

Peer Review File

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Reviewer A

This is a well written retrospective review of a cohort of patients with secondary hyperparathyroidism and renal failure comparing outcomes of subtotal parathyroidectomy (STPX) versus total parathyroidectomy with autograft (TPTX + AT) prior to kidney transplant. The authors noted a higher rate of permanent hypoparathyroidism in the total parathyroidectomy with autograft group. The authors note that both SPTX and TPTX + AT are acceptable and can effectively reduce PTH postoperatively with low risk of recurrence. The authors concluded that STPX may be a safer and more appropriate option in kidney transplant candidates as it could minimize the period of hypocalcemia and risk of long-term hypoparathyroidism.

This is a nice contribution to the literature and will likely be well cited amongst endocrine surgeons.

Reply: Thank you

Can the authors please comment on where they typically place the autograft? In the sternocleidomastoid or in the forearm?

Reply: The autografts were typically placed in the forearm.

Changes in the text: Added to Methods, Para 2

Also, were there any cases where the surgeon could not identify all 4 glands? If so, what was the outcome for that group?

Reply: Four parathyroids were confirmed on final histology in 84% of patients (as mentioned in results), so that does leave 16% that had less than 4. However it's unclear from the data whether this was because the 4th gland wasn't found, or whether it was completely autotransplanted in the TPTX + AT group, or whether it was small enough to just leave behind in the SPTX group.

All of the patients had a biochemical improvement in their post operative PTH and were analysed based on the "intention to treat" of the surgical approach.

Changes in the text: Nil change

Reviewer B

The authors have undertaken work on an interesting, needed topic. There is a lack of work on this important topic in the available scientific literature. Therefore, this manuscript appears to be an important scholarly work. The topic clearly defines the purpose and the abstract refers to the details of the study. The manuscript requires minor but necessary corrections.

Abstract: I have no objections

Introduction:

Page 4, Line 8 - Parathyroidectomy is one of the basic forms of therapy (actually non fundamental), while pharmacotherapy achieves the desired results in a non-invasive way.

Reply: Ok

Changes in text: Changed to common treatment option rather than fundamental

Methods:

Please complete what test was used to assess the normality of the distribution.

Reply: Descriptive analysis

Changes in text: Added to Methods.

Results:

Page 6, Line 12 - It should be added that data are given as a baseline, because there are no results for the dialysis group.

Reply: Page 6, Line 12 is in the methods section and just mentioning data collection. In the results section, it is said that it is baseline data (Page 7, Line 19).

Changes in text: No change

Discussion:

Page 8, Line 21 - The sentence should be edited.

Reply: Not exactly sure what you wished to be edited. But I have added to it to hopefully make it more clear.

Changes in text: Page 9, Lines 1-2

Page 10, Line 1 - "Additionally, after successful kidney transplantation, the symptoms of hypocalcaemia can be exaggerated.(5)" - that's not true.

In original: "After successful kidney transplantation, reverses of the acidosis symptoms of hypocalcaemia can be exaggerated."

Hypercalcemia occurs in 10-50% of patients after kidney transplantation.

Reply: Yes, you are correct. Apologies.

Changes in text: Updated, Page 10, Line 4.

Conclusions: I have no objections

References: The manuscript lacks current references.

1) Walkenhorst Z, Maskin A, Westphal S, Fingeret AL. Factors Associated With Persistent Post-transplant Hyperparathyroidism After Index Renal Transplantation. *J Surg Res.* 2023 May;285:229-235. doi: 10.1016/j.jss.2022.12.030. Epub 2023 Jan 27. PMID: 36709541.

2) Miedziaszczyk M, Lacka K, Tomczak O, Bajon A, Primke M, Idasiak-Piechocka I. Systematic Review of the Treatment of Persistent Hyperparathyroidism Following Kidney Transplantation. *Biomedicines.* 2022 Dec 22;11(1):25. doi: 10.3390/biomedicines11010025. PMID: 36672533; PMCID: PMC9855347

Reply: I did have references from 2021-2022 but thank you. I have updated with some more from 2022-2023.

Changes in text: References updated.

Reviewer C

With interest I have read the paper by Black et al. on the optimal surgical treatment for renal hyperparathyroidism. Although renal hyperparathyroidism is a common phenomenon with chronic kidney disease, only a minority of these patients are referred for parathyroidectomy. Determining the extent of parathyroidectomy for the individual patient is challenging and considers balancing the risk of persistent/recurrent disease against hypoparathyroidism. Multiple factors, such as the prospect for a renal transplant should be taken into account. The paper is well written and reports on a substantial number of patients undergoing parathyroidectomy. Both strategies seem to relieve hyperparathyroidism, but TPTX+AT increases the risk for hypoparathyroidism.

Nevertheless, this reviewer believes that the manuscript could be improved.

Major comments

1. Although the author state that the decision to perform a SPTX or TPTX + AT was dependent on the attending surgeon, it is unclear if these populations are similar. Why haven't the authors considered other methods to deal with these differences such as propensity score matching? For example, Table 1: PTH levels seem different between both groups.

Reply: Propensity score matching was not suitable due to the sample size. A minimum of at least 100 from each group (total 200) would be required.

There was no statistically significant difference between the two groups.

2. Many studies, including RCT and studies with more patients, have compared SPTX versus TPTX +AT. The aim of the study is to determine the extent of PTX for those receiving a kidney transplant. However, this study also includes patients which did not get a renal transplant. The results section combines both groups which makes the paper somewhat unclear. Please report both groups more clearly or focus on those who will potentially be available for a kidney transplant.

Reply: Yes the results section reports the overall combined results between the two techniques (table 2) – again supporting most other papers that SPTX and TPTX + AT can be effective. But then reports the data related to just the patients who went on to get a kidney transplant in a separate paragraph and table - Table 3 and Results, Para 5.

3. In this light, it is unclear if all patients had a prospective for a renal transplant at the time of PTX. Please add these data to the manuscript.

Reply: I do not have this data.

4. Consider reporting figure 2 also for those who received a kidney transplant.

Reply: Ok

Changes in text: Added as figure 2b

5. Table 3, are outcomes reported before or after kidney transplantation?

Reply: After

Minor comments

1. The manuscript contains several typos. i.e, page 5 line 17 'showed. Page 7 line 20 'statistic'.

Reply: Thank you.

Changes in text: Corrected page 5, line 17 and page 7, line 22.

2. The section on statistics should state how continuous and categorical variables are reported.

Reply: Ok

Changes in text: Added to Methods, Para 5 (page 7, lines 10-12)

3. Page 8 line 5. Please add a measure of dispersion for the follow-up. In addition, follow-up time is reported as mean whereas the follow-up time usually is right skewed. In that case, a median + range/IQR is better to report.

Reply: Ok, thank you.

Changes in text: Updated to median + IQR. Results, Para 4. Page 8, Lines 7-8.

4. Discussion: page 8, line 14-15. Some suggest to tailor the PTX for individual patients focusing on how much parathyroid tissue to leave behind instead of how much to resect (<https://erc.bioscientifica.com/view/journals/erc/27/1/ERC-19-0284.xml>). What is the opinion of the authors on this? Could for example intraoperative PTH be of help? Consider to add this to the discussion section.

Reply: Yes the extent of resection is supposed to refer to not only how much to resect, but how much to leave behind. Because that goes hand in hand, and that's always the balance.

And I could touch on intraoperative PTH but it's a whole other discussion and I think it is beyond the scope of this paper. So I've tried to keep this discussion more focused.

5. The authors state that PTX should be performed prior to kidney transplantation. Please consider other papers as well in this debate: <https://pubmed.ncbi.nlm.nih.gov/26366545/>, which state that >50% is cured from hyperparathyroidism after renal transplantation. ‘

Reply: This is addressed in the introduction that successful kidney transplant corrects the majority however persistent post transplant hyperparathyroidism is still seen – and some studies report up to 80%.

6. How many patients had supranumerary parathyroid glands?

Reply: None documented in this series.

7. Did the authors observe any differences in graft outcomes after transplantation?

Reply: Not recorded in this data.

8. Was there any difference on when patients received their renal transplant?

Reply: The time from parathyroid surgery to kidney transplant is mentioned in the results, para 5.