

Intravital methylene blue staining of parathyroid glands and tumours*

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Summary

Previous intravital staining techniques for parathyroid localisation have met with variable success and complications. Modification of these techniques, employing a more consistent dose, combined with a prolonged infusion time has provided more uniform staining of normal and abnormal parathyroid tissue, other tissues showing little or no colour change. Locally induced oedema, not previously described, was found to be a great asset in the dissection of glands. In 38 of 40 patients (95%), 4 glands were demonstrated and in the remaining 2 cases, only 3 glands appeared to be present. One case alone has required re-operation, due to the presence of a fifth gland.

Intra-thyroid and intra-thymic tumours were found easily, as was glandular tissue spilt accidentally. Apart from slight nausea in one patient, there were no complications attributable to the dye, in the series which included 12 patients with chronic renal failure. Uniformly normal postoperative serum calcium levels indicated the accuracy of the method. The technique is safe, inexpensive and easily reproducible, and would seem to have many advantages over other methods of tumour localisation.

Introduction

Anatomical variations in number, size and position complicate the preoperative and intraoperative localisation of parathyroid glands. Atypical anatomical sites include the carotid sheath, superior mediastinum and within both the thymus and thyroid glands; the variation in size and shape of both normal and abnormal glands is recognised, as is the presence of more or less than the usual number of four (1,2).

A number of investigational procedures have been used, with differing degrees of accuracy (3) but these are little help in the dissection of the tissue planes at the time of surgery. In addition it is recognised increasingly that accurate dissection is essential to preserve the delicate gland vasculature, and prevent persistent postoperative hypocalcaemia.

Other workers have used methylene blue as an aid in parathyroid surgery (4-9). The present technique is a modification more in keeping with Hurvitz's initial observations (11), and used prospectively in a series of 40 patients.

Patients and methods

Forty consecutive cases of hyperparathyroidism were treated surgically at East Birmingham Hospital and elsewhere in the

years 1978 to 1982, with the aid of this technique. The majority had primary hyperparathyroidism, although 12 were referred from the hospital's dialysis unit with secondary and tertiary hyperparathyroidism.

All non-dialysis patients were confirmed hypercalcaemic after fasting on at least three occasions, the serum parathyroid hormone level (PTH) being available in the majority. In the dialysis group, the diagnosis had been confirmed with raised serum PTH and alkaline phosphatase levels, with the radiological signs of bone changes, and in many, bone histology. All had undergone medical treatment, but had been referred for surgery when eucalcaemia was increasingly difficult to control or bone changes became symptomatic.

The original technique described by Dudley (4), and later by Rowntree (8), was modified three-fold. The dosage was increased from 5 mg/kg to 7.5 mg/kg, but, in line with Rowntree's observations, was varied according to estimation of the lean body weight. In addition, the infusion time was increased from 1 to 2 hours ending immediately preoperatively and monitored strictly. By increasing the period of contact between the parathyroid tissue and a more constant and effective blood level of the dye, it was anticipated that a more uniform and reproducible staining could be achieved. The technique was explained to the patients preoperatively, particularly forewarning them of the discolouration of the skin and urine.

Although empirical, the adjustment of the total dosage according to lean body weight estimation proved reliable. With apparent obesity, the dose was reduced towards 6.5 mg/kg but increased towards 8.5 mg/kg if the patient was thin; more precise measurements did not appear to be necessary. The infusion was timed to end as the patient entered theatre. The exposure and form of dissection were conventional (13,14). At operation all glands were exposed and demonstrated before any decision was made as to which gland or group of glands were to be removed. This was based not only on size (14), but also on the differential staining characteristic of the technique (4,5,8), frozen section histology being considered too unreliable (14,15). Apparently normal glands were not biopsied routinely after adequate demonstration, to avoid possible disruption of the vasculature. Initially, in the dialysis patients, sub-total parathyroidectomy was performed, but later in the series 6 underwent total parathyroidectomy and autotransplantation into the left sternomastoid muscle (16).

Postoperatively, serum calcium levels were taken at 12 hours and then daily while in hospital. After discharge the

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serum calcium was estimated monthly as an out-patient for 3 months, and then 6-monthly. Vocal cord examination by an independent assessor was done pre and postoperatively in all cases.

Results

The presenting symptoms and signs of the group are shown on Table I. The mean age of the group was 54 years, and the mean elevation of serum calcium in the non-dialysed group 2.90 mmol/l (range 2.7 to 3.4 mmol/l) and in the dialysis group 2.76 mmol/l (range 2.34 to 3.00 mmol/l).

TABLE I Presenting symptoms

Renal colic	8	} Total = 28
Confusion	1	
Malaise	5	} Mean calcium = 2.9 mmol/l
Serendipity	5	
MEA 1	2	} Range 2.7 to 3.43 mmol/l
Hypertension	3	
Oral granuloma	1	
Depression	3	
End stage failure = 12		Mean calcium = 2.76 mmol/l Range 2.34 to 3.00 mmol/l

No problems were associated with administration of the dye, and patient acceptability was excellent, the concern of the majority being only the urine discolouration. There was neither increase in drip site thrombophlebitis, nor systemic symptoms including cardiac arrhythmias, although nausea occurred in one patient due to accidental rapid infusion.

Of the 40 patients, 4 glands were demonstrated in 38 (95%); in the remaining 2 cases only 3 glands being found. Of these, one had had a previous thyroidectomy during which presumably one gland was removed and in the other patient only 3 glands were found despite an extensive search; a solitary adenoma was removed and the patient remains normocalcaemic.

The anatomical siting of the glands was mostly normal, but 4 were found in an intra-thyroid position (2 subcapsular and 2 embedded under the surface) and 3 in thymic tissue. Demonstrable also by the technique were small parathyroid rests in 2 patients as described by Erdheim (17). The dissection appeared to be aided by an increase in local tissue fluid and the staining of the glands could be seen through several tissue planes considerably easing the accurate demonstration of glands.

The only apparent failure of the series, with persistent postoperative hypercalcaemia, was re-explored. A fifth parathyroid gland was found lying lateral to the carotoid sheath in the posterior triangle and was removed easily. Transient recurrent laryngeal nerve palsy occurred in one patient, whose nerve ran an aberrant course. Nerve identification, performed in all cases, was assisted by the technique.

The pathological findings are summarised in Table II, and relate to the routine histology. The operative decision-making based on the demonstrated size of the gland and differential staining between normal and pathological conditions was analysed retrospectively and judged correct in every case, although the nature of the carcinoma in the series was not appreciated initially.

TABLE II Pathological findings

Non-dialysis patients		
Single adenoma	20	} = 28
Double adenoma	4	
Hyperplasia	4	
Dialysis patients		
Hyperplasia	8	} = 12
Tertiary	3	
Carcinoma	1	

The mean 12 hour postoperative serum calcium level in the 28 non-dialysis patients was 2.12 mmol/l (range 1.6 to 2.65 mmol/l), whilst for the 12 dialysis patients 1.78 mmol/l (range 1.35 to 2.17 mmol/l). Except for the patient with the highest level who was re-explored at 5 days, all in the former group were eucalcaemic at 36 hours. The majority of the dialysis patients underwent a period of medical treatment, but all had stabilised at 3 months. Long term follow-up of this group does not appear to show any harmful effects of the dye on the tissue autografts.

Follow-up continues with no recurrence of hypercalcaemia, although 4 of the dialysis and 2 of the adenoma group have since died of causes unrelated to hypercalcaemia.

Discussion

Parathyroid and thyroid surgery are similar in that success relies heavily on accurate localisation and dissection being achieved at the first operation; repeat operations are impaired by previous tissue plane disruption.

The history of preoperative localisation has been erratic, and few surgeons perform this routinely, reserving the largely invasive techniques for recurrent disease; the success in accurate identification being less than 50% (3). At operation the surgeon is aided by the natural position, consistency, mobility and vascularity of the glands, but most of all by its natural colour (8). A dye technique, which accentuates the characteristics and permits the glands to be visualised through several tissue layers, aids surgical dissection. Any technique that allows greater surety for the operator, and reduces the incidence of re-explorations, must be of value in an operation which few surgeons perform regularly.

Selective staining of parathyroid glands was demonstrated in dogs using toluidine blue initially (10, 12), the first clinical series being reported by Hurvitz, who noted that the basis of the method was the differential rate of dye clearance between the thyroid and parathyroid glands (11).

Toluidine blue was withdrawn due to the risk of cardiac arrhythmias, and Dudley re-introduced the technique with the safer dye, methylene blue (4). However, inconsistencies were noted in the staining ability, particularly in relation to body fat, the dye being concentrated in the other tissues (8).

The results of the use of this technique in 40 patients with a variety of parathyroid disease shows that it has aided successfully both the demonstration of normally sited and ectopic glands and assisted the surgical decision-making as to which glands to excise. This was achieved without significant complications and with minimum distress to the patients. The only patient requiring re-operation had an ectopic fifth gland in the carotid sheath. It would appear that the longer infusion time and increased, but weight-adjusted dosage, leads to improved staining characteristics with greater emphasis on the differential clearance between the parathyroid glands and other tissues when compared with previous methods.

The staining of the glands appeared consistent, although normal glands stain less deeply than those which are pathological; adenomata stain a dark blue, whilst hyperplastic glands are a lighter shade. The difference aids differentiation between single and multiple gland disease (4, 5, 8, 9). It is suggested that the more uniform blood levels over the longer period are responsible.

While it is difficult to make qualitative assessments between various surgical techniques, the clear demonstration of all glands in 95% of the patients, the uniformity of the postoperative serum calciums and the reduction in re-explorations, together with the minimum of complications attributable to the surgery or technique, infers the benefits derived.

The other advantages of the technique are its cheapness, no additional equipment being required, its safety, no serious and very limited minor effects being recorded and its reproducibility. Also tissue detached from the gland during dissection, which might have implanted in the wound

leading to recurrence, was easily found and recovered, this advantage being particularly noticeable in the patient with a carcinoma.

In addition it is increasingly recognised that the dissection of normal glands can affect the vascular supply leading to transient and in some cases permanent hypocalcaemia (18, 19). It is suggested that the ability of the dye to demonstrate glands, despite being obscured by thin tissue layers, permits identification to be made with the minimum of dissection, preservation of the delicate vasculature and prevention of postoperative hypocalcaemia. This method would appear to be a useful aid in achieving Cope's concept of parathyroid surgery as being a careful, systematic and bloodless exploration (13).

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Notes on books

Ultrastructural Atlas of the Inner Ear by Imrich Friedmann and John Ballantyne. 329 pages, illustrated. Butterworths, London. £59.00.

This atlas presents the cytoarchitecture of the inner ear. Consequently there are many illustrations, mainly electron micrographs. The introduction displays the overall anatomy of the ear and the techniques used. Subsequent chapters deal with the cochlea, the vestibule and the endolymphatic system. The book is beautifully produced and will undoubtedly be a great success.

Atlas of Stomal Pathology by A Franchini, B Cola and P J d'E Stevens. 112 pages, illustrated. Cortina International Verona—Raven Press, New York. \$87.00.

This beautifully illustrated atlas displays various stomal pathological states both primary and secondary. It deals also with problems in radiotherapy, gynaecology and obstetrics, paediatrics and stomal problems in handicapped patients.

A Textbook of Radiological Diagnosis Volume 1 Head and Central Nervous System edited by G H Du Boulay. 641 pages, illustrated. 5th edition. H K Lewis, London. £48.00.

This is the first of a new 6-volume edition changed in format to two columns of print with the illustrations produced as negatives. It incorporates all the modern methods of radiological investigation of the head and central nervous systems including angiography, pneumoencephalography and computed tomography together with radionuclide studies and nuclear magnetic resonance imaging.

Atlas of Laryngeal Surgery by C W Cummings, D G Sessions, E A Weymuller Jr and Phyllis Wood. 355 pages, illustrated. C V Mosby/Blackwell Scientific, Oxford. £82.00.

All the routinely performed operations on the larynx are illustrated in this book starting with the endoscopy, airway procedures and operations for various lesions. It is heavily illustrated with line drawings.