Total Parathyroidectomy alone or with Autotransplantation for Secondary Hyperparathyroidism in End-Stage Renal Disease Patients: A Systematic Review and Meta-Analysis

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Received Date: 28 October, 2019; Accepted Date: 01 November, 2019; Published Date: 05 November, 2019

Abstract

Purpose: Secondary Hyperparathyroidism (SHPT) is one of the major complications of End-Stage Renal Disease (ESRD) patients. There is ongoing debate on the quality of surgical interventions for these patients. A systematic and meta-analysis was conducted to compare the efficacy and safety of Total Parathyroidectomy (TPTX) alone versus total Parathyroidectomy with autotransplantation (TPTX + AT) on ESRD patients.

Methods: A literature search was undertaken among Cochrane Library, Medline and Embase from inception up to October 2019. Primary outcome included recurrent or persistent SHPT, recurrent SHPT and persistent SHPT. Risk Ratio (RR) was calculated using a fixed effect model.

Results: A total of 4 studies (3 randomized controlled trials and 1 prospective cohort study) comprising 264 patients were analyzed. Compared with TPTX, patients with TPTX + AT have higher risk of “recurrent SHPT” (RR 4.30, 95% confidence interval (CI) 1.13-16.38, P=0.03) and “recurrent or persistent SHPT” (RR 2.89, 95% CI 1.25-6.71, P=0.01, I²=0%). TPTX had shorter operative time than TPTX+AT, but was associated with higher risk of postoperative hypoparathyroidism. No significant difference was found between two groups regarding “persistent SHPT”, “effective”, “ineffective”, duration of hospital stay, permanent recurrent laryngeal nerve palsy or death rate during follow-up.

Conclusions: TPTX as compared with TPTX + AT was associated with a significant reduction in “recurrent SHPT” and “recurrent or persistent SHPT”; and was not associated with an increase in postoperative side effect or mortality. Our findings favored TPTX in the treatment of SHPT in ESRD patients.

Keywords: Chronic; Hyperparathyroidism; Kidney failure; Meta-analysis; Parathyroidectomy; Secondary

Introduction

Secondary Hyperparathyroidism (SHPT) is one of the prevalent disorders of End-Stage Renal Disease (ESRD) patients, and is associated with an increased morbidity and mortality. The conventional approaches for treatment of SHPT include low phosphorus diet, dialysis, and phosphate binders, active vitamin D compounds and calcimimetics. Nevertheless, about 20% ESRD patients still required parathyroidectomy interventions [1]. Total parathyroidectomy (TPTX) and total parathyroidectomy with autotransplantation (TPTX + AT) are the routine surgical interventions for ESRD patients with SHPT. Compared with TPTX + AT, TPTX reduced SHPT recurrence rates [2-7]. Up to date two meta-analyses found that in comparison with TPTX + AT, patients in the TPTX group were associated with lower rates of “recurrence” without severe hypocalcemia or adynamic bone disease [8,9]. However, the conclusions of both studies were based on mainly retrospective cohort studies (only one Randomized Controlled Trial (RCT)) [8,9]. Therefore, we performed an
updated meta-analysis of all RCTs and prospective cohort studies comparing the effectiveness and safety of TPTX versus TPTX + AT in ESRD patients.

**Methods**

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [10].

**Information source and search method**

We searched Cochrane Library, Medline and Embase using the following terms: Chronic Kidney Disease (CKD), CKD, Chronic Renal Failure (CRF), CRF, End-Stage Renal Disease (ESRD), dialysis, Hemodialysis (HD), Renal Hyperparathyroidism, Secondary Hyperparathyroidism (SHPT, 2HPT), SHPT, 2HPT, Renal Hyperparathyroidism (RHPT), (RHPT); parathyroidectomy, parathyroidectomies; autotransplantation, autotransplant before October 31, 2019 with no language restrictions. References and cited papers were screened manually.

**Study selection criteria**

Two investigators (Linsheng Lv and Shaomin Li) independently screened the eligibility of studies. An additional author (Xun Liu) independently resolved disagreements. Inclusion criteria included: (1) studies recruited adult ESRD patients (age >18) who underwent TPTX versus TPTX + AT; (2) studies reported efficacy of operation (including recurrent or SHPT, or effect of surgery defined as “effective” or “ineffective”, reoperation due to persistent or recurrent SHPT), or safety issues regarding operation (including postoperative hypoparathyroidism, postoperative hypocalcemia, delayed parathyroid autotransplantation, operative time, duration of hospital stay, permanent recurrent laryngeal nerve palsy and death during study period); (3) RCTs or prospective cohort studies.

**Data extraction and quality assessment**

Two investigators (Linsheng Lv and Shaomin Li) independently extracted and checked data, and disagreements was resolved by another author (Xun Liu). We extracted data on characteristics of included studies and aforementioned outcomes of interest. Studies were assessed using the Cochrane Collaboration’s tool for assessing risk of bias [11]. The tool evaluated study quality by assessing six domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias and other bias, with each domain ranking from “low risk”, “unclear risk” to “high risk”.

**Statistical analysis**

All the statistical analysis was conducted with Review Manager Version 5.3. Fix effect model was used when no significant heterogeneity was observed; otherwise random effect model was used. The pooled effect was calculated as Risk Ratio (RR) for dichotomous variables and Mean Difference (MD) for continuous variables, and was presented with 95% Confidence Interval (CI). F statistics was used to assess heterogeneity. Significant heterogeneity was defined as F >50% and p<0.05 was defined as statistical significant. For interested outcomes that meta-analysis was unavailable due to lack of data, qualitative analysis was conducted.

**Results**

**Search results**

( Supplementary Figure 1) (see online resource) shows the study selection flow diagram. A total of 666 citations were identified through electronic research. After excluding duplicates and manual selection by screening titles and abstracts, full-texts of 11 studies were retrieved and evaluated in detail. Among them, 6 studies were excluded because they were study protocols [12], had retrospective study design [13-15], had no TPTX+AT arm [16], recruited patients who had reoperative Parathyroidectomy [17], or did not report data on interested outcomes [18]. The other 4 studies involving 264 patients (134 in TPTX+TA group and 130 in TPTX group) were included [5-7,19], of which the main characteristics are summarized in (Table 1). There were three RCTs and one prospective cohort study. Two studies were conducted in China, and the other two were in Germany and Italy respectively. The follow-up time ranged from 3 months to 3 years and the sample varied from 40 to 100 patients. The study by Zhang et al was an abstract and described the efficacy of Parathyroidectomy as “effective” and “ineffective” [19], while the others were published studies reporting persistent or recurrent SHPT after parathyroid operation.

**Methodological quality**

The summary of study quality is presented in (Supplementary Figure 2). All studies except one ranked “low risk” with regard to randomization of participants. Most studies did not perform allocation concealment or blinding of participants and outcome assessment. In general, quality of included studies was moderate.

**Efficacy of TPTX versus TPTX+AT**

Three studies reported 12 “recurrent SHPT” in 182 patients (TPTX+AT vs. TPTX: 89 vs. 93) [5-7]. Pooled analysis showed a significantly higher risk of “recurrent SHPT” (Figure 1). RR 4.30, 95% CI 1.13-16.38, P=0.03, I2=0%) in the TPTX+AT group than the TPTX group. Meta-analysis of two studies involving 140 patients (TPTX+AT vs. TPTX: 68 vs. 72) and 11 “persistent SHPT” showed no difference between two groups (Figure 2. RR 1.86, 95% CI 0.57-6.06, P=0.31, I2=0%) [5,7]. Cases of “recurrent or persistent SHPT” were calculated by sum of “persistent SHPT”...

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample</th>
<th>Study period (month)</th>
<th>Mean age (year)</th>
<th>M/F</th>
<th>Baseline PTH (ng/L) TA/T</th>
<th>Surgical indication</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conzo 2012 [5]</td>
<td>PCS</td>
<td>40</td>
<td>12</td>
<td>52</td>
<td>23/17</td>
<td>1532/1541</td>
<td>PTH levels &gt;800 pg/ml, Ca&gt;10.2 mg/dl, P&gt;5.5 mg/dl, a Ca×P product &gt;55 and worsening symptoms resistant to conventional medical therapy (including cinacalcet, utilized after 2004).</td>
<td>Recurrent SHPT, persistent SHPT, hypoparathyroidism, calcium, PTH, supplement of Ca, improvement of symptoms and radiological changes, death.</td>
</tr>
<tr>
<td>Liang 2015 [6]</td>
<td>RCT</td>
<td>42</td>
<td>6</td>
<td>53.2</td>
<td>NR</td>
<td>1798/1985</td>
<td>Chronic renal failure (uremia stage); preoperative SHPT; no symptom improvement after 3-6 months of standard medical therapy and blood PTH levels of &gt; 1000 pg/ml; severe hypercalcemia or hyperphosphatemia; more than one parathyroid hyperplasia lesion on ultrasonography, with a diameter of &gt; 1 cm; normal hepatic function and parameter of blood coagulation.</td>
<td>Efficacy of operation, recurrent SHPT, recurrent laryngeal nerve injury, hypocalcemia, Ca, PTH, operative time, length of hospital stay.</td>
</tr>
<tr>
<td>Schlosser 2016 [7]</td>
<td>RCT</td>
<td>100</td>
<td>36</td>
<td>49.2</td>
<td>65/35</td>
<td>1163/1330</td>
<td>Patients on long-term (&gt;12 months) dialysis with SHPT (PTH ≥ tenfold above normal value) either with hypercalcemia (developing spontaneously or under treatment with Vitamin D) or with normocalcemia in coincidence with renal osteopathy.</td>
<td>Recurrent SHPT, persistent SHPT, reoperation for SHPT, hypoparathyroidism, calcium, PTH, calcium supplement, vitamin D supplement, operative time, duration of hospital stay, recurrent laryngeal nerve palsy, death.</td>
</tr>
<tr>
<td>Zhang 2013 [19]</td>
<td>RCT</td>
<td>82</td>
<td>3</td>
<td>47.5</td>
<td>42/50</td>
<td>NR</td>
<td>Hemodialysis patients with refractory SHPT.</td>
<td>Efficacy of operation, PTH, Ca, phosphorus, ALP, death, hypocalcemia.</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of included studies.

Abbreviations: ALP: Alkaline Phosphatase; Ca: Calcium; M/F: Male/Female; NR: Not Reported; P: Phosphorus; PCS: Prospective Cohort Study; PTH: Parathyroid Hormone; RCT: Randomized Controlled Trial; SHPT: Secondary Hyperparathyroidism; TA/T: Total Parathyroidectomy with Autotransplantation/Total Parathyroidectomy; TPTX: Total Parathyroidectomy.

and “recurrent SHPT”. Patients who received TPTX+AT were at a significantly higher risk of “recurrent or persistent SHPT” than those received TPTX (Figure 3. RR 2.89; 95% CI 1.25-6.71, P=0.01, I²=0%) [5-7].

Two studies used “significant effective (excellent)”, “effective” and “ineffective” to describe the effect of different surgical procedures on improvement of symptoms and laboratory indexes [6,19]. Data of the groups defined as “significantly effective (excellent)” and “effective” were combined. There was no difference between the two groups with regard to the rates of “effective” or “ineffective” (Figure 4: RR 1.01, 95% CI 0.91-1.12, P=0.84, I²=0%; Figure 5: RR 0.88, 95% CI 0.26-2.97, P=0.84, I²=0%). Schlosser et al. reported 1 reoperation due to persistent SHPT in the TPTX+AT group, while no patient required reoperation in the TPTX group [7]. In the study by Conzo, et al., no patient
Figure 1: Forrest plot of TPTX+AT vs. TPTX on “recurrent SHPT”

Abbreviations: TPTX+AT: Total Parathyroidectomy with Autotransplantation; TPTX: Total Parathyroidectomy; SHPT: Secondary Hyperparathyroidism

Figure 2: Forest plot of TPTX+AT vs. TPTX on “persistent SHPT”.

Abbreviations: TPTX+AT: Total Parathyroidectomy with Autotransplantation; TPTX: Total Parathyroidectomy; SHPT: Secondary Hyperparathyroidism

Figure 3: Forest plot of TPTX+AT vs. TPTX on “recurrent or persistent SHPT”.

Abbreviations: TPTX+AT: Total Parathyroidectomy with Autotransplantation; TPTX: Total Parathyroidectomy; SHPT: Secondary Hyperparathyroidism

required reoperation in the TPTX group due to persistent SHPT, but one patient underwent excision of the transplanted glandular tissue in cubital fossa of the forearm for persistent SHPT [5]. However, non-hyperplastic parathyroid tissue was observed and a further scintigraphy using technetium 99m sestamibi showed tracer uptake in the mediastinum [5]. In this study, reoperation for recurrent SHPT was not described [5].

Safety issues of TPTX versus TPTX+AT

Postoperative hypoparathyroidism was defined as serum parathyroid hormone (PTH) <10 pg/ml in the study by Conzo, et al [5]. Another study reported that PTH level were below the
lower limit (<11 pg/ml) in 7 and 16 patients in TPTX+AT and TPTX group respectively [7]. The pooled analysis indicated that hypoparathyroidism was less common with TPTX+AT than TPTX (Figure 6. RR, 0.39, 95% 0.19-0.80, P=0.01, I²=9%) [5,7]. Five patients in the TPTX+AT and 12 patients in TPTX group developing postoperative hypocalcemia in the study by Liang et al [6]. Conzo, et al. and Zhang et al. respectively reported 26 and 42 cases of hypocalcemia, but the numbers in each group were not specified [5,19]. One study compared the number of patients received oral calcium or vitamin D supplement at discharge and the end of follow-up (3 years after surgery), indicating no significant difference between TPTX+AT and TPTX (at discharge: P=0.31 for calcium supplement, P=0.20 for vitamin D supplement; at end of follow-up, P= 0.29 for calcium supplement, P= 0.63 for Vitamin D supplement) [7]. Schlosser et al. reported no delayed parathyroid autotransplantation in the TPTX group [7]. Relevant data was not described in other studies.

Pool analysis of two RCTs showed that compared with TPTX, TPTX+AT had significantly longer operative time (Supplementary Figure 3, MD, 17.30, 95%CI 4.06-30.53, P=0.01, I²=0%), similar duration of hospital stay (Supplementary Figure 4, MD 0.06, 95%CI -3.95-4.08, P=0.98, I²=86%) and similar risk
of permanent recurrent laryngeal nerve palsy (Supplementary Figure 5, RR 3.12, 95% CI 0.33-29.16, P=0.32, I2=0%) [6,7]. Meta-analysis of two studies including 140 patients suggested no difference between TPTX+AT and TPTX with regard to risk of death during study period (Supplementary Figure 6, RR, 1.31, 95% CI 0.55-3.13, P=0.54, I2=0%) [5,7]. Zhang et al. reported no death during follow-up [19].

**Discussion**

Although new drugs such as calcimimetics had been developed and used for treatment of SHPT, parathyroidectomy was irreplaceable for patients who had no access to or could not afford these drugs, and those had poor effect of pharmacological treatment. TPTX+AT and TPTX were both adopted in clinical practice. However, the optimal surgical procedure for SHPT remained a topic under debate. Thus current meta-analysis was aimed to compare the effect of TPTX+AT and TPTX by summarizing available RCTs or prospective cohort studies. Compared with TPTX+AT, TPTX had significantly lower risks of “recurrent SHPT” and “recurrent or persistent SHPT”, similar treatment effect to relieve SHPT, a higher risk of postoperative hypoparathyroidism and shorter operative time. With regard to the risk of death during follow-up, no difference was observed between two surgery procedures. There was inadequate prospective clinical data on “reoperation due to persistent or recurrent SHPT”, “delayed parathyroid autotransplantation”, “postoperative hypocalcemia”, “calcium supplement” or “vitamin D supplement” for meta-analysis.

In general, current study was in favor of TPTX+AT in view of a lower risk of “recurrent SHPT”, but this finding required further confirmation by large-scale randomized clinical trials. Previous studies reported a higher recurrence rate of SHPT of 8.3% to 33% during follow-up of 6 months to 5 years after TPTX+AT, compared with 1.8% to 4.8% after TPTX [2-7]. The association between TPTX+AT and higher risk of “recurrent SHPT” was also suggested in two previous meta-analyses, with odd ratios varying from 0.08 to 0.20 when comparing TPTX with TPTX+AT [8,9]. Our studies excluded retrospective studies, and the results were consistent. The difference in recurrence rates between two procedures might be partly due to autograft hyperplasia, which accounted for 49% of permanent recurrent laryngeal nerve palsy. The long-term rate of reoperation with two surgery strategies still needed to be further investigated.

A main issue of concern of TPTX was the potential risk of hypoparathyroidism and severe hypocalcemia following operation. A higher risk of hypoparathyroidism was observed in TPTX+AT group, consistent with former studies [8,9]. However, no delayed parathyroid autotransplantation after TPTX+AT was reported in included studies [5,7]. Actually, despite the tendency of developing parathyroidism, following results such as uncontrolled hypocalcemia or adynamic bone disease was rare in patients receiving TPTX+AT according to early studies [22-26]. On the other hand, previous pooled analysis of main prospective studies showed no difference in risks of hypocalcemia between TPTX+AT and TPTX [8,9]. Although meta-analysis on risk of hypocalcemia was not allowed for lack of prospective data in current study, episodes of hypocalcemia were common in both TPTX+AT and TPTX groups in individual studies, and seemed to be temporary and could be corrected by supplement of calcium and vitamin D [5-7,19]. Furthermore, compared with TPTX+AT, TPTX had shorter operative time, similar duration of hospital, risk of permanent recurrent laryngeal nerve palsy and death rate during follow-up. TPTX+AT might be a feasible surgery strategy when parathyroidectomy was required for ESRD patients.

The strength of current study was that only RCTs and prospective cohort studies were included, which avoided information bias that might exist in prospective studies. Meanwhile, the randomized design in most of the included studies reduced selection bias. Importantly, attention should be paid to several limitations of our study. First, only 4 studies with a small sample were included in this meta-analysis, which prevent the drawing of convincing conclusion and limited the power of our study to discover difference between TPTX+AT and TPTX on some interested results like reoperation. Second, the definition of outcome such as “recurrent SHPT” varied in individual studies. Third, the study period in most included studies was not longer than 1 year, which was inadequate for assessment of long-term effect of different surgery procedures such as mortality.

**Conclusions**

Compared with TPTX + AT, TPTX was equally effective and significantly lowered the risk of “recurrent SHPT” and “recurrent or persistent SHPT”. Although TPTX was associated with a higher rate of postoperative hypoparathyroidism, it was temporary and rectifiable. TPTX had shorter operative time and no increased risks of operative complication compared with TPTX + AT. Our findings derived from prospective data favored TPTX in the treatment of SHPT in ESRD patients.
References


