

REVIEW

Can intraoperative suturing reduce the incidence of posttonsillectomy hemorrhage? A systematic review and meta-analysis

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Funding information

Department of Science and Technology of Sichuan Province, Grant/Award Numbers: 2019YFS0207, 2020YFS0113; National Natural Science Foundation of China, Grant/Award Number: 81802468

Abstract

Objective: This study was to compare tonsillectomy with intraoperative suturing (TIS) and tonsillectomy without intraoperative suturing (TsIS) in preventing postoperative tonsillectomy hemorrhage (PTH).

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was followed. Articles compare TIS and TsIS in preventing PTH were included. The quality of eligible studies was assessed with the Newcastle-Ottawa Scale (NOS) by two independent investigators. Random effect models were used to determine odds ratio (OR) with 95% CIs.

Results: A total of 15 studies were analyzed. The pooled results showed the PTH rate was lower in the TIS group (OR = 0.64; 95% CI, 0.47–0.88). The TIS group had a lower primary and secondary PTH rate than the TsIS group with OR values of 0.44 (95% CI, 0.30–0.64) and 0.70 (95% CI, 0.54–0.90), respectively. However, suturing did not show an advantage in reducing the risk of returning to the operation room for hemostasis (OR = 0.57; 95% CI, 0.13–2.47). Adults might benefit from the intraoperative suturing procedure (OR = 0.31; 95% CI, 0.16–0.60). Patients with more than three stitches on each side had a lower PTH rate (OR: 0.44; 95% CI, 0.32–0.60). Suturing the tonsillar fossa and pillars simultaneously could reduce the PTH rate (OR = 0.47; 95% CI, 0.34–0.64).

Conclusions: Intraoperative suturing is a good strategy for preventing PTH. More multicenter randomized controlled studies should be conducted to demonstrate the efficacy of this procedure.

Level of Evidence: 5.

KEYWORDS

meta-analysis, postoperative hemorrhage, suture, tonsillectomy

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1 | INTRODUCTION

Tonsillectomy is a common operation performed in the ENT department. Although postoperative complications are rare, hemorrhage is the most serious and may even be fatal. Reported rates of postoperative hemorrhage range from 0.1% to 3%.^{1,2} Otolaryngologists continue to seek ways to effectively avoid postoperative hemorrhage and alleviate patient anxiety.

Postoperative tonsillectomy hemorrhage (PTH) is a multidimensional and multifactorial problem. Studies have shown that age, gender, anesthesia, and hemostatic methods, might affect the risk of postoperative hemorrhage.³⁻⁵ Though many studies have focused on the effect of different devices, we believe that intraoperative skill plays an essential role in preventing PTH.

With the increased use of hot devices, such as coblation, ultrasonic knife, monopolar/bipolar diathermy, tonsillectomy procedures have significantly changed. Consequently, intraoperative suturing, as a basic surgical skill, likely less frequently used in tonsillectomy. It is a reliable hemostatic method, used mainly for difficult intraoperative hemostasis and postoperative bleeding. Overall, PTH remains an intractable and serious problem in tonsillectomy patients. However, there is still a lack of consensus regarding the ideal procedure. The purpose of the current systematic review was to assess the value of intraoperative suturing and summarize its efficacy in preventing PTH.

2 | MATERIALS AND METHODS

2.1 | Search strategy

Two authors (BL and MW) independently performed electronic searches in the Pubmed, Embase, Cochrane Library, and Web of Science to find relevant PTH studies. The data collection period was from inception through March 1, 2021. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were followed. The following search terms were used to conduct the literature search: (“stitch[Title/Abstract]” OR “suture[Title/Abstract]”) AND (“tonsillectomy[Title/Abstract]” OR “adenotonsillectomy[Title/Abstract]”) AND (“hemorrhage[Title/Abstract]” OR “bleeding[Title/Abstract]”). The searches were limited to English publications. The reference lists of articles and reviews were also searched manually for potentially relevant studies. The eligible studies were screened and cross-checked for further evaluation by the two reviewers.

2.2 | Inclusion and exclusion criteria

Studies were included in the meta-analysis if they met the following criteria for population, interventions, comparison, and outcomes (PICO): *Population*: the patients underwent total tonsillectomy, and there were no age or race limitations; *Interventions*: tonsillectomy with

intraoperative suturing (TIS), tonsillectomy without intraoperative suturing (T₁S); *Comparison*: TIS and T₁S; *Outcomes*: primary outcome (the rate of PTH, including primary and secondary hemorrhage). Secondary outcomes: time points of primary and secondary PTH, the rate of patients returning to the operation room for hemostasis. *Definition of PTH*: the definition of PTH was if the episode was recorded in the medical notes.

We excluded animal studies, conference abstracts, letters, reviews, expert opinions, studies on partial resection (intracapsular tonsillectomy) or uvulopalatopharyngoplasty, case series reporting on fewer than 20 patients, and studies that provided insufficient data.

2.3 | Study quality and level of evidence

This meta-analysis was done in strict accordance with the PRISMA guidelines. The methodological quality of the included studies was evaluated independently by two of the authors using the Newcastle-Ottawa quality assessment Scale (NOS)⁶ for both prospective and retrospective studies. The studies were assigned to a quality level according to the following score ranges: low (0–3), moderate (4–6), and high (7–9). Any disagreements in study inclusion, data extraction, or scoring were resolved through discussion with a third investigator (LZ).

2.4 | Data extraction and outcomes of interest

Relevant data were independently extracted from the included literature by two researchers (MW and YW). A third reviewer (LZ) was consulted in the case of any disagreement or uncertainty. The following data were extracted from each study: the name of the first author, year of publication, study type, number of participants in each treatment group, participants' age, interventions, follow-up period, suturing methods details of the experimental and control groups, and outcomes. The primary outcome of interest was the number of postoperative hemorrhages, including primary and secondary bleeding. Meanwhile, other parameters, such as the number of patients who needed to go back to the operation room for hemostasis, postoperative pain, duration of operation, and bleeding time, were extracted as indicators of the secondary outcomes.

2.5 | Statistical analysis and meta-analysis

The meta-analysis was performed using the STATA 14 SE software package (StataCorp, College Station, TX). Odds ratio (OR) with 95% confidence intervals (CIs) were used as the summary statistics for dichotomous variables. The weighted mean difference with 95% CI was used for continuous outcomes. A random-effect model was selected according to the heterogeneity between the articles. I^2 was used to test the heterogeneity of each study. An I^2 index >50%

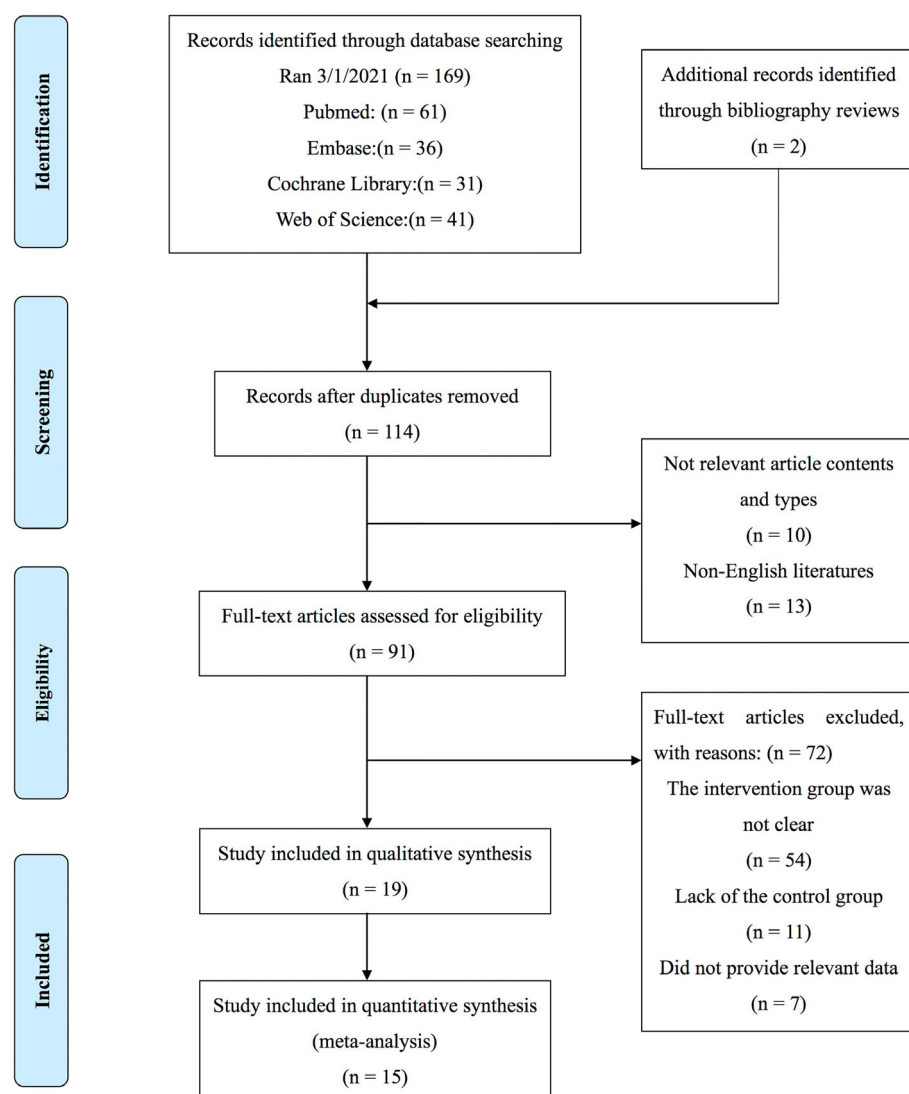


FIGURE 1 PRISMA flowchart of the study selection process. The reasons for exclusion are indicated at each step

indicated significant heterogeneity. Subgroup analyses were performed to assess the risk factors for PTH. Sensitivity analysis was done to assess the effect of a single study on the overall result. A visual inspection of funnel plots was used to check for publication bias, and Egger's test was performed to verify the result. For all statistical analyses, a p value of $<.05$ was considered statistically significant.

3 | RESULTS

3.1 | Identification and selection of studies

The literature search retrieved a total of 171 articles. Duplicate and irrelevant articles were removed, and a title and abstract review was performed. This resulted in 114 articles for full-text review. The review identified 91 articles on intraoperative suturing in tonsillectomy, 72 of which were excluded for various reasons, including insufficient description or a lack of quantifiable data. Ultimately, 15 studies were included in this meta-analysis (Figure 1).

3.2 | Characteristics of the studies

Table 1 depicts the patient demographics of the included studies. The included papers were published between 1986 and 2021. Eleven of the 15 studies used between-participant comparisons (BPC), and the remaining four studies used self-control comparisons (SCC), the left side versus right side of the participant's body. Our meta-analysis of 15 studies included 16 657 patients. Of these, 15 027 were BPC, and 1630 were SCC. The study qualities ranged between 4 and 9, that is, overall moderate or high quality (Table 1).⁷⁻²⁵

3.3 | Primary outcome

3.3.1 | Rate of PTH

All of the included studies recorded the PTH data (Table 2). Three of the 15 studies indicated that TsIS decreased the rate of PTH, while 12 studies suggested TIS was useful. The rate of PTH was 2.38% in the TIS group,

TABLE 1 General characteristics and quality assessment of included studies

Study	Publish year	Country/region	Data collection	Comparison design	Follow-up period	Assessment of outcome	Quality (NOS)
Weighill ⁷	1986	UK	Prospective	SCC	6 weeks	Medical records	8
Nandapalan ⁸	1995	UK	Prospective	SCC	>10 days	Medical records	8
Genc ⁹	2006	Turkey	Prospective	SCC	10 days	questionnaire	6
Gilbey ¹⁰	2008	Israel	Retrospective	BPC	NG	Medical records	6
Sendi ¹¹	2009	Saudi Arabia	Prospective	SCC	10 days	Medical records and questionnaire	6
Matt ¹²	2012	USA	Prospective	SCC	>28 days	Medical records and questionnaire	9
Senska ¹³	2012	Germany	Retrospective	BPC	>13 days	Medical records	6
Chiu ¹⁴	2013	Taiwan	Prospective	BPC	3–4 months	Medical records and questionnaire	6
Nguyen ¹⁵	2014	Australia	Retrospective	BPC	4 weeks	Medical records	7
Elkholy ¹⁶	2016	Egypt	Prospective	BPC	1 week	Medical records	4
Cetiner ¹⁷	2017	Turkey	Prospective	SCC	10 days	Medical records	7
Reusser ¹⁸	2017	USA	Retrospective	BPC	NG	Medical records	5
Akan ¹⁹	2018	Turkey	Prospective	BPC	10 days	Medical records	6
Cassano ²⁰	2018	Italy	Prospective	BPC	10 days	Medical records and questionnaire	6
Fehrm ²¹	2018	Sweden	Prospective	BPC	6 months	Medical records	7
Galindo Torres ²²	2018	Spain	Retrospective	BPC	43.51 days	Medical records	5
Shu ²³	2018	China	Prospective	BPC	NG	Medical records	6
Zhang ²⁴	2020	China	Retrospective	BPC	3 weeks	Medical records	7
Li ²⁵	2021	China	Prospective	BPC	3 weeks	Medical records	7

Abbreviations: BPC, between-participant comparisons; NG, not given; SCC, self-control comparisons.

and the figure increased to 3.21% in the TsIS group. The overall OR for PTH between TIS and TsIS groups was 0.64 (95% CI, 0.47–0.88, $I^2 = 52.3\%$). This result was statistically significant and showed a lower PTH rate in the TIS group than in the TsIS group (Figure 2).

3.4 | Secondary outcomes

3.4.1 | Primary PTH

Ten studies reported primary PTH (bleeding occurring within 24 h of surgery), which was more than twice as likely to happen with TsIS (OR = 0.44, 95% CI, 0.30–0.64) and was statistically significant. The value of I^2 suggested homogeneity ($I^2 = 0.0\%$, $p = .480$). Two studies reported no primary PTH events and one study did not include patients with primary bleeding in the study protocol (Figure 3A).

3.5 | Secondary PTH

Eleven studies reported secondary PTH (bleeding occurring any time after 24 h postoperatively). Secondary PTH was likely to happen in

the TsIS group with an OR value of 0.70 (95% CI, 0.54–0.90). The pooled analysis result showed a statistically significant difference between the two groups, and there was no heterogeneity found ($I^2 = 0.0\%$, $p = .455$; Figure 3B).

3.6 | Return to the operation room for hemostasis

Five studies reported data on the need for patients to be taken back to the operation room for hemostasis. There was no statistical difference (OR = 0.57; 95% CI, 0.13–2.47). The pooled analysis result showed high heterogeneity ($I^2 = 79.4\%$, $p = .001$; Figure 3C).

3.7 | Heterogeneity and subgroup analysis

Moderate heterogeneity was found through the value of I^2 (52.3%, $p = 0.009$). Subsequently, subgroup analyses were carried out according to the temporal direction of the study data. These included acquisition (prospective vs. retrospective), comparison model (SCC vs. BPC), age of patients (children vs. adults), suturing methods (suturing the tonsillar pillars [STP] vs. suturing the tonsil fossa and pillars

TABLE 2 Demographic and surgical details of studies included in the meta-analysis

Study	Age (years)	Number of participants	Tonsillectomy method	Procedure in study group	Type of sutures	Outcomes	Number of PTH
Weighill	>16	Study: 57 Con: 57	Dissection	Suture the pillar 3 stitches	3-0 catgut	Hemorrhage, pain relief, hematoma	Study: 0 Con: 1
Nandapalan	>15	Study: 50 Con: 50	Dissection & Snare	Suture the tonsillar fossa 3 stitches	2-0 Polydioxanone	Hemorrhage, pain score (VAS)	Study: 0 Con: 1
Gilbey	1.9-56	Study: 319 Con: 241	Cold dissection & Harmonic scalpel	Suture the pillars and bed	NG	Hemorrhage, operation time, blood loss, back to OR	Study: 5 Con: 6
Matt	0.67-22	Study: 763 Con: 763	Electrocautery Or cold dissection & Snare, Harmonic scalpel	Suture the pillars 2-3 stitches	3-0 chronic	Hemorrhage, pain (0-5), experience of surgeon on pain or bleeding	Study: 21 Con: 22
Senska	1-77	Study: 1000 Con: 1000	Dissection & Snare	Suture the pillars with 2 chain- block sutures	NG	Hemorrhage, time of occurrence of bleeding, back to the OR	Study: 5 Con: 23
Nguyen	1-68	Study: 158 Con: 264	Monopolar diathermy	Tonsillar bed oversew 1 stitch	2-0 silk or vicryl	Hemorrhage, back to OR	Study: 9 Con: 20
Elkholy	3-20	Study: 400 Con: 400	Dissection	Suture the pillars 3-4 stitches	2-0 chronic or vicryl	Hemorrhage, take back to OR, palatal hematoma	Study: 18 Con: 40
Cetiner	4-35	Study: 760 Con: 760	Scissor and elevator	Tonsillar bed and pillars 3 stitches	3-0 Vicryl	Hemorrhage, pain (FPS-R)	Study: 8 Con: 23
Reusser	<18	Study: 1633 Con: 3177	Coblation	Suture the pillars	3-0 Vicryl	Hemorrhage, bleeding time, back to OR	Study: 28 Con: 33
Cassano	NG	Study: 30 Con: 31	Cold steel dissection	Suture the superior and inferior poles 2 stitches	0 Vicryl	Hemorrhage, pain (WBFS), resumption of normal diet	Study: 0 Con: 2
Fehrm	2-5	Study: 30 Con: 44	Cold knife dissection	Suture the pillars 2 stitches	4-0 monocryl	Hemorrhage, OAH score, OSA-18	Study: 1 Con: 1
Galindo Torres	14-76	Study: 132 Con: 194	NG	Suture the pillars	NG	Hemorrhage	Study: 8 Con: 9
Shu	3-12	Study: 328 Con: 275	Dissection & snare	Suture the fossa and pillars	4-0 Chromic	Hemorrhage, wound characteristics, velopharyngeal function	Study: 3 Con: 12
Zhang	19.71 ± 9.42	Study: 2491 Con: 2596	Coblation	Suture the archs and fossa 3 stitches	3-0 absorbable	Hemorrhage, time of bleeding, operation time	Study: 27 Con: 51
Liu	18-71	Study: 142 Con: 142	Coblation	Suture the archs and fossa 3 stitches	3-0 Vicryl	Hemorrhage, pain (VAS), back to OR	Study: 4 Con: 15

Abbreviations: Con, control; FPS-R, faces pain scale-revised; NG, not given; OR, operation room; OSA-18, obstructive sleep apnea-18; VAS, visual analogue scale; WBFS, Wong-Baker faces scale.

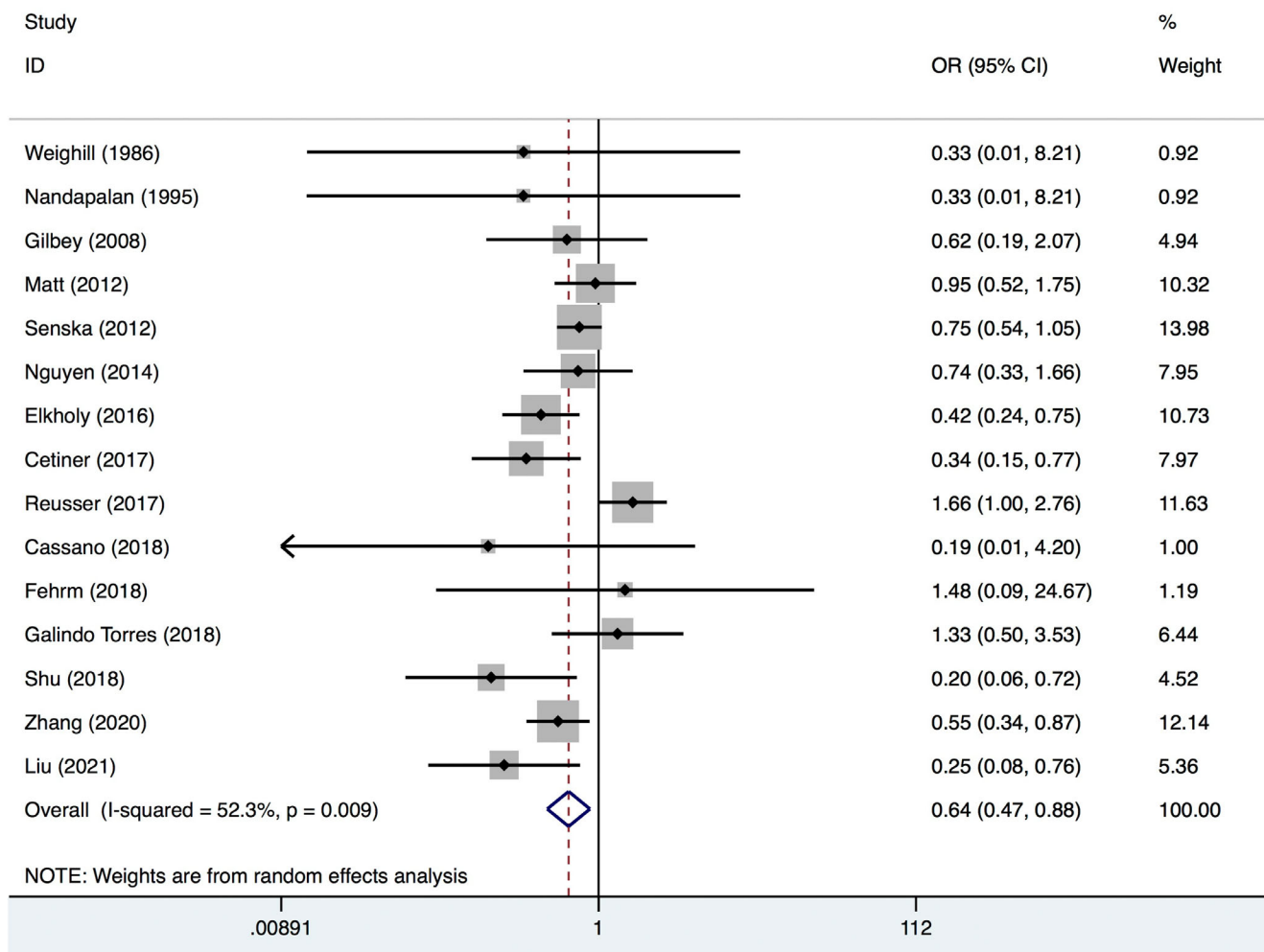


FIGURE 2 Primary outcome. Forest plot comparing the rates of PTH (odds ratio [OR] with 95% confidence interval [CI]). Events represent the number of patients with PTH

simultaneously [STFP]), surgical details (<3 stitches vs. more than three stitches).

Nine studies prospectively collected their data, and the results indicated that patients could benefit from suturing, with an OR value of 0.45 (95% CI; 0.29–0.68, $I^2 = 19.6\%$). The remaining six were retrospective studies, and there was no significant difference (OR = 0.86; 95% CI, 0.59–1.27, $I^2 = 57.5\%$; Figure 4A).

Four of the 15 included studies were designed as SCC, and 11 were designed as BPC. When we analyzed the data from the SCC studies, it showed that suturing did not reduce the PTH rate with an OR of 0.58 (95% CI, 0.29–1.16, $I^2 = 30.4\%$). However, there was a significant difference in the PTH rate when we compared the BPC-designed studies for the effect of sutures (OR = 0.65; 95% CI, 0.45–0.95, $I^2 = 59.8\%$; Figure 4B).

We divided the patients into children (≤ 18 years old) and adults (> 18 years old). Five studies recorded the PTH data in the children's group, and two studies supplied the data of adults. The results showed adults would benefit from intraoperative suturing with an OR value of 0.31 (95% CI, 0.16–0.60, $I^2 = 0.0\%$), while there was no significant difference in the children's group (OR: 0.72, 95% CI, 0.31–1.67, $I^2 = 66.8\%$; Figure 4C).

To assess the effect of the different suturing methods on the PTH rate, we divided the TIS population into STP and STFP. The pooled analysis showed STFP had a lower PTH rate with an OR value of 0.47 (95% CI, 0.34–0.64, $I^2 = 0.0\%$) while STP showed no statistically significant difference when compared with the TsIS group (OR = 0.89; 95% CI, 0.58–1.35, $I^2 = 58.0\%$; Figure 4D).

We divided TIS into two subgroups according to the surgical details. In patients with fewer than three stitches, there was no significant difference in the PTH rate between the TIS and TsIS groups (OR = 0.72; 95% CI, 0.34–1.52, $I^2 = 0.0\%$). Patients who received more than three stitches during surgery had a lower PTH rate with an OR of 0.44 (95% CI, 0.32–0.60, $I^2 = 0.0\%$; Figure 4E).

3.8 | Sensitivity analysis and publication bias

Funnel plots are presented as a nearly symmetrical distribution in Figure 5A. The plots indicated no obvious publication bias. No significant study bias was detected with Egger's regression test ($p = .270$).

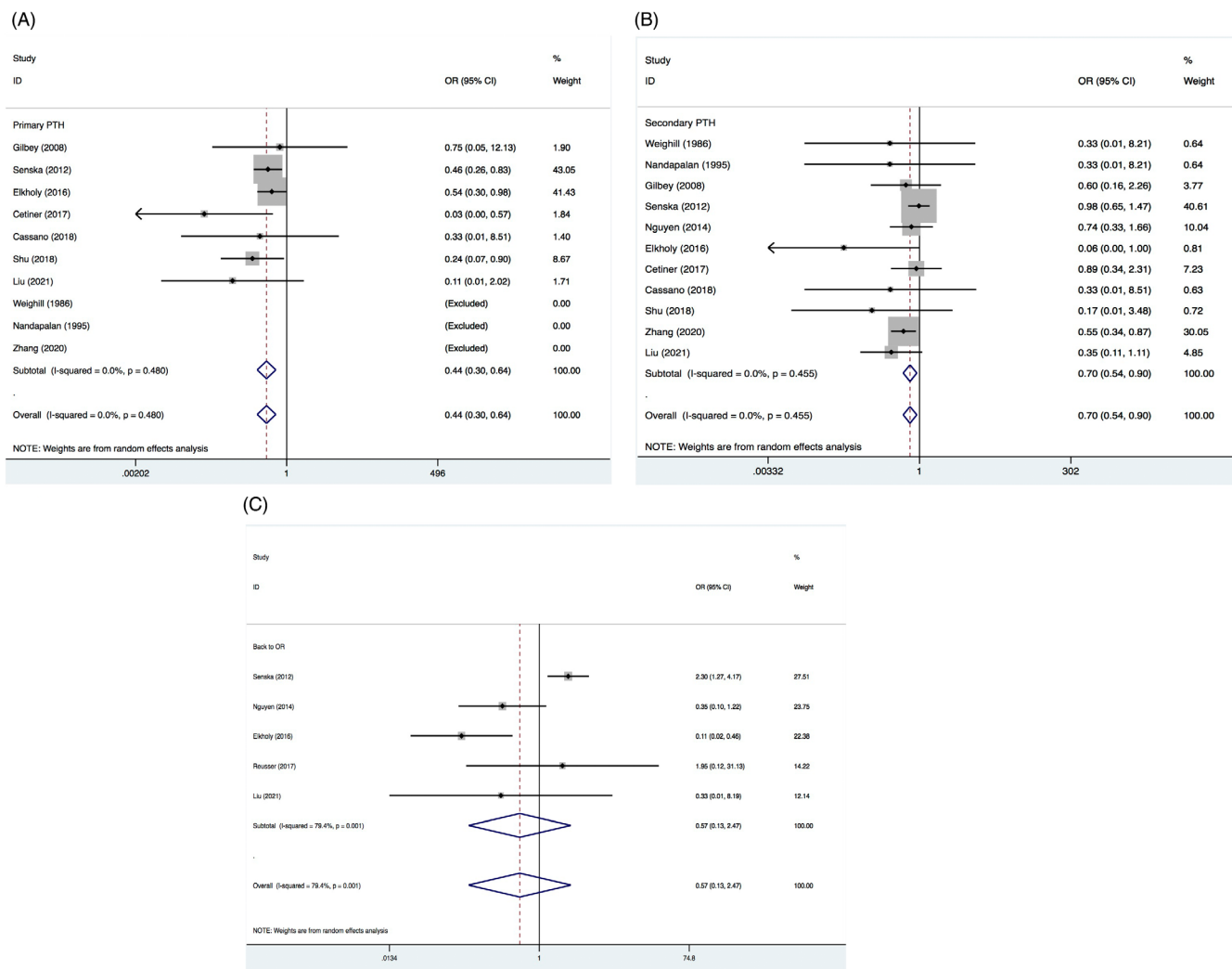


FIGURE 3 Secondary outcomes. Forest plot of odds ratio with 95% confidence interval (CI) of patients with primary PTH (A), secondary PTH (B), and returning to the operation room for hemostasis (C)

According to Galbraith plot, Reusser's study¹⁸ seemed to be the source of heterogeneity (Figure 5B), but no study impacted the overall sensitivity analysis (Figure 5C).

4 | DISCUSSION

This meta-analysis of 16,657 subjects who underwent tonsillectomy showed a significant pooled OR regarding intraoperative suturing in relation to PTH. In the included studies, the rate of PTH was lower in the TIS group (2.38%, 198/8331) than in the TsIS group (3.21%, 322/10041). Additionally, in the meta-analysis, the ORs indicate that intraoperative suturing could reduce the rate of primary and secondary PTH.

Is it necessary to close the tonsillar fossa or to suture the tonsillar pillars to prevent PTH? A matched-pair study, in which patients act as their control, indicated that closure of the tonsillar fossa could decrease postoperative bleeding incidence.¹⁷ Our study showed that

patients could benefit from the intraoperative suturing process with a lower risk of PTH.

At present, there is no unified standard for the degree of PTH. Postoperative bleeding can be divided into two categories: primary hemorrhage, which occurs within 24 h of surgery, and secondary postoperative bleeding, which occurs 24 h or more after surgery. Poor surgical procedure, such as incomplete hemostasis, usually causes primary hemorrhage. Overall, the incidence of primary bleeding is extremely low.¹ Windfuhr et al. reported that the PTH rate was higher in the suture hemostasis group.²⁶ According to a 10-question survey completed at a national congress, suture ligating the lower pole and suturing faucial pillars were the main methods surgeons would choose to prevent PTH.²⁷ Our results showed a significant difference in the incidence of primary PTH between the TIS and TsIS groups. Mechanical blockage of the potential bleeding area may provide more reliable protection against postoperative cough, temporary increase of blood pressure, or impaired coagulation, which might cause primary PTH.

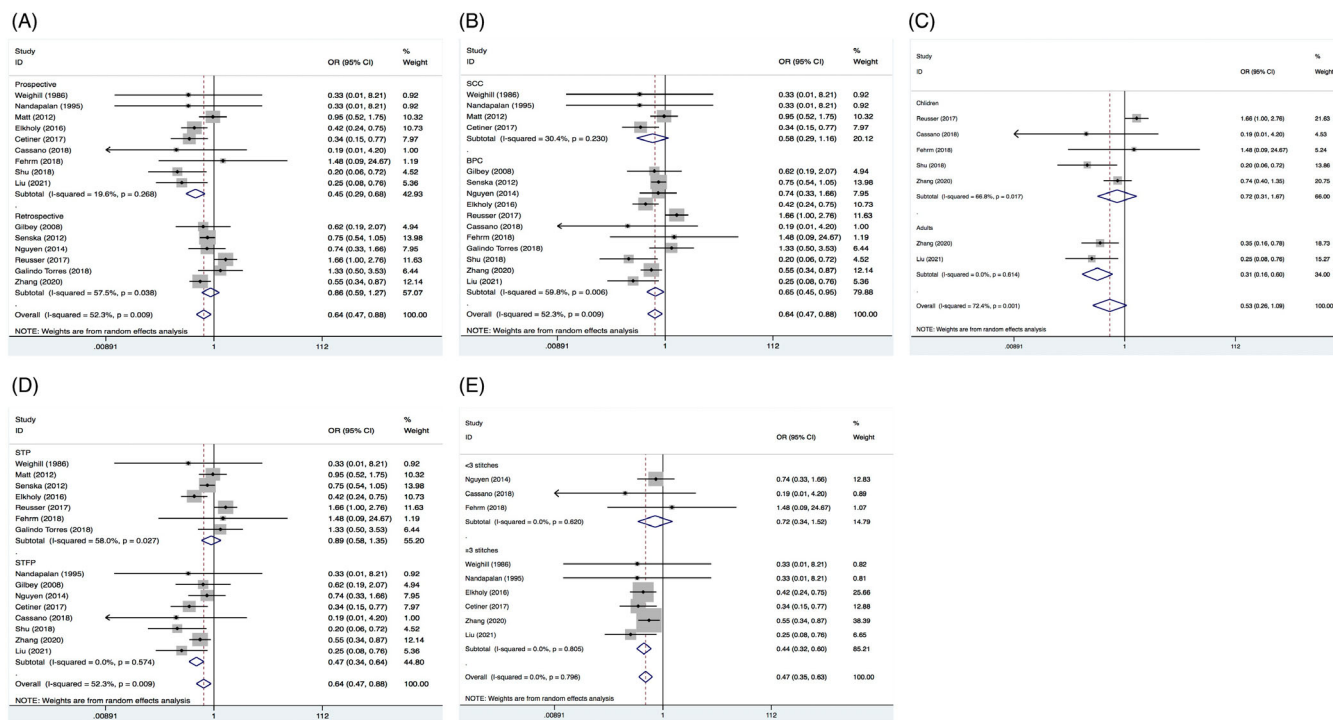


FIGURE 4 The results of subgroup analyses. Odds Ratio of the effect of different data acquisition (A), comparison models (B), suturing methods (C), surgical details (D), and age discrimination (E) on the PTH rate

Although the time interval of secondary PTH is very wide, it usually occurs around the 10th postoperative day.^{12,24} In our opinion, secondary hemorrhage is more related to wound healing, which might be greatly affected by different hemostasis methods. Thermal instruments achieve hemostasis differently from sutures. Heat denatures tissue protein and achieves contraction and coagulation of the peripheral blood vessels through thermal injury. In contrast, sutures compress or obstruct the vessels. Thermal instruments create a layer of necrotic tissue due to thermal damage on the wound surface. This reduces the local mucosal barrier function, which facilitates infection by commensal pathogens in the oral cavity.²⁸

Meanwhile, the risk of secondary hemorrhage in operations using bipolar diathermy for hemostasis was 1.5 times higher than the same operations using only ties and packs.²⁹ White pseudomembranes in the non-suturing group would take longer to slough off.²³ Infection or the sloughing of fibrin clots might expose and erode the small vessels. Therefore, we considered the existence of a suture might protect against secondary hemorrhage caused by blood vessels or mucosa. Our study supports this view, showing that a lower risk of secondary hemorrhage was found in the TIS group. Further, we assessed whether suturing would affect the rate of patients returning to the operation room for hemostasis. The results showed there was no difference. There are some differences between suturing tonsil pillars and the tonsillar fossa. Some authors have proposed reducing the aperture between the anterior and posterior palatal arches with stitches.^{13,17,30} They suggested the procedure could promote healing of the tonsillar fossa wounds and reduce bleeding. Centier preferred

to finish the suturing procedure by fixing it directly to the tonsillar bed.¹⁷ Nevertheless, both methods are for a particular purpose, tonsillar fossa closure. Our subgroup analysis showed that the STFP group had a lower PTH rate than the STP group. Tonsillar fossa closure appears to have some advantages. For example, the procedure can directly compress the damaged tissue and blood vessels, reducing the direct stimulation caused by food, saliva, or swallowing. Further, the nerve fibers in the lateral pharyngeal wall may be protected, reducing pain and hastening the recovery of oral intake.²⁰ In comparison, STP does not eliminate the dead space caused by the operation. If food lodged there, it could cause infection, which might lead to bleeding. Appropriate suturing of the tonsillar fossa before STP seems to reduce such events.

The differences in PTH rate might also depend on factors related to the surgeon, such as operating method and experience.³¹ Suturing used to be considered the most reliable way to achieve physical obstruction of the tissue or bleeding vessels. However, there are disadvantages such as suture infection, granulomas, and sinuses caused by bacterial infiltration.³² Further, the anticipation of suture removal may increase the anxiety and discomfort of patients. Though the use of absorbable suture materials in operation can alleviate anxiety, there is still controversy on the choice of suture material.^{32,33} Absorbable sutures might cause a higher wound infection rate due to the greater inflammatory response or tissue reactivity.^{34,35} However, a meta-analysis showed that suturing the pillars did not increase the rate of suture site infection.³⁶ The majority of the studies in this meta-analysis preferred absorbable sutures. We divided the patients into two groups, according to the number of stitches at operation. Patients

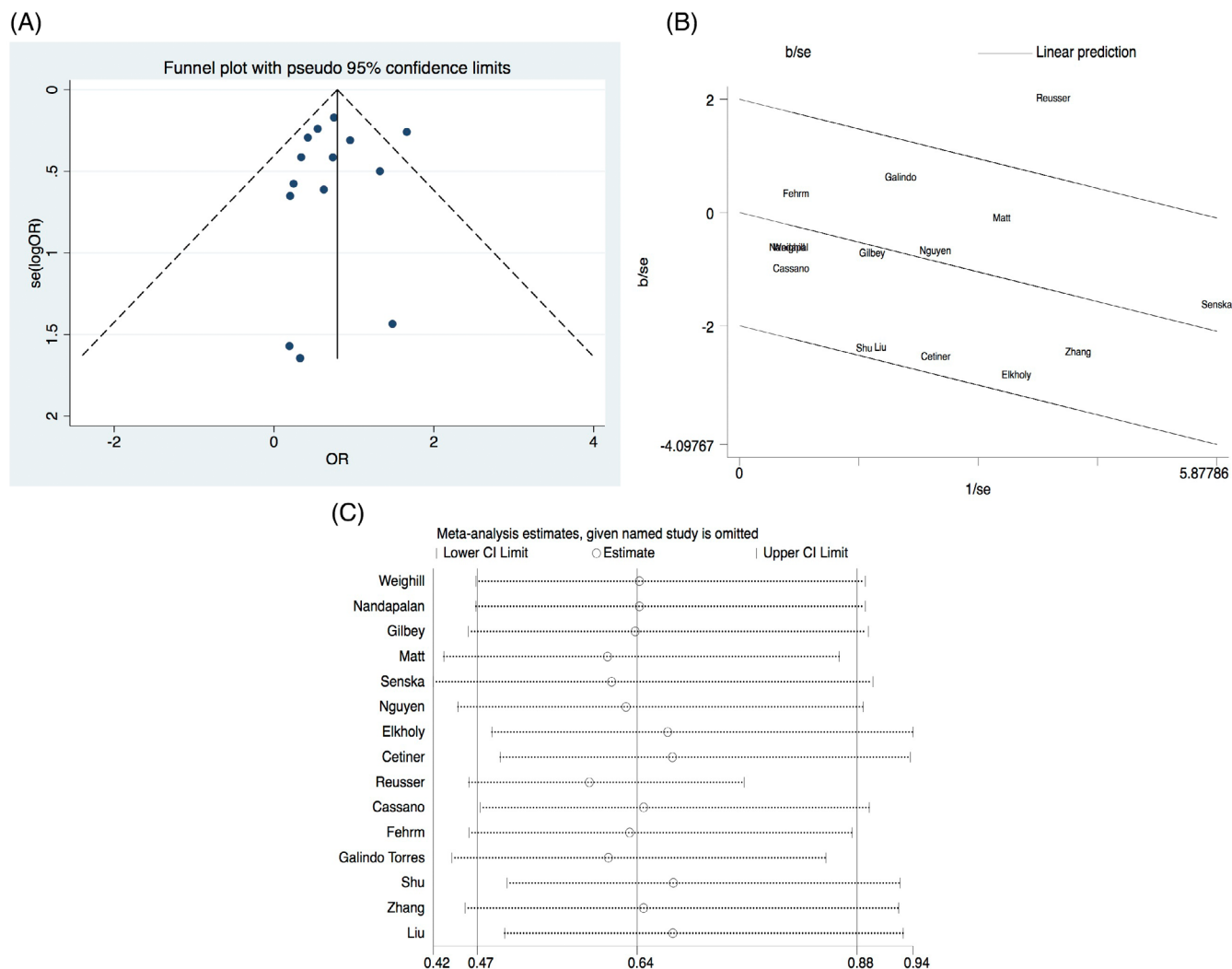


FIGURE 5 Sensitivity analysis and publication bias of this meta-analysis. (A) Funnel plot of meta-analysis of TIS versus TsIS studies. (B) Galbraith plot for the included studies. (C) Sensitivity analysis for the included studies.

who received more than three stitches had a lower PTH rate than patients without suturing, and those who received < three stitches had the same risk of PTH as the TsIS group.

5 | STRENGTHS AND LIMITATIONS

There has been no systematic review or meta-analysis assessing the effect of intraoperative suturing on PTH until now. Our study included all eligible studies analyzing the influence of suturing on the times of PTH and the rate of returning to the operation room for hemostasis. Additionally, we analyzed the effects of two suturing methods and the different surgical details on the PTH. Although our results support intraoperative suturing during a tonsillectomy, there were some limitations to this study. Firstly, the quality of the included studies is limited. Nearly 40 percent of them are retrospective, which might lead to memory biases. Secondly, this meta-analysis did not include secondary outcomes such as operation time and postoperative

pain control because there was a lack of such data, or there were inconsistencies, such as with methods of assessing pain. Thirdly, there were diverse operative techniques and choice of suture material. Different operational details might influence the final result. Thus, the research scheme based on homogenization design could solve this limitation.

6 | CONCLUSION

PTH is a rare but crucial complication, which can be life-threatening, and might necessitate an emergency operation. Although thermal devices have been frequently used in tonsillectomy, intraoperative suturing is a reasonable choice for preventing PTH. There is no consensus on universal operation criteria, surgical details such as suturing methods might influence PTH risk. A multicenter randomized controlled study should be designed to explore which would be beneficial in this area.

AUTHOR CONTRIBUTIONS

Bo Li: conception and design, data analysis and interpretation, drafting of manuscript, final approval. **Miaowei Wang:** data collection, drafting of manuscript, final approval. **Yanwen Wang:** data collection, final approval. **Lingyun Zhou:** conception and design, data analysis and interpretation, final approval.

FUNDING INFORMATION

This study was supported by Sichuan Science and Technology Program (2020YFS0113), (2019YFS0207) and Natural Science Foundation of China (81802468).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Li B, Wang M, Wang Y, Zhou L. Can intraoperative suturing reduce the incidence of posttonsillectomy hemorrhage? A systematic review and meta-analysis. *Laryngoscope Investigative Otolaryngology*. 2022; 7(4):1206-1216. doi:[10.1002/liv.2.835](https://doi.org/10.1002/liv.2.835)