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Review

Thermal ablation versus parathyroidectomy for secondary hyperparathyroidism: A meta-analysis

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ABSTRACT

Objective: Thermal ablation and parathyroidectomy (PTX) have been recommended for patients with secondary hyperparathyroidism (SHPT). However, it is uncertain which is the better method. The aim of the present meta-analysis was to evaluate the efficacy and surgical complications of the two treatment methods.

Methods: The following databases were searched from inception to December 31, 2018: PubMed, EMBASE, the Cochrane Library, CNKI, and Wanfang. Eligible studies comparing thermal ablation and PTX for SHPT were included. Data were analysed using Review Manager Version 5.3.

Results: Six studies were included in the meta-analysis. Four cohort studies and two randomized controlled trials involving 326 patients with SHPT were identified. There was no difference concerning parathyroid hormone (PTH) levels (MD 58.04, 95% CI -17.60–133.68, P = 0.13), calcium levels (MD -0.07, 95% CI -0.17–0.04, P = 0.21), phosphorus levels (MD 0.21, 95% CI -0.18–0.61, P = 0.29), or hoarseness (OR 0.53, 95% CI 0.24–1.16, P = 0.11) between the two surgical methods. Compared with PTX, thermal ablation reduced the risk of hypocalcaemia (OR 0.23, 95% CI 0.11–0.47, P < 0.01). However, thermal ablation increased the risk of SHPT persistence and/or recurrence compared with PTX (OR 4.24, 95% CI 1.44–15.76, P = 0.03).

Conclusion: Thermal ablation and PTX were effective surgical approaches for SHTP. Thermal ablation reduced the risk of hypocalcaemia and increased the risk of SHPT persistence and recurrence. More large multicentre randomized controlled trials are necessary to confirm the conclusions.

1. Introduction

Secondary hyperparathyroidism (SHPT) is a common complication of end-stage renal disease (ESRD) [1]. SHPT is characterized by persistently increased parathyroid hormone (PTH) levels due to hypocalcaemia, hyperphosphataemia, and vitamin D deficiency in ESRD [2]. Clinical features of SHPT include soft tissue calcification, vascular calcification, bone pain and fracture, which can affect quality of life and increase mortality [3–5]. In the early stage, SHPT can be managed by drug therapy. For refractory SHPT, parathyroidectomy (PTX) is recommended in most practical guidelines [4,6]. PTX can significantly reduce PTH levels, relieve symptoms, and decrease complications and mortality [7–10]. However, many patients, especially those with poor cardiopulmonary function, cannot tolerate PTX because PTX is invasive and traumatic.

Recently, thermal ablation has been used to treat patients with refractory SHPT [11–13]. Thermal ablation, including microwave ablation (MWA), radiofrequency ablation (RFA), and laser ablation, aims to achieve thermal necrosis of the parathyroid gland. Compared with PTX, thermal ablation has advantages of minimal invasiveness, ease of operation, fast recovery, and repeatable use [14], but the efficacy and surgical complications of thermal ablation are uncertain. To date, some studies in China have been performed to compare the efficacy and surgical complications between the two treatment methods. Therefore, this meta-analysis was conducted based on the published literature to evaluate the efficacy and surgical complications of the two treatment methods in patients with SHPT.

2. Materials and methods

2.1. Search strategy

This meta-analysis is reported in line with the Assessing the methodological quality of systematic reviews (AMSTAR) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and was registered at the International Prospective Register

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of Systematic Reviews (registration number: CRD42019126396).

We searched the following databases from inception to December 31, 2018: PubMed, EMBASE, the Cochrane Library, CNKI (China National Knowledge Infrastructure), and Wanfang. The combined text and MeSH terms included secondary hyperparathyroidism, parathyroidectomy, surgical procedures, operative, ablation, and interventional. In addition, the relevant references and cited papers were searched manually to identify additional studies meeting the inclusion criteria. There were no language restrictions.

2.2. Inclusion and exclusion criteria

The inclusion criteria were (1) randomized controlled trials (RCTs) and cohort or case-control studies; (2) studies of severe SHPT, defined as high PTH levels (> 800 pg/ml) and parathyroid gland hyperplasia diagnosed by ultrasound or radionuclide imaging; (3) studies that compared outcomes between thermal ablation and PTX; and (4) studies with outcomes that included at least one of the following indicators: PTH, calcium, phosphorus, persistent and/or recurrent hyperparathyroidism, hypocalcaemia, or hoarseness after thermal ablation and PTX. The exclusion criteria were (1) case series, comments, and reviews; (2) studies consisting of patients with primary hyperparathyroidism or tertiary hyperparathyroidism; and (3) studies with a lack of relevant outcome data.

2.3. Data extraction and quality assessment

Data were extracted independently by two investigators using standard data extraction forms. In the case of disagreement, a third investigator was consulted. We extracted characteristics including first author, year of publication, location, study design, sample size, mean age, sex, follow-up period, specific methods of operation, and treatment outcomes. The Cochrane assessment tool was used to assess the quality of the RCTs, whereas the Newcastle–Ottawa scale (NOS) was used to assess the quality of the non-randomized studies. The work has been reported in accordance with Assessing the Methodological Quality of Systematic Review (AMSTAR) guidelines.

2.4. Statistical analysis

This meta-analysis was performed using Review Manager Version 5.3 (Cochrane Collaboration). We summarized treatment outcomes as odds ratios (OR) for categorical variables and weighted mean differences for continuous variables with 95% confidence interval(CI). $P < 0.05$ was considered statistically significant. The I^2 statistic was used to assess heterogeneity among studies. $I^2 > 50\%$ and $P < 0.10$ were considered to indicate significant heterogeneity. Meta-analysis with statistically insignificant heterogeneity was performed using the fixed-effects model. For meta-analyses with significant heterogeneity, the random-effects model was used. Publication bias was assessed using subgroup analysis or sensitivity analysis.

3. Results

3.1. Study selection and characteristics

A flow diagram of the selection process is shown in Fig. 1. A total of six studies from China were ultimately included in this analysis [15–20]. Of the six studies, four were cohort studies, and two were RCTs. Four studies [17–20] were published in Chinese journals. In total, 157 patients were included in the thermal ablation group, and 169 patients were included in the PTX group. The follow-up period ranged from 1 month to 29 months. The baseline characteristics of these studies are listed in Table 1. NOS assessments are listed in Table 2, and the Cochrane assessment is listed in Table 3.

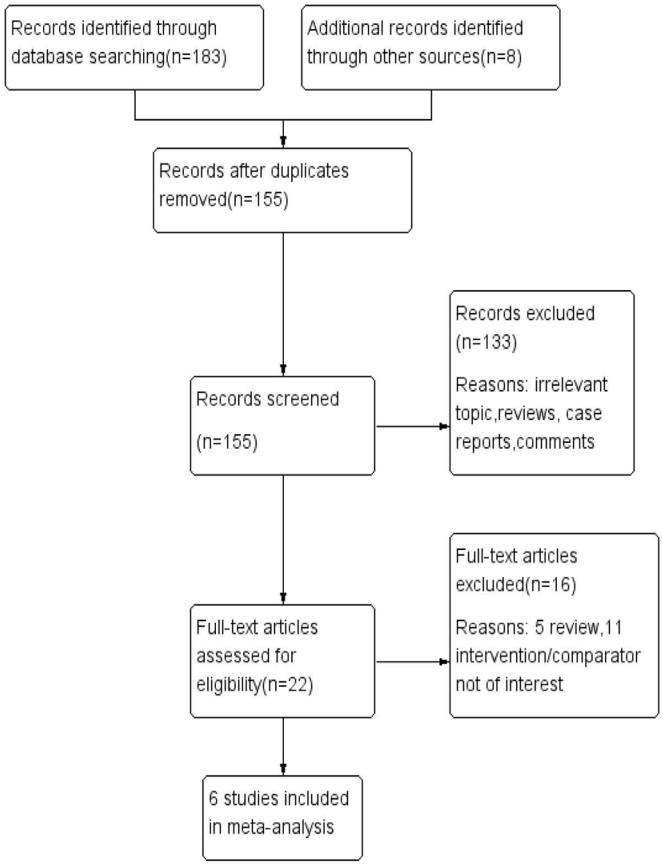

Fig. 1. Flow diagram of the literature search.

3.2. Meta-analysis results

3.2.1. PTH level

Data about PTH levels were reported in all articles. There was significant heterogeneity among the studies ($P < 0.10$, $I^2 = 88\%$), so the random-effects model was ultimately used for the meta-analysis. The PTH levels of the thermal ablation group were higher than those of the PTX group, but the difference was not statistically significant (MD 58.04, 95% CI -17.60–133.68, P = 0.13) (Fig. 2).

3.2.2. Calcium level

Data about calcium levels were reported in four articles. The heterogeneity between these studies was not significant ($P = 0.81$, $I^2 = 0\%$), so the fixed-effects model was used for the meta-analysis. There was no significant difference between the groups concerning calcium levels (MD -0.07, 95% CI -0.17–0.04, P = 0.21) (Fig. 3).

3.2.3. Phosphorus level

Data about phosphorus levels were reported in four studies. There was significant heterogeneity among the studies ($P < 0.10$, $I^2 = 94\%$), so the random-effects model was ultimately used for the meta-analysis. There was no significant difference between the groups concerning phosphorus levels (MD 0.21, 95% CI -0.18–0.61, P = 0.29) (Fig. 4).

3.2.4. Persistent and/or recurrent hyperparathyroidism

Three studies reported data about hyperparathyroidism persistence and/or recurrence: 9/86 (10.5%) patients in the thermal ablation group and 3/90 (3.3%) patients in the PTX group. The heterogeneity between these studies was not significant ($P = 0.21$, $I^2 = 35\%$), so the fixed-effects model was used for the meta-analysis. Compared with the PTX group, the thermal ablation group had a higher risk of hyperparathyroidism persistence and/or recurrence (OR 4.24, 95% CI 1.44–15.76,

Table 1
Characteristics of the included studies.

Study(year)	Country	Design	Follow-up period	Sample size	Mean age (years)	Male (%)	The method of ablation	The method of PTX
Zongli Diao, 2016	China	Cohort study	29 months	Ablation:18 PTX:12	57.06 ± 9.14 57.17 ± 8.03	4(22.2) 6(50.0)	The average number of parathyroid gland ablated was 2.22 ± 1.00	SPTX:2 TPTX + AT:4 TPTX:6
Dongliang Zhang, 2016	China	RCT	12 months	Ablation:21 PTX:20	52.0 55.2	11(78.3) 9(63.8)	–	–
Jianchuan Yang, 2018	China	Cohort study	6 months	Ablation:32 PTX:47	47.75 ± 13.77 49.02 ± 11.82	11(34.4) 30(63.8)	More than ninety percent of parathyroid was ablated	SPTX or TPTX
Jilong Rong, 2017	China	Cohort study	1 month	Ablation:12 PTX:20	50.3 + 13.6 53.5 ± 11.1	5(41.7) 9(45.0)	–	TPTX + AT
Jinzhou Liu,2017	China	RCT	6 months	Ablation:34 PTX:34	43.05 ± 7.71 42.09 ± 7.81	20(58.8) 18(52.9)	The fourth parathyroid gland was partially ablated until the PTH levels met target	SPTX
Xiangfei Ding,2017	China	Cohort study	6 months	Ablation:40 PTX:36	53	–	The fourth parathyroid gland was partially ablated until the PTH levels met target	SPTX or TPTX + AT

Table 2
Quality assessment of cohort studies.

Studies	Selection	Comparability	Outcome	Score
Zongli Diao,2016	★★★	★	★★★	7
Jianchuan Yang,2018	★★★★	★	★★★	8
Jilong Rong,2017	★★★	★	★★	6
Xiangfei Ding,2017	★★★★	★	★★★	8

P = 0.03) (Fig. 5).

3.2.5. Hypocalcaemia

All studies reported data about the incidence rate of hypocalcaemia: 16/157 (10.2%) patients in the thermal ablation group and 41/169 (24.3%) patients in the PTX group. The heterogeneity between these studies was not significant (P = 0.11, I^2 = 44%), so the fixed-effects model was used for the meta-analysis. Compared with the PTX group, the thermal ablation group had a lower risk of hypocalcaemia (OR 0.23, 95% CI 0.11–0.47, P < 0.01) (Fig. 6).

3.2.6. Hoarseness

All studies reported data about the incidence rate of hoarseness: 11/157 (7.0%) patients in the thermal ablation group and 20/169 (11.8%) patients in the PTX group. The heterogeneity between these studies was not significant (P = 0.55, I^2 = 0%), so the fixed-effects model was used for the meta-analysis. The incidence rate of hoarseness in the thermal ablation group was lower than that in the PTX group, but the difference was not statistically significant (OR 0.53, 95% CI 0.24–1.16, P = 0.11) (Fig. 7).

3.3. Sensitivity analyses

A sensitivity analysis for PTH levels after the two surgical treatments was used to judge the dependability of the results. We deleted one study at a time; the heterogeneity was still significant, and the results still showed no difference.

4. Discussion

In the clinical practice guidelines of Kidney Disease: Improving Global Outcomes (KDIGO), PTX was recommended for patients with severe SHPT who failed to respond to medical therapy [21]. Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines also recommended PTX for patients with severe SHPT [4]. PTX is the classic treatment for severe SHPT and has been used for more than a half-century. PTX includes total PTX, subtotal PTX, and total PTX with autotransplantation, all of which are effective methods for improving the quality of life and for decreasing the complications and mortality associated with severe SHPT [22,23]. However, in some studies, thermal ablation, including MWA, RFA, and laser ablation, has been proven to be effective for treating SHPT [11–13]. Thermal ablation can destroy local tissue by raising the temperature but does little damage to the surrounding tissue [24]. The greatest advantage of thermal ablation compared with PTX is that it is less invasive. At present, no definite evidence has proven which method is better concerning efficacy and complications. Our systematic review aimed to appraise the efficacy and complications of the two treatment methods for SHPT.

Our findings revealed that there was no difference between the two surgical methods concerning PTH levels, calcium levels, phosphorus levels, or hoarseness. Compared with PTX, thermal ablation reduced the risk of hypocalcaemia. However, thermal ablation increased the risk of hyperparathyroidism persistence and/or recurrence.

The PTH levels after the two surgical treatments represented an important indicator related to clinical efficacy. Thermal ablation and PTX were both certainly beneficial in decreasing the PTH levels. All

Table 3
Risk of bias of randomized control trial.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Selective reporting	Other bias
Dongliang Zhang, 2016	Unclear	Low risk	Unclear	Low risk	Low risk	Unclear
Jinzhou Liu,2017	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear

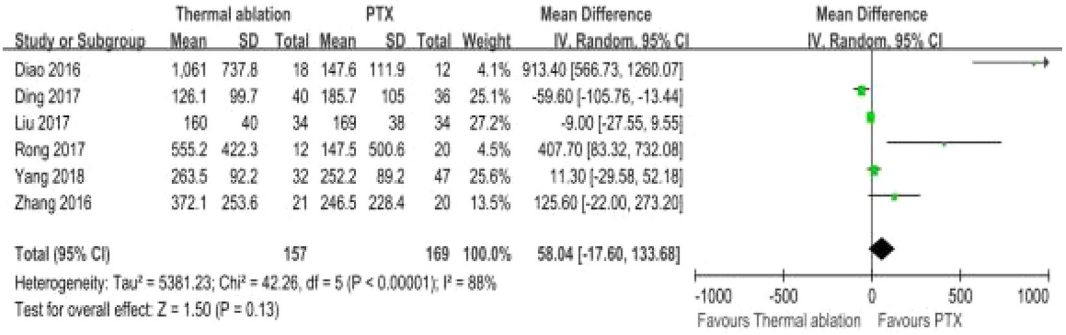

Fig. 2. Forest plots comparing PTH levels between thermal ablation and PTX.

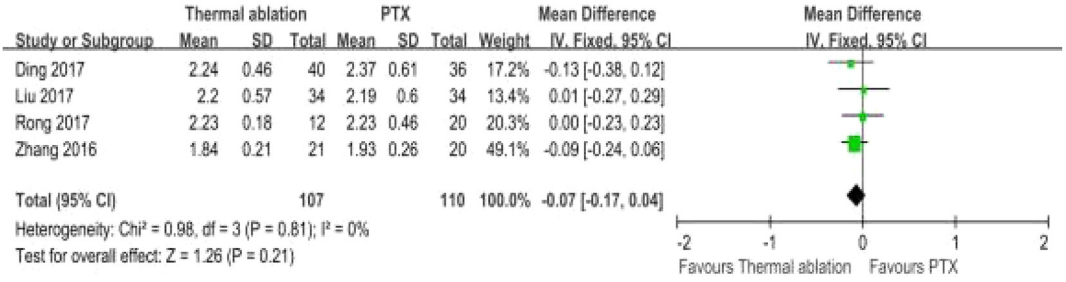

Fig. 3. Forest plots comparing calcium levels between thermal ablation and PTX.

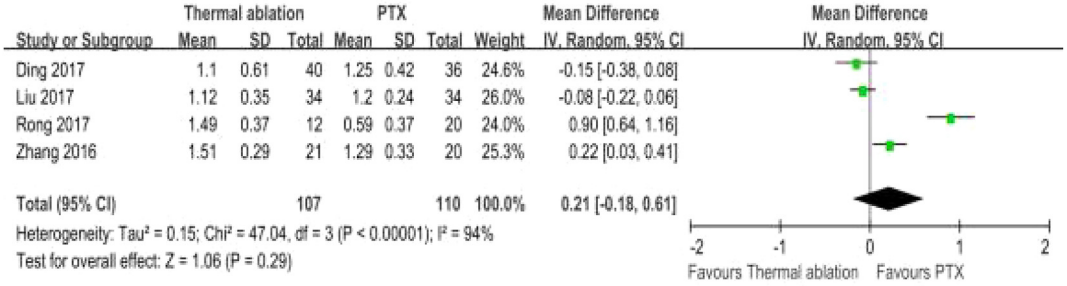

Fig. 4. Forest plots comparing phosphorus levels between thermal ablation and PTX.

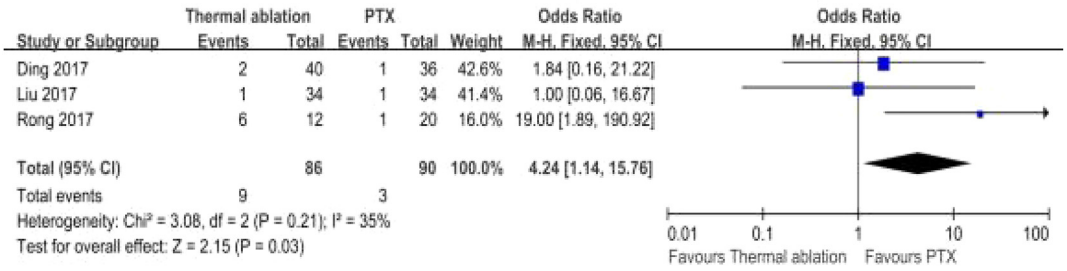

Fig. 5. Forest plots comparing hyperparathyroidism persistence and/or recurrence between thermal ablation and PTX.

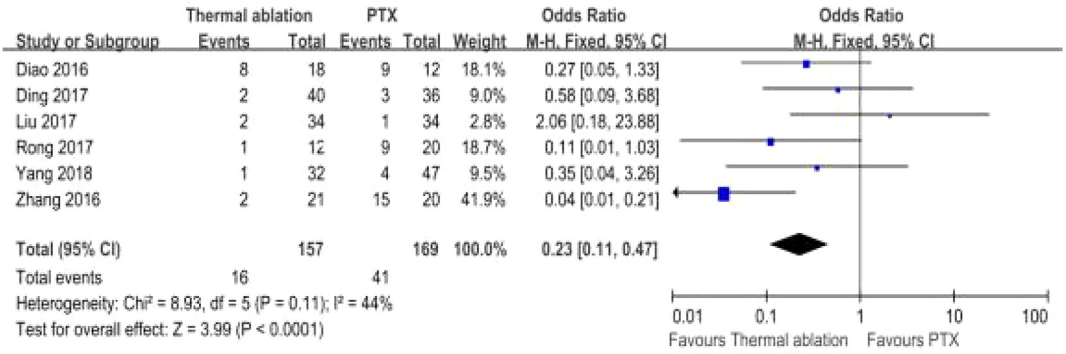

Fig. 6. Forest plots comparing hypocalcaemia between thermal ablation and PTX.

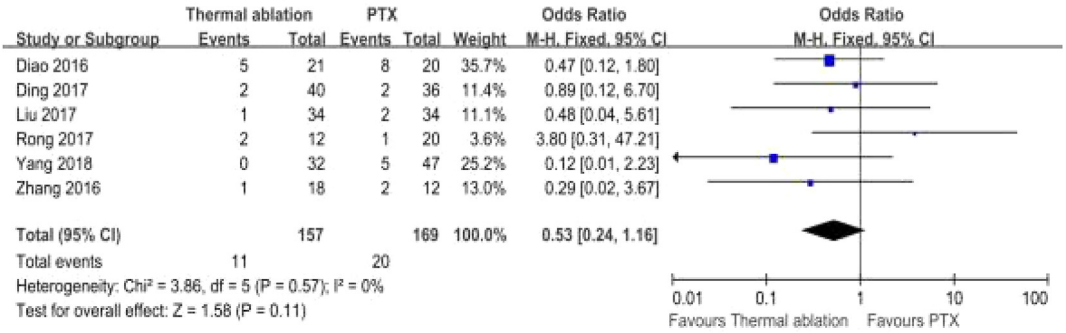

Fig. 7. Forest plots comparing hoarseness between thermal ablation and PTX.

included studies showed that the PTH average value remained within the ideal range (150–300 pg/ml) after PTX, but two included studies [15,18] showed that the PTH average values were still above 500 pg/ml after thermal ablation. Furthermore, some other Chinese self-control studies [25,26] also indicated that the PTH average value remained high after thermal ablation, possibly because some parathyroid tissue was not completely removed by thermal ablation.

Persistent hyperparathyroidism and recurrent hyperparathyroidism after the two surgical treatments were the serious complications related to clinical efficacy. Our findings revealed that thermal ablation increased the risk of hyperparathyroidism persistence and/or recurrence compared with PTX. The reasons for the difference between the two surgical treatments were as follows. First, the parathyroid gland was easily removed in total after PTX because PTX was performed under direct observation. However, the parathyroid gland might not have been completely removed by thermal ablation because thermal ablation was not performed under direct observation. Second, PTX is a classic treatment that has been used for many years, and thermal ablation is a new treatment. Compared with the technology of thermal ablation, that of PTX is more mature, and surgeons performing PTX are more proficient [15]. In brief, residual parathyroid glands can result in persistent or recurrent hyperparathyroidism.

Hypocalcaemia is a common complication of PTX. It occurs because the PTH value suddenly decreases after PTX [27,28]. Hypocalcaemia is mostly transitory. Our findings revealed that thermal ablation reduced the risk of hypocalcaemia compared with PTX Because the PTH value remained relatively high after thermal ablation. It is worth noting that there was no significant difference between the groups regarding serum calcium levels. However, all standard deviations (SDs) of serum calcium levels were higher in the PTX group than in the MWA group. This implied that the incidence of hypocalcaemia might be higher in the PTX group than in the MWA group.

Hoarseness is another complication of surgical treatment. Although thermal ablation is minimally invasive, our findings revealed that thermal ablation did not reduce the risk of hoarseness. Thermal ablation was not performed under direct observation, and the surgeon might have been unskilled, so hoarseness still occurred.

There were some limitations in our meta-analysis. First, most included studies had a small sample size, so our meta-analysis may not be adequate to judge the effectiveness and safety of the two surgical treatments. Second, surgical procedures for both thermal ablation and PTX were not uniform in our study. Third, the specific definitions of persistent hyperparathyroidism and recurrent hyperparathyroidism were not mentioned in most studies that were included in the meta-analysis. Fourth, only one study reported data about hypoparathyroidism, which is a serious complication.

5. Conclusions

Our meta-analysis revealed that thermal ablation and PTX were effective surgical approaches for SHTP. Thermal ablation reduced the risk of hypocalcaemia. However, thermal ablation increased the risk of hyperparathyroidism persistence and recurrence. To further confirm the conclusions, more large multicentre randomized controlled trials comparing the two surgical treatments are necessary.

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Conflicts of interest

The author declares no conflicts of interest.

Ethical Approval

Ethical Approval is not applicable.

Sources of funding

The authors declare no relevant conflict of interest.

Author contribution

The authors on this meta-analysis all participated in study design. All authors have read and approved this version of the article, and due care has been taken to ensure the integrity of the work. The material of this article is original research and no part of this paper has been previously published. The material has also not been submitted for publication elsewhere while under consideration. No conflict of interest exits in the submission of this manuscript. All authors have the appropriate permissions and rights to the reported data.

Conflicts of interest

The authors declare no relevant conflict of interest.

Trial registry number

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Data statement

Data Statementhasbeenlisted beloweach figure and table.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.08.004.

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