Routine Parathyroid Auto-Transplantation During Subtotal Thyroidectomy For Benign Thyroid Disease

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Abstract

Objective: To evaluate the incidence of post-operative hypoparathyroidism (PoH) following subtotal thyroidectomy for benign thyroid disease with routine parathyroid autotransplantation (PTHAT) and to compare it with in situ preservation of parathyroid glands.

Methods: In a prospective study, 40 cases of benign thyroid disease undergoing bilateral subtotal thyroidectomy were randomly divided into two groups of routine PTHAT (study group) and in situ preservation of parathyroid glands (control group). Post-operative clinical and biochemical monitoring was done to look for incidence and degree of PoH among cases of both the groups. Follow up was done at 15 days and one year to look for transient and permanent PoH respectively.

Results: Pre-operative and intra-operative parameters were comparable among cases of the two groups. In the post-operative period, clinical hypocalcemia was observed in almost half of the cases of both groups. Biochemical hypocalcemia was observed in three cases of the control group and none of the study group cases. Transient PoH was observed in three cases of the control group and none of the study group. Permanent PoH was seen in one case of the control group and none of the study group cases. However, the difference was not statistically significant (p>0.05), possibly due to the small size of the study.

Conclusion: PoH is a debilitating condition following bilateral thyroid surgery and it can safely and easily be prevented by routine PTHAT of at least one parathyroid gland.

INTRODUCTION

Hypoparathyroidism after thyroidectomy is a debilitating morbid condition with an incidence ranging from 1 to $32\%_{1,2,3}$ In recent years, however, attention has been paid to the fact that even milder forms of PoH with normal or slightly reduced serum calcium can be the cause of fatigue, mental and neuromuscular symptoms and ectodermal changes.4 The suggested causes of hypoparathyroidism are ischemia, inadvertent removal and direct trauma to parathyroids during surgery due to their small size and usual anatomic position adjacent to the thyroid gland.1,5,6,7,8,9 PoH can be reduced by preservation of the parathyroid glands in situ with an intact vascular supply or by removal and autotransplantation of parathyroid tissue. It is also shown that patients who underwent PTHAT had significantly less risk of developing permanent hypoparathyroidism compared with patients who did not undergo PTHAT when they developed postoperative hypocalcemia.10,11 Investigators who adopted a policy of selective PTHAT for inadvertently

removed or devascularized parathyroid glands during thyroidectomy reported an incidence of permanent PoH of less than 6% (0-4.4%)._{9,10,11,12,13} On the other hand, incidence of permanent PoH has been reported to be 0% after routine PTHAT following thyroidectomy.₁₄ In view of the decreased incidence of PoH, PTHAT after thyroidectomy for thyroid carcinoma is widely accepted. However there are only occasional reports of PTHAT following bilateral thyroid surgery for benign thyroid disease._{15,16} The present study was therefore conducted to compare the incidence of postoperative hypocalcemia and PoH following subtotal thyroidectomy for benign thyroid disease with or without routine PTHAT.

MATERIAL & METHODS

A prospective study of 40 cases with benign thyroid disease undergoing bilateral subtotal thyroidectomy was carried out in the Department of Surgery, Post-Graduate Institute of Medical Sciences, a tertiary care centre in North India, from July 2001 to July 2004. Cases were randomly divided into Group A (in situ preservation of parathyroid glands) and Group B (routine parathyroid autotrasplantation). The two groups were matched for age, sex and preoperative status as closely as possible. Cases undergoing lobectomy where opposite partahyroids were not subjected to surgical dissection were excluded from the study.

In group A (control group), bilateral subtotal thyroidectomy was performed while taking care to preserve all parathyroid glands in situ. Inadvertently damaged or devascularized parathyroid glands were left in situ in thyroid bed. In group B (study group), bilateral subtotal thyroidectomy was performed while taking care to preserve all parathyroid glands. An attempt was made to ligate the individual branches of inferior thyroid arteries after they had given branches of parathyroid glands. The inadvertently removed parathyroid gland/glands in the resected specimen were removed routinely for immediate autotranplantation. In the absence of identifiable damaged parathyroid glands, routine removal of at least one parathyroid gland was performed for autotransplantation. Identification of all parathyroid glands was attempted, but excessive dissection to look for missing glands was avoided to prevent any damage to remaining parathyroid glands. The removed gland was minced into small pieces and an imprint cytology smear was prepared for the cytological confirmation of parathyroid. This material was immediately autotransplanted in a pocket created in the right sternocleidomastoid muscle.

Serum levels of total calcium, ionic calcium, albumin adjusted serum calcium and serum phosphorus were estimated in all patients of both groups preoperatively for baseline evaluation of parathyroid function. In the postoperative period, apart from clinical monitoring of symptoms and signs, the same biochemical parameters were estimated again on the first, second and third postoperative day to look for the incidence and degree of hypocalcemia due to parathyroid damage during surgery. In case of hypocalcemia, the patients required prolonged hospitalization and were treated with intravenous and/or oral calcium therapy. All the patients were followed up after 15 days, 3 months and 1 year for clinical as well as biochemical assessment of hypocalcemia and hypoparathyroidism.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 10.0.1 (SPSS Inc, Chicago, IL, USA). Results are shown as mean \pm standard deviation (SD). Significant differences between the

two groups were determined using either unpaired Student's t test or the Mann-Whitney U test for interval variables when appropriate. Probabilities equal to or smaller than 0.05 were considered to be significant.

OBSERVATIONS

The two groups were comparable in terms of age, sex ratio, clinical signs and symptoms, type of pathology and extent of thyroidectomy. Most of the patients were in the age group of 20-60 years. All the patients were females except one male in group A. Indications for surgery included colloid goiter (50%), multinodular goiter (37.5%) and hyperplastic goiter (12.5%). Pre-operative biochemical parameters (T3, T4, TSH, serum calcium, albumin corrected serum calcium, ionic calcium and serum phosphorus) were comparable between the two groups. One patient in group A and 3 patients in group B were hyperthyroid and were rendered euthyroid with anti-thyroid drugs before surgery. All the patients underwent subtotal thyroidectomy leaving about 3-4 grams of residual thyroid parenchyma. In group B, imprint cytology smears revealed parathyroid tissue in 19 (95%) cases while 1 (5%) smear had shown cells of thyroid origin. In this case another parathyroid was dissected out, confirmed with imprint cytology and then autotransplanted. Table-1 shows the number of parathyroid glands identified, cytologically verified and autotransplanted during thyroid resection.

Figure 1

Table 1: Number of parathyroids autotransplanted after cytological verification

	Identifie I	d pa II	uratîn III	yroid IV	Cytologically venified Aut parathyroid (n=20)	totransplanted I II III IV
Group A (n=20) 5	12	1	2		-
Group B (n=20) 5	11	2	2	19+1*	17300

*one parathyroid verified cytologically on second attempt

Time taken for surgery was 60-140 minutes (90.5 ± 21.97) in group A and 70-120 minutes (91 ± 14.38) in group B and the difference was statistically insignificant (p>0.05). The weight of the resected thyroid gland ranged from 20-300 grams (66.5 ± 66.21) in group A and 20-280 grams (71.85 ± 61.51) in group B and was comparable. No case in either group had postoperative hoarseness of voice suggestive of recurrent laryngeal nerve damage. Clinical hypocalcemia was observed in the post-operative period in almost half the cases of both groups but the difference was not statistically significant (p>0.05). The signs and symptoms of hypocalcemia were more on day 1 and decreased on day 2 and day 3 in cases of both the groups (Table-2).

Figure 2

Table 2: Clinical signs and symptoms of PoH

	Group A (n=20)					Group B (n=20)						
PS	NS	CPS	CS	TS	Anx	PS	NS	CPS	CS	TS	Anx	
10	10	2	9	9		9	11	0	7	6	1	_
10	10	0	6	7		8	7	0	4	2	1	
4	4	0	б	6		6	7	0	4	3	1	
	PS 10 10 4	PS NS 10 10 10 10 4 4	Group A PS NS CPS 10 10 2 10 10 0 4 4 0	Group A (n=2 PS NS CPS CS 10 10 2 9 10 10 0 6 4 4 0 6	Group A (n=20) PS NS CPS CS TS 10 10 2 9 9 10 10 0 6 7 4 4 0 6 6	Group A (n=20) PS NS CPS CS TS Anx 10 10 2 9 9 - 10 10 0 6 7 - 4 4 0 6 6 -	Group A (n=20) PS NS CPS CS TS Anx PS 10 10 2 9 9 - 9 10 10 0 6 7 - 8 4 4 0 6 6 - 6	Group A (n=20) Group A (n=20) PS NS CPS CS TS Anx PS NS 10 10 2 9 9 - 9 11 10 10 0 6 7 - 8 7 4 4 0 6 6 - 6 7	Group A (n=20) Group B PS NS CPS CS TS Anx PS NS CPS 10 10 2 9 9 - 9 11 0 10 10 0 6 7 - 8 7 0 4 4 0 6 6 - 6 7 0	Group A (n=20) Group B (n=20) PS NS CPS CS TS Anx PS NS CPS CS 10 10 2 9 9 - 9 11 0 7 10 10 0 6 7 - 8 7 0 4 4 4 0 6 6 - 6 7 0 4	Group A (n=20) PS NS CPS CS TS Anx PS NS CPS CS TS 10 10 2 9 9 - 9 11 0 7 6 10 10 0 6 7 - 8 7 0 4 2 4 4 0 6 6 - 6 7 0 4 3	Group A (n=20) Group B (n=20) PS NS CPS CS TS Anx PS NS CPS CS TS Anx 10 10 2 9 9 - 9 11 0 7 6 1 10 10 0 6 7 - 8 7 0 4 2 1 4 4 0 6 6 - 6 7 0 4 3 1

PS: Paresthesia, NS: Numbness, CPS: Carpo-pedal spasm, CS: Chvostek's sign,

TS: Trausseau's sign, Anx: Anxiety

Biochemical hypocalcemia was observed in 3 cases of group A on post-operative day 1 only and in none of the cases of group B and the difference was not statistically significant (p>0.05). One patient each from group A and group B required parenteral calcium supplementation up to day 5 for management of hypocalcemia. Ten patients (50%) of group A and 14 patients (70%) of group B were discharged on the third post-operative day. Those patients with persistent severe symptoms with or without biochemical hypocalcemia were kept under observation. In group A, prolonged hospitalization was required in 4 patients (20%) up to day 4 and in 3 patients (15%) up to day 5. In group B, two patients (10%) each required prolonged hospitalization up to day 4 and day 5 due to PoH. One patient (5%) each from group A and B required hospitalization up to the seventh postoperative day due to clinical hypocalcemia. None of the patients from either group required prolonged hospitalization due to wound complications.

At 15 days follow-up, 3 cases (15%) of group A and 2 cases (10%) of group B had clinical hypocalcemia although the difference was not statistically significant (p>0.05). At 3 months and 1 year follow-up no case from group B and only one case (5%) of group A had clinical hypocalcemia suggesting permanent PoH. On biochemical analysis, only the patient of group A with permanent PoH had decreased levels of albumin corrected serum calcium on day 15, 3 months as well as 1 year follow up. This 40-year-old female patient had undergone subtotal thyroidectomy for multinodular goiter. Only 2 parathyroids were identified during surgery and the weight of the resected specimen was

50 grams. The patient required parenteral calcium supplementation in the post-operative period for clinical hypocalcemia and was discharged on the 6th post-operative day with normal biochemical parameters.

DISCUSSION

Postoperative hypoparathyroidism (PoH) is a debilitating condition arising in connection with bilateral thyroid surgery. Many authors believe that refinement in surgical techniques with preservation of parathyroid glands in situ, meticulous dissection of the precarious blood supply of the parathyroid glands, dissection and ligation of the inferior thyroid artery close to the thyroid gland, and less radical resection short of total thyroidectomy have been used to avoid this complication.9,10,11,12,13 However, problems encountered during in situ preservation of the parathyroid glands are difficulty in dissecting, risk of ischemic damage during dissection and fear of incomplete surgery.17,18,19 Another solution for this problem proposed by different authors is parathyroid autotransplanation (PTHAT) for inadvertently removed or devascularized parathyroid glands during thyroidectomy. However, PTHAT has the technical difficulty of identifying a parathyroid gland since it needs differentiation from fat globules, lymph nodes, thyroid tissue as well as thymus.15,20Also, there is wide variation in location, number, size, shape and color of the parathyroid glands. Although proponents of parathyroid glands preservation through meticulous dissection reported a permanent hypoparathyroidism rate of less than $2\%_{3,21,22,23}$, some investigators have questioned whether these results can be attained by most surgeons and the percentage of hypoparathyroidism ranged from 4% to 32% in other series.2,12,16,24,25,26 Investigators who routinely or selectively use PTHAT reported an incidence of hypoparathyroidism of less than $6\%_{11,15,27,28,29,30}$ with more recent series reporting an incidence of $\pm 1\%$.27,28,31,32

Despite the obvious advantages of parathyroid autotransplantation after thyroidectomy in the literature, there are many controversies regarding number of parathyroids to be autotransplanted, site of autotransplantation, routine versus selective autotransplantation, need for intra-operative frozen section for parathyroid identification and an ideal method to assess the viability of parathyroid glands.

DOES PTHAT TISSUE REGENERATE?

Autopsy findings of three patients with PTHAT, who died 2-15 months after surgery, identified PTHAT tissue of the

same size on gross examination and confirmed the presence of regenerated parathyroid cells on microscopic examination.₄ The physiological tests have also suggested that the regeneration of glands was complete in 4-5 weeks.₄ It has been proven by selective venous sampling from the forearm after PTHAT that the autotransplanted parathyroids synthesize and secrete parathyroid hormone._{33'34}

INTRA-OPERATIVE IDENTIFICATION OF PARATHYROIDS

Although experienced surgeons are often able to identify the parathyroid glands, sometimes it is difficult to differentiate them from other contiguous tissues. Intra-venous administration of methylene blue,35 contact endoscopy,36 frozen section₂₉ and intra-operative cytology₃₇ are various methods described for identifying parathyroids. Out of these, intra-operative frozen section and cytology appear to be more practical in approach. Intra-operative frozen section, apart from prolonging the operative time, leads to loss of parathyroid tissue in section preparation. In the present study loss of tissue was avoided by mincing the parathyroid gland over a glass slide and the same slide was used for preparing imprint cytology smear. It did not prolong the surgery since operating time was comparable between the cases of both groups. Moreover, parathyroid tissue was identified in 95% of cases. One case (5%) showing thyroid tissue on imprint smear underwent PTHAT from another parathyroid gland after cytological confirmation during the same procedure. Thus imprint cytology was able to identify parathyroids in 100% cases.

During thyroidectomy all the four parathyroid glands were identified in most of the cases (60% in group A and 55% in group B) on gross examination. In the remaining cases, 1-3 parathyroids were identified. Studies conducted in the past have shown that unnecessary dissection to identify all the parathyroids should be avoided to reduce the incidence of ischemic injury._{1,3,4} The same principle has been followed in the present study.

SITE OF PTHAT

Most of the authors have shown their preference for autotransplanting parathyroid glands in the exposed sternocleidomastoid muscle._{12,14,30,38}The same principle has been followed in the present study because of the convenience of the procedure. However, other sites used for PTHAT are pectoralis major muscle, cephalad portion of strap muscles and non-dominant forearm. These sites are used especially when staged bilateral modified neck dissection is anticipated and in case of malignancies.29,30

NUMBER OF PARATHYROIDS FOR PTHAT

In the literature, there is controversy in the number of parathyroid glands to be autotransplanted to prevent permanent hypoparathyroidism. The frequency of hypocalcemia was found to increase when the number of autotransplanted parathyroids increased._{28,38}However, Funahashi et al. transplanted 2.94 glands on an average in each case and concluded that transplantation of only one gland leads to permanent hypoparathyroidism and suggested that the higher the number of glands autotransplanted the better would be the outcome.₃₂In the present study, the majority of the patients (85%) had autotransplantation of only one gland and in the remaining cases (15%), two glands were autotransplanted one or two parathyroids._{13,14,15,30,38}

ROUTINE VERSUS SELECTIVE AUTOTRANSPLANTATION

Lo and Lam (1998) did selective parathyroid autotransplantation only in cases with damaged parathyroid glands with doubtful viability in 36% of the patients of their study. Transient hypocalcemia occurred more often in patients with PTHAT (21%) than without PTHAT (8%), while permanent hypocalcemia occurred only in patients who did not undergo PTHAT (2.6%).₁₂After routine parathyroid autotransplantation, Skinner₃₉ found that only one patient had permanent hypoparathyroidism, while Zedenius₁₄ reported an incidence of 0% for permanent hypoparathyroidism. Results of other workers are shown in Table-3. In the present study, routine PTHAT was done in 20 cases and the incidence of transient and permanent PoH was 10% and 0%, respectively.

Figure 3

Table 3: Incidence of PoH after PTHAT and in situ preservation of parathyroids

Study	Number of patients with PTHAT / In situ preservation	PTHAT	Transient PoH (%) PTHAT/ In situ preservation	Permanent PoH (%) PTHAT / In situ preservation	
Paloyan et al. ²⁹	68/54	S	54/46	0/3	
Smith et al. ³⁰	54/34	S	24/29	2/3	
Olson et al. ²⁸	104/90	s	54	1	
Skinner et al. ³⁹	32/0	R		3	
Lo and Lam ¹²	98/173	S	21.4/8.1	0/2.6	
Zedenius et al. ¹⁷	4 74/0	R	19	0	
Lo and Lam ¹⁵	144/0	s	19.6	0	
Thomusch et al.	16 120/0	s	15	0	
Present study	20/20	R	10/15	0/5	

R: Routine PTHAT, S: Selective PTHAT

POH WITH OR WITHOUT PTHAT

In the literature, time duration for deciding onset of permanent PoH ranges from three months to one year._{14,15,24,38}In the present study, postoperative hypocalcemia was defined as patients requiring medications to maintain normocalcemia when they were discharged from the hospital. Patients were regarded as having transient PoH if they became clinically as well as biochemically normal up to 2 weeks after stopping all medications during follow-up. Postoperatively, hypocalcemia requiring treatment to maintain normocalcemia and to control signs and symptoms at one year follow-up was regarded as permanent PoH.

In the present study, the difference in the incidence of symptoms and signs of PoH between the patients of the two groups was found to be statistically insignificant (p>0.05). However, signs and symptoms of PoH were more frequent on day 1 and day 2 and became less frequent on day 3 in patients of both the groups (Table-2). This is probably because of trauma to the parathyroid glands during operation causing venous congestion severe enough to produce temporary embarrassment of arterial supply and a reversible injury.

All the biochemical parameters were measured preoperatively. Although PTH level is the most sensitive indicator of parathyroid function, it could not be done because of lack of availability of this investigation in our setup. However, albumin corrected calcium and ionic levels are equally sensitive indicators of parathyroid function and were measured in the present study. The levels were normal in most of the cases and there was no statistically significant difference between the two groups (p>0.05). In our control group cases, albumin corrected calcium levels were low only in 3 patients (15%) on day 1 and in none of the patients (0%) on day 2 and day 3. In the study group, decreased levels of albumin corrected calcium were observed in none of the patients (0%) from day 1 to day 3. This is probably due to the fact that early calcium supplementation was started on clinical findings of PoH leading to normal serum calcium levels in all cases of PoH in both groups.

The incidence of transient PoH was 15% in the control group and 10% in the study group while the incidence of permanent PoH was 5% in the control group and 0% in the study group. The incidence of transient and permanent PoH as reported by other authors is shown in Table 3. In previous studies, the incidence of transient as well as permanent PoH is much higher probably because a large number of cases in them had thyroid malignancies which required near total/total thyroidectomy while the present study dealt only with benign thyroid lesions requiring subtotal thyroidectomy. These observations prove that PoH can occur following surgery for malignant as well as benign thyroid lesions.

Although the incidence of both transient and permanent PoH was high in the control group as compared to the study group, there was no statistically significant difference (p>0.05) probably due to the small size of the study. However, an important observation was that in the control group, although all patients had normal serum calcium levels up to the day of discharge, one patient started developing biochemical hypocalcemia at the time of follow up on day 15 and this persisted up to 1 year despite calcium supplementation. But none of the patients in the study group developed biochemical hypocalcemia during hospital stay or during follow-up.

This finding reiterates the hypothesis that ischemic damage occurs to the parathyroid glands during dissection which is transient in most cases but can be permanent sometimes leading to permanent PoH. This complication can safely and easily be avoided by routine PTHAT of at least one parathyroid gland which gets revascularised over a period of time and prevents permanent PoH.

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