

POSTOPERATIVE MANAGEMENT OF PRIMARY HYPERPARATHYROIDISM

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ABSTRACT

Postoperative management of patients with primary hyperparathyroidism requires to determine whether the operation has succeeded or not in early postoperative days as well as to deal with postoperative hypoparathyroidism. Twenty three surgically managed patients with primary hyperparathyroidism were studied.

Attention was focused on the time course of postoperative serum calcium levels and postoperative hypocalcemic signs. The following conclusion were obtained.

When the surgery was successful, the serum total calcium levels fell to normal range within 48 hours, then below normal range and gradually returned to normal. It took about one to three months for the serum calcium levels to return to normal.

Severe postoperative hypocalcemic signs were observed in those patients with extensive bone disease and high serum alkaline phosphatase activities, in those where initial hypocalcemic signs appeared within 24 hours after surgery, and in those where plasma total calcium levels continued to decrease after the fourth postoperative day.

Calcium should be administered only to patients with severe hypocalcemic signs or to those with postoperative congestive heart failure.

The second exploration should be performed without delay when the fluctuating hypercalcemia persists after the operation.

INTRODUCTION

In recent years, surgeons have been called upon to manage increasing numbers of patients with primary hyperparathyroidism. There are several problems in postoperative management^{1,2,3)}, such as tetany, paresis of vocal cords, hemorrhage, hypomagnesaemia, recurrence of the disease and others, after parathyroid surgery for primary hyperparathyroidism.

Among these the three major problems are: first, to determine whether the operation has succeeded or not in early postoperative days; second, how to deal with postoperative hypoparathyroidism; and third, how to find out the recurrence of the disease.

As to the last, there are several reports in the literature concerned with long-term follow up of surgically treated hyperparathyroidism^{4,5)}. But there are very

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few reports discussing in detail the first and the second problems mentioned above. In the present communication, we tried to find a solution to the problems mentioned above by considering a small group of selected patients with surgically managed primary hyperparathyroidism.

MATERIALS AND METHODS

During the past 10 years from 1964 to 1973, 27 patients with primary hyperparathyroidism were operated upon at the First Department of Surgery of Nagoya University Hospital. The clinical diagnosis in all patients was confirmed by pathological examination of the removed tissue.

There were 19 cases of single adenoma, two of multiple adenomas, five of hyperplasia and one of carcinoma. Of the 27 patients, four were not suitable for precise analysis; one of them was an 11 month female infant in whom calcium metabolism was considered to be different from that of an adult,⁶⁾ and the other patients were a man with hyperparathyroid crisis who died two days after the operation and a woman with hemorrhagic and necrotic tumor who showed preoperative spontaneous remission. The fourth case was a patient who was not followed up sufficiently after the operation. The remaining 23 patients were included in this study. The operative procedure for primary hyperparathyroidism at our department was the selective removal of only obviously diseased tissue. After the exploration of all four parathyroid glands, they were diagnosed as single adenoma, multiple adenomas or hyperplasia by inspection and by microscopic examination of the frozen sections. Frozen sections of all four glands were examined if necessary. In patients with a single adenoma, the adenoma was extirpated, and those with multiple adenomas or hyperplasia underwent subtotal parathyroidectomy. Among these 23 patients, two were operated twice and one three times. Serum total calcium level was measured in all cases. Signs and symptoms of postoperative patients were carefully observed during the hospitalization. The serum calcium levels were not corrected for plasma protein concentration. Severe transient symptoms of hypocalcemia were treated with intravenous calcium gluconate injection.

All patients were followed up to July-31, 1974, after their discharge. During this period one patient died of traffic accident, but had no evidence of recurrence by that time. In the remainder, there were also no clinical evidence of recurrence of hyperparathyroidism.

RESULTS

1) *Postoperative hypocalcemia*

Twenty two patients with successful parathyroidectomy were divided into two groups; one group that showed severe hypocalcemic signs and treated with intravenous calcium (treated group) and another group that did not show severe signs and not treated with calcium (non-treated group).

(1) Preoperative and operative findings

Clinical findings

The sex and age distribution of these two groups are shown in table 1. There were three males and eight females in the treated group. The oldest patient was 43 years old, the youngest 20. The average was 29.5 years. Non-treated group consisted of three males and eight females whose ages ranged from 20 to 55, with a mean of 34.3 years. There was no significant difference in sex and age between these two groups.

Table 2 shows the principal signs and symptoms of the patients in these two groups at admittance. The signs and symptoms are classified into three groups; bone symptoms, urolithiasis and other signs. The number of patients with bone symptoms in the treated group were more than in the non-treated group. The duration of the symptoms up to time of hospitalization was approximately the same in both groups.

Table 1. Sex and Age Distribution

	No. of patients		Age (yrs. o.) (mean)
	Male	Female	
Treated group	3	8	20 - 43 (29.5)
Non-treated group	3	8	20 - 55 (34.3)

Table 2. Principal Signs and Symptoms

	Signs and symptoms			Duration of symptoms (mean)
	Bone symptoms	Urolithiasis	Others	
Treated group	7	3	1	8 m. - 16 yrs. (5.1 yrs.)
Non-treated group	3	5	3	0 - 10 yrs. (4.7 yrs.)

Table 3 shows histological findings of each group. Treated group consisted of 8 patients with single adenoma, one multiple adenomas, one hyperplasia and one cancer, while the 11 non-treated patients consisted of nine patients with single adenoma, one with multiple adenomas and one with hyperplasia. The weight of single adenoma of the treated group ranged from 2.0 - 6.0 g with a mean of 4.06 g and of the non-treated group 0.4 - 20.08 g with a mean of 4.64 g. There was no significant difference in histological findings and tumor weight.

Laboratory findings (Table 4)

In the preoperative state, the highest serum calcium level ranged from 11.8 - 15.1 mg/dl with a mean of 13.2 in the treated group and 11.4 - 15.4 with a mean of 13.0 in the non-treated group. There was no significant difference between the two groups. The lowest serum inorganic phosphate levels were not significantly different in the two groups. Alkaline phosphatase activities in the serum of the treated group ranged from 50 - 188 Unit (K.A.) with a mean of 58.36. However, the phosphatase activities in the serum of the non-treated group were lower than 50 Units and the mean value was 24.95. Patients with bone symptoms had high

Table 3. Histological Findings

	Adenoma	Hyperplasia	Cancer
Treated group	9	1	1
Non-treated group	10	1	0

Table 4. Laboratory Findings

	Highest serum Ca mg/dl	Lowest inorganic P mg/dl	Al - Pase Unit (K.A.)	TRP %
Treated group	11.8 - 15.1 (13.2)	1.0 - 2.7 (1.9)	50 - 188 (58.36)	55 - 86 (68.38)
Non-treated group	11.4 - 15.4 (12.99)	1.6 - 2.7 (2.2)	7 - 37 (24.95)	33.5-74 (59.14)

() : mean values

alkaline phosphatase activities exceeding 30 Units while patients with urolithiasis or other manifestations had activities lower than 30 Units, as shown in Fig. 1. Namely, patients with high serum alkaline phosphatase activities had bone disease and most of them belonged to the treated group. Tubular phosphorous reabsorption (TRP) values were lower than 80 percent in all patients except one. Cortisone test (predonine 40 mg daily was administered orally for 10 days) failed to reduce the serum calcium level to the normal range in all patients.

(2) Postoperative serum calcium changes

Postoperative serum calcium changes of the two groups are shown in Fig.2-A. The mean serum calcium levels of both groups decreased rapidly within 12 hours after operation. In all patients except for one that belonged to the non-treated, the serum calcium levels returned to normal in 24 hours and in 48 hours in that

particular patient. The decrease in total serum calcium levels of the treated group was much more rapid than of the non-treated group. In the non-treated group, the mean serum calcium levels fell continuously and reached the lowest value on about the third postoperative day, stayed at this level for about four weeks and returned to normal by the 35th day. In all postoperative patients of the treated group, the serum calcium concentration decreased and reached the normal range within 12 hours after operation. Observed values of serum calcium continued to fall and reached the lowest levels on the 10th postoperative day and began to rise after the 25th postoperative day. It took about three months for the mean calcium

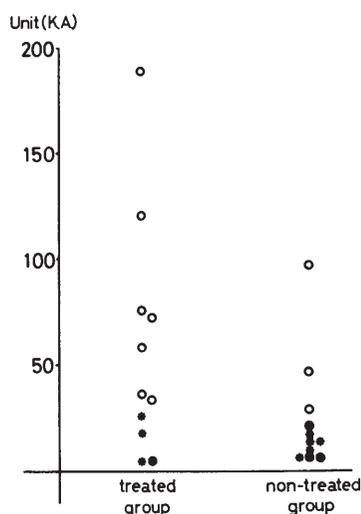


Fig. 1. Highest serum alkaline phosphatase activities in patients with primary hyperparathyroidism before surgery.

Values depicted as ○ were obtained from patients with bone symptoms, as * obtained from patients with urolithiasis and as ● from patients with other symptoms.

level to return to the normal range. The lowest values were in the range of 8.5 - 4.8 mg/dl with a mean of 6.28 in the treated group and 8.8 - 6.0 mg/dl with a mean of 7.61 in the non-treated group.

(3) Hypocalcemic signs

Hypocalcemic signs of patients are shown in Table 5. Numbness and tingling were the most common hypocalcemic symptoms and were seen in all patients of the treated group and in nine of 11 of the non-treated group. Numbness and tingling observed in patients varied from mild to severe; for example, from localized numbness in finger tips or periorally to whole body numbness. Some of them complained of paresthesia and rigidity of face, extremities and the tongue associated with speech disturbances. These symptoms were often triggered by cold stimuli (i.e. change of temperature in the morning or the evening and washing of face

with cold water etc.) and hunger. Severe hypocalcemic signs such as muscular cramps, dyspnea, chest discomfort were often observed in patients of the treated group. Edema of face or leg and oliguria were also seen in some patients. One patient of the non-treated group showed no hypocalcemic sign throughout the postoperative course. Trousseau's sign and Chvostek's sign were not observed in three non-treated patients.

Fig. 2-B shows the onsets and durations of hypocalcemic signs in treated and non-treated patients. In non-treated patients, hypocalcemic symptoms were not seen before 18 hours after the operation and most of them were seen after 24 hours. The severest hypocalcemic symptoms occurred by the third postoperative day and most of them disappeared in two weeks. In all of the treated group, the initial hypocalcemic signs were seen from 3 to 24 hours. In patients with muscular cramps, the initial hypocalcemic signs appeared within 18 hours. The severest symptoms such as muscular cramps were seen from the second to 14th day but were occasionally seen even one month after the operation. Thereafter, these symptoms became mild but persisted for about one month. However, in a few patients they were seen for three months. The serum calcium levels of patients with muscular cramps were below 6.6 mg/dl except for one whose serum calcium level was 8.2 and 10.2 mg/dl when muscular cramp occurred. This particular patient also had very low serum calcium level (5.4 and 5.6 mg/dl) before and after the day of muscular

Table 5. Hypocalcemic Signs & Symptoms

Signs & Symptoms	No. of patients	
	Treated group	Non-treated group
Numbness & Tingling		
Finger tip	7	5
Face	6	6
Tongue	1	
Extremities	7	4
Whole body	5	
Paresthesia	4	2
Rigidity		
Face	1	
Tongue	2	
Speech disturbance	1	1
Dyspnea	2	
Chest discomfort	1	
Tetany	6	
Headache	1	1
Vertigo	1	
Nausea		2
Anorexia		1
General fatigue	2	
Oliguria	1	
Edema		
Face	4	1
Extremities	3	

cramp. No severe sign was seen in one patient with low serum calcium level of 4.8 mg/dl and calcium administration was not necessary. It was recognized that the severity of symptoms in postoperative hypoparathyroidism was not always correlated with the serum calcium level. It may be safely said that severe hypocalcemic symptoms are apt to be seen in patients with bone symptoms and with high alkaline phosphatase activities, in patients in whom initial hypocalcemic signs are seen within 24 hours after the operation, and in those whose serum calcium levels continue to fall after the third postoperative day.

2) *Unsuccessful cases*

Two patients had a second operation and one patient underwent operation three times. Parathyroids of these three patients were hyperplasia. The causes of

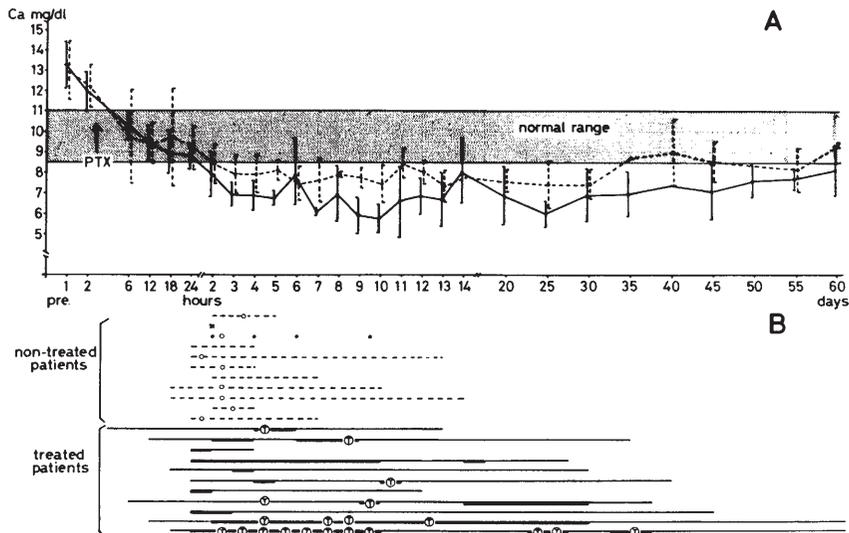


Fig. 2. The relationship between serum calcium changes and duration of hypocalcemic signs.

Fig. 2-A shows mean calcium levels as a function of time in treated and non-treated groups after surgery. A solid line indicates the calcium levels of treated group and a broken line that of non-treated group. Vertical bars indicate standard deviations.

Fig. 2-B shows duration of hypocalcemic signs in each patient (solid lines: treated group, broken lines: non-treated group). Thick parts of solid lines indicate duration of intravenous administration of calcium and the letter "T" the occurrence of muscular cramps. Open circles on broken lines indicate the days when the most severe signs were observed in non-treated patients. A mark \times indicates a patient without hypocalcemic signs.

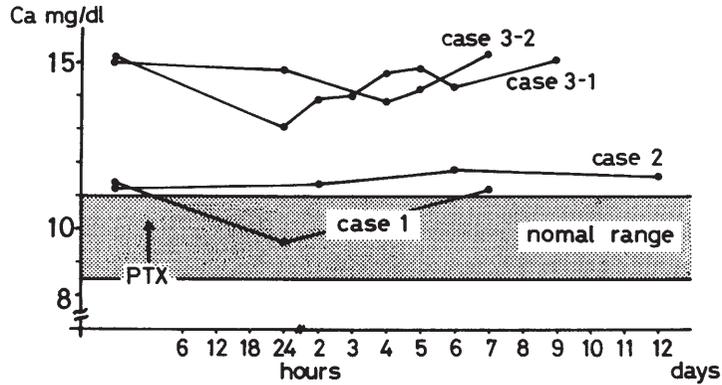


Fig. 3. Postoperative serum total calcium levels as a function of time in three patients in whom operations were unsuccessful. Parathyroids of all patients were hyperplasia. In case one, lower two parathyroid glands were removed and half of each superior gland was resected, in other words, approximately three glands were resected in all. In case 2, biopsy specimens were misdiagnosed as multiple adenoma in frozen section and only two glands were extirpated. In case 3, the first operation (Case 3-1) was removal of three hyperplastic glands and the second operation (Case 3-2) was total thyroidectomy.

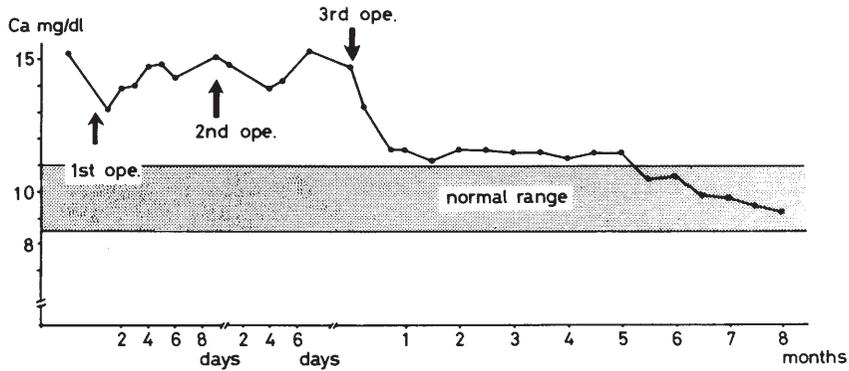


Fig. 4. Postoperative serum total calcium levels as a function of time in a patient who was operated three times. The first operation was total parathyroidectomy of three hyperplastic glands. The second operation was total thyroidectomy. The last was mediastinal exploration but no parathyroid gland was found. Calcium changes after the first and second operations are those shown in Fig. 3 as case 3-1 and case 3-2.

the unsuccessful exploration were removal of insufficient amount of parathyroid tissue due to improper operation, histological misdiagnosis as multiple adenomas in frozen section and intramediastinal dislocation.

Postoperative changes of serum calcium levels in unsuccessful cases are shown in Fig. 3. In one case, the serum calcium levels fell to the normal range 24 hours after the operation, and rose again to elevated levels after a short period of normocalcemia. The hypercalcemia of over 11.0 mg/dl persisted in the remaining three unsuccessful cases until the next operation. In two patients operated twice, the serum calcium levels returned to normal after the second operation. The third case (Fig. 4) was a 34 year old man. At the first neck exploration three hyperplastic glands were found, and all were removed but hypercalcemia still remained. At the second neck exploration nine days after the first operation, no parathyroid was found and total thyroidectomy was next performed but the serum calcium level did not fall. Mediastinal exploration was undertaken 50 days after the second operation but no parathyroid tissue was found, and only fatty tissue was removed. The serum calcium levels slowly dropped without fluctuation and returned to the normal range six months after the third operation. There has been no clinical evidence of recurrence of hyperparathyroidism or hypocalcemia and recent determination of serum calcium level revealed it to be 9.2 mg/dl (nine years after the third operation).

DISCUSSION

When a patient is diagnosed to have primary hyperparathyroidism, parathyroid exploration is the only treatment. Sometimes it is difficult, however, to find abnormal hyperfunctioning parathyroid glands because of their dislocation or abnormality of number. We utilize several examinations to diagnose abnormal parathyroid localization before and during surgery^{7,8,9}. Due to dislocation of parathyroid glands or abnormality of their numbers, satisfactory removal of abnormal parathyroid gland is often difficult. Then, it is judged in our laboratory that the parathyroid exploration is successful only when the serum calcium levels are permanently normalized by the surgical treatment. When surgery is successful, the serum calcium levels fall to normal range, as shown in Fig. 1, within 48 hours, then to below normal range, and gradually returns to normal. In unsuccessful cases, hypercalcemia persists postoperatively or serum total calcium values return to elevated levels within a few days, following a period of temporary normocalcemia.

Several authors^{10,11,12} pointed out that the second exploration should be postponed for at least three months after the first operation to see whether spontaneous improvement takes place. However, we believe that the second operation should be performed without delay when fluctuating hypercalcemia persists after the operation because fluctuating postoperative hypercalcemia is never normalized (see Fig. 3) and worsens the condition of patients. As shown in Fig. 4, when postoperative serum calcium levels remain high but not fluctuating with a tendency to

fall, it is not necessary to operate immediately. The reason why the high serum calcium level in this patient returned to normal after six months is presumably that the vascular damage at operation caused remnant parathyroid atrophy or infarction.

Various hypocalcemic signs or symptoms were observed as shown in Table 5. Generally, mild hypocalcemic signs such as numbness and tingling were observed in patients with slight hypocalcemia and severe signs such as muscular cramps in patients with severe hypocalcemia. But the severity of symptoms is not always correlated with the total serum calcium level. Hypocalcemic manifestations always precede the changes of total serum calcium levels. Some of the patients exhibit mild hypocalcemic signs just after the parathyroidectomy, though their serum total calcium levels are still at the upper limit of normal values. On the contrary, the hypocalcemic sign becomes milder before the serum calcium level begins to rise to normal in convalescence.

It is likely that parathyroidectomy causes sudden decrease of PTH excretion which induces a sudden decrease of ionized calcium levels accompanied with hypocalcemic signs, while total calcium levels remain high. In convalescent patients, total serum calcium is consumed by bone recalcification and remains at low levels, but recovery of parathyroid function causes a significant increase in serum PTH concentration, which results in increase of ionized/protein bound calcium ratio, and hypocalcemic signs become mild. Hypocalcemic signs are correlated with the decrease in plasma ionized calcium which is much more rapid than the decrease in total calcium. Accordingly, there is no significant difference in total calcium change between treated and non-treated groups as expected from the clinical signs. It could be that the serum calcium content of the treated group was lower than the value shown in Fig. 2-A if the patients had not received injections of calcium gluconate.

A remedy for the hypocalcemia is important to ease pain and recovery of the remnant parathyroid function. It is important to know the occurrence of severe hypocalcemia or hypocalcemic symptoms beforehand in order to administer adequate calcium. The severity of the postoperative hypocalcemia is not dependent on age, sex, duration of symptoms, preoperative serum calcium levels and tumor size, but is dependent on the degree of bone decalcification and elevation of the serum alkaline phosphatase levels. Persistent hypocalcemia may occur in patients with bone symptoms because recalcification in bone starts after parathyroidectomy. These patients should be treated by oral or intravenous administration of calcium after the operation.

It is also possible to know the possibility of occurrence of severe hypocalcemic attacks by careful observation of the postoperative clinical course as well as the changes in total serum calcium levels. Severe hypocalcemic symptoms occur in patients whose initial sign appears within 24 hours after surgery (i.e.; sudden decrease in PTH secretion) and in those whose plasma total calcium levels continue to

decrease after the fourth postoperative day. Those patients should be observed carefully. Tetany is likely to be seen after the fourth postoperative day and also appears when the plasma total calcium levels fall below 7.0 mg/dl. Many patients tolerate mild hypocalcemia but some need calcium administration. The emotional states of the patients seem to be an important factor inducing hypocalcemic signs. Hunger or cold stimulus such as changes in room temperature and washing face and hands with cold water also seem to induce hypocalcemic symptoms. Face and/or foot edema and oliguria were seen in some patients. These signs were observed in patients with lasting hypocalcemia and were considered to be due to temporary congestive heart failure by hypocalcemia. In animal experiments hypocalcemia has been shown to lead to cardiac decompensation (Schulman J.L. et al.)¹³⁾. Aryanpur I., Farhoud A. et al.¹⁴⁾ and Antebi L., Bouchard R. et al.¹⁵⁾ reported that the occurrence of congestive heart failure resulting from hypocalcemia was quite rare and observed only in children. Pratley S. K., Posen S. et al.²⁾ reported five cases of cardiac failure after parathyroidectomy. Our studies also demonstrate that postoperative hypocalcemia leads to congestive heart failure not only in children but also in adults which disappeared after the administration of calcium gluconate. Calcium gluconate should be injected to these patients even if they do not complain of severe tetany.

Routine administration of calcium or various vitamin D compounds after parathyroidectomy is questionable, though some surgeons treat routinely these patients with these compounds. It is important to know the decrease in serum calcium in order to determine whether sufficient parathyroid tissue has been removed or not by the operation. Inadequate calcium administration may not only obscure the judgement of successful operation but may also cause hypercalcemia in spite of successful parathyroidectomy¹⁶⁾. The remnant normal parathyroid glands may be atrophic or hypofunctioning due to raised serum calcium levels caused by hyperfunctioning adenoma. These atrophic or hypofunctioning parathyroid glands are normalized by feed back mechanism through the decrease of serum calcium induced by surgical removal of the hyperfunctioning adenoma. It seems probable that the administration of calcium might prevent this recovery of atrophic or hypofunctioning gland. Persistent hypocalcemia does not occur after primary neck operation for a single parathyroid adenoma. The immediate postoperative hypocalcemia often disappears spontaneously.

Accordingly, there is no reason for treating asymptomatic hypocalcemia with calcium during the immediate postoperative period. Therefore, if the patients are relatively free from symptoms, we withhold the treatment of hypocalcemia with calcium or vitamin D. In parathyroidectomized patients, calcium should be administered adequately based on pre- and postoperative states of patients as well as serum calcium levels. Calcium should be administered only to those patients with extensive bone disease, those with severe hypocalcemic signs, those whose initial hypocalcemic signs appear within 24 hours or calcium levels continue to fall after the

fourth postoperative day and those with postoperative congestive heart failure. Needless to say, long lasting or permanent hypocalcemia should be treated with calcium.

As a diagnostic tool for parathyroid function, determination of PTH or ionized plasma calcium may be more helpful than total plasma calcium. But measurement of PTH or ionized calcium level takes much more time and is troublesome. It is difficult to detect low concentration of PTH and to obtain constantly accurate ionized calcium values. Serum total calcium levels can be measured easily and accurately by the use of an autoanalyzer. It is possible to know the postoperative course of the patients by measuring total serum calcium periodically. We believe measurement of total calcium is suitable for routine laboratory examination for checking the states of postoperative patients.

Lately some surgeons perform subtotal parathyroidectomy even on patients with single adenoma^{17,18,19)}. While Wade J.S.H., Fourman P. et al.²⁰⁾ reported that subtotal parathyroidectomy is likely to cause persistent hypocalcemia, we prefer selective removal of abnormal parathyroids to subtotal parathyroidectomy because there was no recurrence of hyperparathyroidism in selectively removed cases when followed up for more than ten years. When subtotal parathyroidectomy is performed, serum calcium levels of patients with postoperative hypocalcemia must be followed up until they become normal because hypocalcemia does not always present obvious symptoms such as paresthesia or tetany.

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