

Experience with Post Transplant Parathyroidectomy in Gulf Region and Literature Review

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ABSTRACT

Sustained elevation of parathyroid hormone (PTH) levels is not uncommon post renal transplantation. Though in the majority of patients, it gradually normalizes, on average 5% of transplanted patients require parathyroidectomy (PTX). However, PTX itself has been associated with deterioration in allograft function and even completes graft loss seen with both total and subtotal PTX as well as an increased rate of acute rejection. The aim of this study was to determine the effect of post transplant partial PTX on allograft function in our patients as well as the incidence of acute rejection. Our results show that post transplantation, subtotal PTX, was successful in achieving metabolic control while preserving graft function without an increased incidence of acute rejection. Retention of sufficient residual parathyroid tissue with partial PTX might account for favorable outcome in our study. Despite this, surgery for advanced hyperparathyroidism should optimally take place in the pre-transplant period.

Keywords: Parathyroidectomy; Renal Transplantation; Parathyroid Hormone; Hyperparathyroidism

1. Background

Sustained elevation of PTH levels is not uncommon post renal transplantation occurring at a rate of 8.89 per 1000 person-years at risk [1]. In fact, in the majority of patients, it gradually normalizes over the first post transplant year [2], on average 5% of transplanted patients require PTX with a range reported between 1.3 and 20% [3-7]. Although, persistent secondary hyperparathyroidism and hypercalcemia are quite detrimental to graft function, PTX itself is not without its own deleterious effects. It can lead to deterioration in allograft function [2,8-12] and even complete graft loss [2] seen with both total and subtotal PTX [2]. This can be transient [13,14] but has been noted to persist in patients with preexisting renal dysfunction [2]. In addition, an increased rate of acute rejection [7] has also been observed post PTX.

The aim of this study was to review our experience

with post transplant partial PTX related to its effect on short and long term allograft function, as well as the incidence of acute rejection.

2. Method

This was a Gulf region multicenter retrospective chart review of patients who have undergone PTX post renal transplantation. The database included a total of 2000 patients, from 2 centers in UAE and 1 center in Saudi Arabia, patients transplanted between 1995 and 2005.

3. Results

18 patients were identified who had undergone post transplant PTX, 16 subtotal and 2 total as shown in **Table 1**. This was due to protocol prevalent in each centre and the surgical expertise available in the centres. Their mean age was 41.1 ± 13.9 years with a female preponderance.

Table 1. Demographics of patients with post transplant PTX.

#of pts undergone PTX	18 (Subtotal 16, total 2)
Mean Age in years	41.1 ± 13.9 (range 23 - 61)
Male:Female	5:13
Duration of HD (months)	37.2 ± 25.4 (range 5 - 156)
TX Type:	#patients:
CAD	3
LRD	7
LNR	8
Baseline PTH (pre-transplantation) pg/ml	776.11 ± 61.3
Duration between Transplantation & PTX (months)	26.33 ± 23.45
Parathyroid Pathology	Adenoma in 6 patients and hyperplasia in the rest 12 patients
Adenoma diagnosis on preop U/S	6 patients (100% pathologic correlation)

The average duration on hemodialysis (HD) prior to transplantation was 37.2 ± 25.4 months and the majority received kidneys from living donors. Most had significant secondary hyperparathyroidism prior to transplantation with 1/3 associated with parathyroid adenoma. The average time between transplantation and PTX was 26.33 ± 23.45 months signifying sufficient time for spontaneous involution. No patients had renal stones pre PTX.

The post operative course was uneventful in all patients with no significant complications. Surgery was also successful in controlling PTH and calcium, phosphate levels and their product as shown in **Table 2**. More importantly, renal function was preserved as reflected by both serum creatinine (SCr) and eGFR up to 27 months of follow up. Only 4 episodes of rejection were reported in these patients 2 of which occurred prior to PTX. The two occurring post PTX were in patients with previous history of rejection and were appropriately treated with no long term impact on final graft function. One patient suffered graft loss during follow up, which was due to noncompliance to immunosuppression

4. Discussion

Secondary hyperparathyroidism is a common problem among ESRD patients, when advanced or progresses to tertiary form may necessitate PTX. [2]. However following successful renal transplantation, as GFR normalizes, spontaneous resolution occurs in the majority [24,5,15]. This is mainly dependent on the degree of parathyroid gland hyperplasia and its ability to involute post renal transplantation [16]. Unable to regress are those with the most severe changes such as nodular hyperplasia [3] or adenomatous transformation. They have persistent and tertiary hyperparathyroidism (tHPT) re-

spectively. The latter was present in 1/3 of our patients with preoperative ultrasound findings that later on confirmed by histopathology pathology. Importantly however, parathyroid glands apoptosis might also be influenced by genetic and gender determinants which likely explains the female preponderance, as seen in our cohort.

In clinical practice, persistent hyperparathyroidism requiring PTX after renal transplantation is not uncommon and on an average 5% of transplanted patients require PTX with a reported range between 1.3% - 20% [2-7]. Our observed rate is in the lower end at less than 1%, possibly explained by fewer patients with advanced irreversible pathologies such as adenomas. Alternatively, this might be related to population-specific genetic determinants. It has been noted, that especially at risk are females with high pre transplant PTH and calcium levels [1] signifying severe hyperparathyroidism and typically associated with long duration on dialysis [17,18]. In keeping with this, our patients did demonstrate severe elevation of PTH levels with significant hypercalcemia.

It is established that secondary as well as tertiary hyperparathyroidism (tHPT) have many detrimental systemic effects including serious risk to allograft function [3]. Persistent hyperparathyroidism worsens hypercalcemia and induces hypophosphatemia which can result in acute tubular necrosis in the renal allograft [19-22]. Tertiary HPT in particular may also lead to hypertension and hypercalciuria with kidney stones, especially problematic for the graft [23,24]. More importantly, their management is controversial [2] since PTX itself can lead to allograft dysfunction. Thus surgery within the first year is reserved only for cases of tHPT [2] with failure of medical treatment. Indications include asymptomatic hypercalcemia more than 1 year post transplant,

Table 2. Laboratory indices in patients with post transplant PTX.

	PTH (pg/ml)	Ca ⁺⁺ (mg/dl)	PO ₄ (mg/dl)	CaxPO ₄	ALP (iu/l)	SCr (mg/dl)	eGFR (ml/min)	Complications
Base line pre tx	776.11 ± 61.3	10.81 ± 0.68	3.09 ± 0.71	33.40	169.86 ± 36	5.92 ± 0.56	11.24 ± 1.8	
1 month Post-Tx	407.2 ± 37.4	10.76 ± 0.72	3.06 ± 0.89	32.92 ± 0.64	153.75 ± 85	1.42 ± 0.33	64.25 ± 21.09	2 episodes rejection
3 Months Post-PTX	50.01 ± 44.77	9.24 ± 0.56	3.56 ± 0.61	32.89 ± 0.34	104.50 ± 33.73 #	1.51 ± 0.49 †	61.63 ± 18.56†	No renal stone 1 long-term graft loss
Long-term F/U*						1.51 ± 0.48‡‡	61.63 ± 18.56‡‡	

*At Followup of 27.25 months (range 6 - 76); †p value vs baseline 0.89 and 0.83 respectively; ‡‡p value vs baseline 0.43 and 0.27 respectively; #statistically significant.

nephrocalcinosis, renal stones, progressive severe renal osteodystrophy, soft tissue calcification, muscle or bone pain, pruritus or rapid decline in graft function likely due to tHPT [2,4,8,23,25-29].

As mentioned, PTX itself can lead to deterioration in allograft function [2,3,8-12] and even complete graft loss [2], seen with both total and subtotal PTX [2]. Significant deterioration in graft function has been reported shortly after total PTX which is reversible [13] but persisted in patients with preoperative renal dysfunction [13]. Evenepoel [1,14] noted similar results even in patients who underwent incomplete or subtotal PTX. Furthermore, sustained impact on allograft function has been reported post PTX with significant increase in serum creatinine seen within 6 months of PTX [30] and reduced graft survival by 60% at 6 years [31]. Similarly, Schlosser [2] found a decline in graft function after PTX in all patients, with 27% (19/69) showing accelerated deterioration 53% of whom had to restart permanent dialysis within the first post-op year. These patients had already compromised grafts and hence were at greater risk [2]. Moreover, an increase in the rate of acute rejection has been reported post PTX by Schmid [7] suggesting some immunologic involvement [3]. These findings however, are not meant to imply that hyperparathyroidism should be untreated, since animal studies show that its control is protective against progression to CKD [32,33]. Pathologic confirmation of this has been published by Gwinner [34] who showed the development of calcification on protocol allograft biopsies as early as 6 months post transplantation in patients with higher PTH and calcium levels. Not surprisingly, this correlated with an inferior graft function at 1 year.

Our findings, however, are more favorable and in strong contrast with the literature reports. We observed no increased risk of acute rejection compared with preoperative baseline. In addition, there was no impact on short or long term allograft function in transplant recipients following PTX, as reflected by stable serum creatinine and eGFR. This might be related to later sur-

gical intervention in the post transplant period and preservation of more residual parathyroid tissue. The latter is a likely possibility since the surgical technique itself has been shown to impact post op allograft function such that total PTX is reportedly associated with significant renal impairment compared with partial [2]. Several papers describe the benefits of subtotal PTX suggesting that an aggressive approach may not be necessary [20,23,35-37] hence advocating its selection [2]. The proposed mechanism by which PTX may induce allograft dysfunction is via the effects of PTH on renal perfusion [2] where it has a vasodilatory effect on preglomerular vessels [38]. Human studies show that infusion of PTH-related peptide has potent dose dependent effect on renal plasma flow [39]. Hence rapid decline in PTH levels caused by PTX may account for the acute deterioration in allograft function. Schwarz [12] confirmed this by showing a direct correlation between the degree of fall in PTH level and that of the subsequent decline in creatinine clearance post PTX; a finding which was also observed by Schlosser [2]. The increased risk of rejection, on the other hand, might be mediated by an immunologic phenomenon [7].

As with the role of calcimimetics, in obviating the need for surgical intervention, notwithstanding economic considerations, the question becomes life long medications vs a permanent solution. Since a subtotal PTX provides definitive cure, it must be considered the treatment of choice. This must be weighed against the risk of decline in graft function and the theoretical benefits of calcimimetic-induced fluctuations in PTH against bone loss. Moreover, whether calcimimetics will provide better graft survival as compared with PTX remains to be seen [3]. Recent small studies demonstrate the effectiveness of Cinacalcet in the treatment of SHPT [40-42] in transplant recipients however variable effects on renal function have been demonstrated [40-42] with no increased risk of rejection [40]. Therefore the jury is still not out on these agents. However in patients with severe secondary hyperparathyroidism who are already treated with calcimimetics before transplantation, the question is whether to

continue it thereafter. Though there are no clinical studies available to guide us, it is recommended to wait for the same reasons that PTX is not recommended immediately after transplantation [3].

5. Conclusion

Though the ideal time to address advanced hyperparathyroidism is in the pre-transplant period, cases discovered post-transplantation might necessitate PTX after allowing for spontaneous involution. Despite positive impact on metabolic abnormalities, PTX poses risks to allograft function, especially in those particularly susceptible. Our results however show favorable outcomes following subtotal PTX with attainment of excellent metabolic control, preservation of allograft function and no increased incidence of acute rejection. This might be related to later surgical intervention in the post transplant period. Alternatively, it could be attributable to PTH—induced hemodynamic benefits resulting from incomplete removal of parathyroid tissue. This therefore, provides support for advocating partial rather than total PTX, not to be performed early post transplantation. Whether calcimimetics will provide better graft survival as compared with PTX remains to be seen [3] since the experience with them is only recent [3]. Nevertheless, the need for lifelong medication is less favourable as compared to the more permanent surgical solution. However, these agents might have a role in high risk patients.

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