH monitoring (PTH <1.5 pmol/l) at the immediate postoperative period and next mané serum calcium (Ca^{2+} <2.0 mmol/l).

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