Systematic Reviews

SYSTEMATIC REVIEW UPDATE

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The effectiveness of fibrin sealants in head and neck surgery: a systematic review and meta-analysis

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Abstract

Background Fibrin sealants are increasingly used in head and neck surgery to aid hemostasis, but individual studies lack conclusive evidence. This systematic review investigates their effectiveness compared to placebo or usual care in head and neck surgery.

Methods Studies comparing fibrin sealant to placebo or usual care in patients 18 years or older who have undergone soft tissue surgery of the head and neck with drain placement were included. Primary outcomes include wound complications and time to surgical drain removal postoperatively. Secondary outcomes include length of hospital stay, drain volume output, surgical management of hematoma, blood transfusion rates, and adverse reactions. Electronic databases were searched on October 2023 for randomized controlled and quasi-experimental studies. Studies underwent independent screening, review, and appraisal by two reviewers using JBI appraisal tools. Certainty was assessed with GRADE, and meta-analysis was conducted using JBI SUMARI, presenting effect sizes as relative risk ratios or mean differences with 95% confidence intervals.

Results Fourteen studies were included examining 904 patients. The fibrin sealant group exhibited reduced postoperative wound complications (hematoma, seroma, wound dehiscence, wound infection) (RR = 0.64, 95% CI = 0.45–0.92), shorter drain removal times (MD = −0.49 days, 95% CI = −0.68 to −0.29), decreased drain output (MD = −16.52 mL, 95% CI = −18.56 to −14.52), and shorter hospital stay (MD = −0.84 days, 95% CI = −1.11 to −0.57) compared to controls. There was no statistically significant difference on the rate of intervention for postoperative hematoma and the rate of adverse reactions.

Discussion Evidence demonstrates with low certainty that fibrin sealant use is associated with a modest reduction in the rate of wound complications, drain duration, and length of stay, and a small reduction in drain volume output. Methodological weaknesses and clinical heterogeneity limit these findings. Further research should focus on enhancing methodological quality and exploring the cost-effectiveness of fibrin sealant use in surgery.

Systematic review registration CRD42023412820.

Funding Nil.

Keywords Fibrin tissue adhesive, Head and neck surgery, Hemostasis, Surgical drainage, Systematic review

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Background

Ensuring patient safety in surgery necessitates the proficient management of bleeding [1]. Fibrin sealants, among surgical tissue adhesives, have been developed to improve hemostasis [2]. The significance of controlling bleeding is heightened in head and neck surgery due to the potential involvement of critical structures, including the airway, which can elevate both morbidity and mortality risks. Swelling in the neck can be life-threatening due to the risk of airway obstruction. Anemia can also result from blood loss, and this is associated with prolonged recovery and increased mortality [1]. Furthermore, prolonged or excessive bleeding may lengthen duration of surgical drain retention in a patient, increase duration of hospital stay, and increase risk of wound infection [3–5].

Achieving hemostasis can be accomplished through mechanical, thermal, or chemical means [6]. Mechanical techniques include direct pressure, suturing, ligation, or bone wax. These techniques tamponade bleeding vessels and allow time for blood to coagulate. Thermal techniques employ heat to seal off blood vessels. This is often seen through the use of an electric current in electrocoagulation [7]. Chemical techniques may utilize caustic or physiologic agents. Caustic agents, such as silver nitrate, achieve clotting through protein denaturation. Unfortunately, heat and caustic agents may inflict damage on surrounding tissues and impede wound healing [6]. In contrast, surgical tissue adhesives, derived from biocompatible and biodegradable materials such as gelatin, cellulose, bovine collagen, thrombin, or fibrin, represent a more physiological approach with minimal perceived complications. While effective against mild to moderate bleeding, tissue adhesives are frequently employed in conjunction with other hemostatic techniques, including suturing, ligation, and electrocoagulation [7].

Depending on the type of surgery, patient factors, and surgeon preferences, surgical drains may be inserted to help remove excess fluid and prevent the formation of a hematoma or seroma. These drains are removed sometime afterwards when the amount of drainage is deemed to be minimal. Although drains serve an important role in preventing potentially life-threatening complications, achieving a reduction in the duration of drain retention can translate into reduced drain-related complications (i.e., wound infection) and improved patient comfort.

This review specifically addresses surgical procedures involving the soft tissues of the head and neck region, encompassing interventions such as laryngectomy, thyroidectomy, parotidectomy, skin flaps, and neck dissections [8]. While these surgeries are commonly employed for conditions like cancer, salivary gland disease, thyroid disease, injuries, infections, and surgical reconstruction, their indications are not strictly limited to these cases [9]. Soft tissue is a broad category of tissues that is commonly encountered in the head and neck region. Unlike skeletal tissue (i.e., bones), soft tissue is pliable and flexible. It plays an important role in providing structural support, connecting organs, and facilitating movement. Various types of tissues can have different properties which affect the management of bleeding from these sites. For example, hemostasis in bone necessitates a distinct approach from soft tissue procedures due to the continuous flow of blood through non-collapsible channels. Therefore, the application of bone wax or putties serves as an effective means to tamponade bleeding channels [7]. Surgeries involving bony resection are excluded from this study due to this difference. Major types of soft tissues in the body include muscle, connective tissue, adipose tissue, nervous tissue, epithelial tissue, and blood vessels. Hemostasis in nervous tissue, such as the brain and spinal cord, presents with unique challenges related to its delicate nature and critical function. For this reason, surgeries involving nervous tissue are also be excluded from this study. Bleeding from large-sized blood vessels, such as arteries and veins, often require ligation using sutures, ties, clips, or clamps. As these vessels are collapsible and carry a significant volume of blood, ligation provides a secure and stable method of hemostasis [10]. For smaller-sized blood vessels, hemostatic agents, such as fibrin sealants, collagen-based products, or synthetic materials, are useful in the control of bleeding.

Fibrin sealants are the most effective surgical tissue adhesives available, gaining approval for commercial use in 1998 after their initial development in the 1980s [7, 11]. Consisting of concentrated fibrinogen and thrombin, these sealants are sprayed onto wounds to form a thin film, expediting clot formation, and effectively sealing bleeding vessels and dead space [12]. This review explores the application of fibrin sealants in cases where conventional methods of hemostasis are already integrated into standard surgical practice.

A few studies have demonstrated that the application of fibrin sealants can lead to decreased surgical drain retention time, reduced drain volume output, shorter hospital stays, diminished postoperative pain, and a lower occurrence of hematoma or seroma formation. Studies exploring fibrin sealant usage in hernia repairs indicated a lower risk of postoperative complications, shortened recovery times, and a decreased likelihood of experiencing postoperative and chronic pain [13]. A meta-analysis focusing on patients undergoing axillary lymphadenectomy revealed that fibrin sealants contributed to a reduction in drainage output, fewer days requiring drainage, and a shortened hospital stay ($p < 0.0001$, $p < 0.005$, $p = 0.008$ respectively) [14]. In the context of bariatric surgery, the fibrin sealant group had a significantly diminished

incidence of bleeding (RR 0.42, 95% CI 0.18–0.97) compared to controls; however, no notable effects were observed regarding the reduction of the reoperation rate, or length of hospital stay [15]. Similarly, a meta-analysis investigating thyroidectomy patients found that fibrin sealant use was associated with reduced total wound drainage ($p=0.009$) but not with duration of surgical drain and length of hospital stay [16]. It is important to note that the overall evidence concerning the efficacy of hemostatic agents, regardless of the surgical procedure, remains inconclusive based on current research [17, 18].

To date, there exists a solitary systematic review exploring the effectiveness of fibrin sealants in soft tissue surgery of the head and neck [19]. Among the 11 randomized controlled trials (RCTs) included in the review, there was a trend indicating a reduction in the mean total drainage volume by 26.86 mL (95% CI 10.31–43.41, $I^2=97\%$). While a decrease in surgical drain retention time by 1.24 days and hospital length of stay by 2.09 days was suggested, these findings did not reach statistical significance. It was proposed that fibrin sealants had a protective effect against all surgical complications (RR 0.69); however, the 95% CI (0.35–1.38) raised the possibility of a harmful effect. Hence, the ability to draw definitive conclusions was limited and likely related to the significant clinical and statistical heterogeneity present within the included studies. Since its publication, numerous primary studies have emerged, and this systematic review aims to meticulously explore the literature to investigate the impact of fibrin sealants in head and neck surgery.

A preliminary search of International Prospective Register of Systematic Reviews (PROSPERO), PubMed, the Cochrane Database of Systematic Reviews, and JBI Evidence Synthesis was conducted, and no current or in-progress systematic reviews on the topic were identified.

The objective of this systematic review is to determine the effect of fibrin sealants in adult patients undergoing soft tissue surgery of the head and neck on the time to removal of surgical drains postoperatively and rate of wound complications, including hematoma. The effect of fibrin sealant on length of hospital stay, total drain volume output, rate of blood transfusion, surgical management of postoperative hematoma, and adverse events are also investigated. The null hypothesis is that the use of fibrin sealants in head and neck surgery does not result in earlier drain removal or reduction in wound complications compared to standard care or placebo.

Review questions

What is the effectiveness of fibrin sealants in reducing wound complications and time to surgical drain removal postoperatively in adult patients undergoing head and neck surgery compared to placebo or a non-exposed group?

Additionally, do fibrin sealants influence the length of hospital stay, total drain volume output, rate of blood transfusion, and surgical management of postoperative hematoma? What are the adverse reactions associated with fibrin sealant use?

Inclusion criteria

Participants

This review includes patients 18 years of age or older who have undergone head and neck surgery requiring drain placement. Patients identified as having a confirmed or suspected "chyle leak" as a surgical complication are excluded as this injury is not related to bleeding and requires a surgical drain to remain in situ for ongoing management.

Intervention

The intervention of interest is fibrin tissue sealant in head and neck surgery. The administration of fibrin sealant may be of any dosage or brand delivered at any time during the surgery. The use of fibrin sealant for bone, cartilage, dental, ocular, middle ear, or intracranial tissues is excluded.

Comparators

This review considers studies that compare the intervention to placebo (i.e., saline) or a non-exposed group receiving usual care.

Outcomes

This review considers studies that include the following primary outcomes:

1. Time to removal of surgical drain postoperatively (days): The time between insertion of surgical drain/s during the operation to removal of all surgical site drains from the patient. Time units provided are converted into days. Fibrin sealants may reduce bleeding that may otherwise prolong the retention of surgical drains. Extended time with a surgical drain correlates with longer length of stay, increased wound infection risk, and patient discomfort [9–11]. The indications for drain removal may vary by institution; however, the protocol for drain removal would presumably be applied consistently to both the interventional and control arms of each study.
2. Rate of wound complications within 6 weeks postoperatively: By reducing the amount surgical site bleeding, fibrin sealants may also reduce the incidence of hematoma and seroma formation and subsequent wound infection and dehiscence [2, 18]. Minimizing

these complications may reduce length of stay and the likelihood of readmission.

Secondary outcomes considered in this review are as follows:

1. Total drain volume output (mL): Volume of wound drainage from time of drain insertion to drain removal. Calculated as the sum of fluid in all collection canisters/bags used. This outcome is objective and clinically important.
2. Rate of blood transfusion: Patients who receive a blood transfusion intra-operatively or postoperatively during the same admission are included. It is used in patients with significant blood loss as anemia is associated with prolonged recovery and increased mortality [1]. Although anemia is multifactorial in origin, the need for a blood transfusion often reflects the patient's overall clinical status and will be interpreted in the context of the patient population and type of surgery [1]. The indications and thresholds for blood transfusion may vary between institutions; however, the transfusion protocol would presumably be applied consistently to both the interventional and control groups of each study.
3. Length of hospital stay measured in days: Prolonged drain output and anemia are associated with longer hospital stay which has clinical and economic significance [1, 9].
4. Rate of intervention for postoperative hematoma: Excess bleeding from a closed surgical site may result in formation of a hematoma. Small hematomas may resorb with time. Large or symptomatic hematomas (i.e., pain, airway obstruction) may necessitate surgical management to evacuate the hematoma and arrest any active bleeding [20].
5. Adverse reactions: Unwanted harmful effects from fibrin sealants. There are documented and theoretical risks including air/gas embolism, hypotension, blood-borne disease, immune-mediated coagulopathy, and allergic reaction [21].

Types of studies

This review considered both experimental and quasi-experimental study designs including randomized controlled trials (RCTs), non-randomized controlled trials, before and after studies, and interrupted time-series studies.

Methods

This systematic review was conducted in accordance with JBI methodology for systematic reviews of effectiveness and reported in accordance with the PRISMA check list [20]. The a priori protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023412820) [21].

Search strategy

The search strategy for effectiveness studies aimed to find both published and unpublished studies. A three-step search strategy was utilized in this review. First, an initial limited search of PubMed (NLM) and CINAHL (EBSCOhost) was undertaken, followed by analysis of the text words contained in the title and abstract and the index terms used to describe the articles. The search strategy, including all identified keywords and index terms, was adapted for each included information source, and a second search was undertaken in October 2023. The full search strategies are provided in Appendix I. Finally, the reference list of a systematic review of the same topic was screened for additional studies [19]. The search strategy was reviewed by authors and a third-party expert experienced in literature search.

Studies published in any language were included. This was a deviation from the study protocol to reduce the risk of language bias. Google Translate was utilized to translate relevant studies to English [22]. Only one study included in this review required translation [23]. Studies published from 1975 when fibrin sealants became commercially available to present were included [11].

The databases that were searched included PubMed (NLM), CINAHL (EBSCOhost), EMBASE (Ovid), Scopus, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Sources of unpublished studies and gray literature searched included ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, MedNar, and Dissertations & Theses database (ProQuest). Study authors were directly contacted through email if a full-text paper could not be obtained by other means.

Study selection

Following the search, all identified citations were collated and uploaded into EndNote X9 (Clarivate Analytics, PA, USA), and duplicates were removed manually. Following a pilot test by the primary author, titles and abstracts were screened by 2 independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant studies were retrieved in full, and their citation details were imported into the Covidence (Veritas Health Innovation Ltd, Melbourne, Australia). Citations

for full-text review were assessed against the inclusion criteria by two independent reviewers. Full-text studies that did not meet the inclusion criteria were excluded, and reasons for their exclusion are provided in Appendix II. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer. The results of the search are presented in Fig. 1 in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [24].

Assessment of methodological quality

Eligible studies were critically appraised by 2 independent reviewers for methodological quality using JBI standardized critical appraisal instruments for experimental and quasi-experimental studies [20, 25]. Appraisals were documented using the JBI System for the Unified Management, Assessment, and Review of Information (JBI SUMARI; JBI, Adelaide, Australia) [26]. Authors of papers were contacted to request missing or additional data for clarification, where required. Authors who did not respond after two contact attempts resulted in the data being excluded. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer.

For each critical appraisal question, a "yes" rating was given if there was clear evidence and discussion of the criterion. A "no" was given if the paper did not address the question. An "unclear" rating was given if information was incomplete. "Not applicable" (N/A) ratings were given if the question did not apply to the study. All studies regardless of methodological quality underwent data extraction and synthesis where possible. Assessment of risk of bias and certainty guides the analysis and interpretation of the results of the individual studies (see Assessing Certainty of Findings).

Data extraction

Data were extracted from studies included in the review by 2 independent reviewers using Microsoft Excel (Redmond, Washington, USA). The protocol reports the data extraction form used [21]. The data extracted included specific details about the participants, study methods, interventions, and outcomes of significance to the review objective. These parameters include age, sex, country, type of surgery, diagnosis/indication for surgery, fibrin sealant brand, fibrin sealant dose, number of drains inserted, longest time to drain removal postoperatively (days), total drain volume output until drain removal (mL), rate of blood transfusion, length of hospital stay (days), rate of wound complications, rate of surgical management of postoperative hematoma, and the rate and types of adverse reactions.

The extraction tool used was independently piloted by the review team before formal use. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer. Authors of papers were contacted to request missing or additional data, where required. Authors who did not respond after two contact attempts resulted in the data being excluded or transformed (Appendix III).

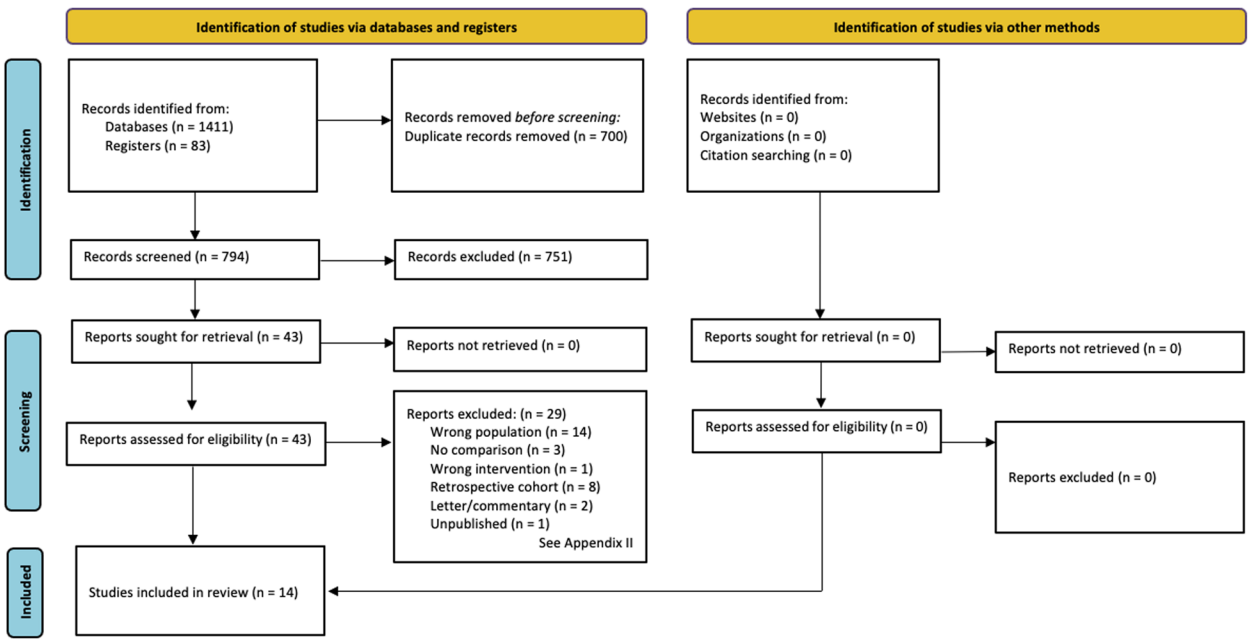

Fig. 1 Search results and study selection and inclusion process [24]

Data synthesis

Studies were, where possible, pooled with statistical meta-analysis using JBI SUMARI. Effect sizes were expressed as either relative risk ratios (for dichotomous data) or weighted (for standardized) final post-intervention mean differences (for continuous data), and their 95% confidence intervals were calculated for analysis.

A statistician was consulted for advice regarding skewed and missing data. As treatment effects were not reported in any of the studies, missing means and standard deviations were calculated according to the Cochrane handbook where appropriate and included in the meta-analysis [27]. Medians and interquartile ranges were converted to means and standard deviations respectively using established formulas [28]. Similarly, standard deviation was derived from standard error by utilizing a formula outlined in the Cochrane handbook. Where a study lacked information on variability or ranges were only present, a mean standard deviation was calculated from other included studies, and this value was imputed into the meta-analysis for the study.

Statistical analyses were performed using a fixed effect model [29]. The statistical methods used in the analysis were inverse variance for continuous outcomes, and Mantel–Haenszel for dichotomous outcomes. Mantel–Haenszel was selected due to its appropriateness for data sets with low event rates as seen in some included studies [27].

As reported in the protocol, subgroup analyses were conducted where there were sufficient data to investigate. If a subgroup contained two or more studies with more than zero events in at least one arm of each study, an analysis was pursued. In this review, subgrouping was possible for three types of surgery to further investigate the associations between the type of surgery and outcomes. This included thyroidectomy (drain volume, length of stay), rhytidectomy (wound complication rate, drain volume), and salivary gland surgery (time to drain removal, drain volume, length of stay).

Sensitivity analyses were conducted to test statistical assumptions made in the analysis and to investigate potential sources of heterogeneity. A randomized effects model was applied to the meta-analysis and compared with results derived from a fixed effect model. The effect of excluding studies that required imputation for missing values was analyzed to evaluate the impact of assumptions based on estimates and calculations. In addition, two studies that included patients with coagulation disorders or antiplatelet/anticoagulation medication were excluded to examine the effect on the rate of hematoma formation [30, 31].

Heterogeneity was assessed statistically using the standard χ^2 and I^2 tests. For χ^2 statistic, a cut-off significance level of < 0.10 was used due to the small number of studies included. Variation across studies that is due to true heterogeneity was classified as low, moderate, or high (I^2 25%, 50%, 75%, respectively) [32]. Heterogeneity was also assessed through visual inspection of forest plots and results derived from subgroup analyses.

A funnel plot was generated using RevMan (Copenhagen: The Nordic Cochrane Centre, Cochrane) to assess publication bias. Statistical tests for funnel plot asymmetry were performed only if appropriate.

Assessing certainty in the findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence was followed [33], and a Summary of Findings (SoF) was created using GRADEpro GDT 2015 (McMaster University, ON, Canada). This was undertaken by 2 independent reviewers at the outcome level. Any disagreements that arose between the reviewers were resolved through discussion or with a third reviewer. Authors of papers were contacted to request missing or additional data for clarification, where required.

The SoF presents the following information: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision, and risk of publication bias of the review results. The outcomes reported in the SoF include the following: time of surgical drain removal, drain volume output, rate of blood transfusion, length of hospital stay, wound complications, rate of surgical management of postoperative hematoma, and adverse reactions. Certainty of evidence for each outcome was downgraded based on the presence of imprecision, inconsistency, risk of bias, indirectness, and publication bias.

Results

Study inclusion

The comprehensive search yielded 1494 studies, and of these, 700 duplicates were removed, and 751 records were excluded through screening of title and abstract. Of the remaining 43 studies assessed for eligibility, 29 were excluded following full-text review. Reasons for exclusion included the following: ineligible population (wrong procedure, no drain use, included chyle leak, included patients less than 18 years old), no comparison group, wrong intervention, retrospective cohort, paper in the form of a letter or commentary, and unpublished work (see Appendix II). A PRISMA flow diagram of the search and study selection process is presented in Fig. 1.

Methodological quality

The methodological quality of the fourteen included publications is outlined in Tables 1 and 2. Thirteen studies were RCTs and one study was a quasi-experimental design. Overall, the quality of the studies is moderate based on the results of the critical appraisal. The risk of selection and allocation bias was unclear in eight RCTs. The most common reason for this was the lack of information provided regarding allocation concealment (question 2) [23, 34–40]. Two studies failed to describe if true randomization was utilized for group assignment (question 1) [35, 36]. Another two studies did not provide sufficient information regarding the baseline similarities between treatment groups (question 3) [34, 38]. The risk of bias related to the administration of the fibrin sealant was present in all included RCTs. All studies blinded participants to group assignment (question 4) and treated both groups identically apart from the use of fibrin sealant (question 7); however, none were able to demonstrate blinding of personnel delivering the intervention. Concerns regarding bias related to assessment, detection, and measurement of the outcomes were raised in several studies. Outcome assessors were not blind to treatment assignment in five studies (question 6) [34, 35, 39, 41, 42]. This was also unclear in a further two studies due to limited information provided [38, 40]. Five studies also failed to specify who and how certain outcomes were assessed (question 11) [23, 39–41]. Reassuringly, outcomes were measured in the same way for both groups in all studies (question 10). Bias related to participant retention was a concern in numerous studies. Five studies had incomplete follow-up that were not properly described and analyzed (question 8) [35, 36, 38, 41, 42]. Only six studies reported analysis of all participants in the groups to which they were randomized (question 9) [23, 31, 34, 37, 41, 43]. Three studies were unclear on the

Table 1 Critical appraisal results of eligible randomized controlled studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Song et al. [41]	Y	Y	Y	Y	N	N	Y	N	Y	Y	U	Y	Y
Erdas et al. [30]	Y	Y	Y	Y	N	Y	Y	U	U	Y	U	Y	Y
Maharaj et al. [42]	Y	Y	Y	Y	N	N	Y	N	N	Y	Y	Y	Y
Uwiera et al. [34]	Y	U	U	Y	N	N	Y	Y	Y	Y	Y	N	Y
Hester, Shire et al. [35]	U	U	Y	Y	N	N	Y	N	N	Y	Y	Y	Y
Hester, Gerut et al. [36]	U	U	Y	Y	N	Y	Y	N	N	Y	Y	U	Y
Oliver et al. [37]	Y	U	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Hornig et al. [38]	Y	U	U	Y	N	U	Y	N	N	Y	Y	Y	Y
Kim et al. [43]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Marchac et al. [39]	Y	U	Y	Y	N	N	Y	U	U	Y	U	Y	Y
Huang et al. [40]	Y	U	Y	Y	N	U	Y	Y	N	Y	U	Y	Y
Vidal-Perez et al. [23]	Y	U	Y	Y	N	Y	Y	U	Y	Y	U	N	Y
Bajwa et al. [31]	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
Total %	**85**	**38**	**85**	**100**	**0**	**46**	**100**	**38**	**46**	**100**	**72**	**62**	**100**

Y yes, *N* no, *U* unclear; JBI critical appraisal checklist for randomized controlled trials: Q1 = Was true randomization used for assignment of participants to treatment groups? Q2 = Was allocation to treatment groups concealed? Q3 = Were treatment groups similar at baseline? Q4 = Were participants blind to treatment assignment? Q5 = Were those delivering treatment blind to treatment assignment? Q6 = Were outcome assessors blind to treatment assignment? Q7 = Were treatment groups treated identically other than the intervention of interest? Q8 = Was follow-up complete, and if not, were strategies to address incomplete follow-up utilized? Q9 = Were participants analyzed in the groups to which they were randomized? Q10 = Were outcomes measured in the same way for treatment groups? Q11 = Were outcomes measured in a reliable way? Q12 = Was appropriate statistical analysis used? Q13 = Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Table 2 Critical appraisal results of eligible quasi-experimental studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Tartaglia et al. [44]	Y	Y	Y	Y	N/A	U	Y	U	Y
Total %	**100**	**100**	**100**	**100**	**-**	**0**	**100**	**0**	**100**

Y yes, *N* no, *U* unclear, *N/A* not applicable; JBI critical appraisal checklist for quasi-experimental trials: Q1 = Is it clear in the study what is the 'cause' and what is the 'effect'? Q2 = Were the participants included in any comparisons similar? Q3 = Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? Q4 = Was there a control group? Q5 = Were there multiple measurements of the outcome both pre and post the intervention/exposure? Q6 = Was follow-up complete and if not, were differences between groups in terms of their follow-up adequately described and analyzed? Q7 = Were the outcomes of participants included in any comparisons measured in the same way? Q8 = Were outcomes measured in a reliable way? Q9 = Was appropriate statistical analysis used?

risk of bias related to participant retention due to limited information provided by authors [23, 30, 39]. For the one included quasi-experimental study (Table 2), the methodological quality was moderate [44]. Question 5 was deemed not applicable as it is impossible to have outcomes, such as drain output and length of hospital stay, present prior to surgery where fibrin sealant is administered. This study did not clarify completeness of follow-up (question 6), and it was unclear who measured the outcome for wound complications and how (question 8). Regarding statistical conclusion validity, all 14 studies utilized appropriate trial designs. Almost all studies utilized appropriate statistical analysis methods except for three. One was unclear due to lack of information provided regarding the chosen statistical methods [36]. Two studies inappropriately used a paired *T*-test when comparing two independent samples [23, 34]. Six studies did not perform calculations for sample size; however, most of these were early studies where prior data was likely limited [34, 37, 39, 40, 42, 44].

Characteristics of included studies

The key characteristics of the final 14 included studies are summarized in Appendix IV. The sample sizes ranged from 15 to 157 patients, with a total of 904 patients. The clinical setting was mainly in hospitals with surgical facilities in Europe (6 studies), America (5 studies), and Asia (3 studies). Four studies examined patients undergoing rhytidectomy. These four studies were $N=1$ trials in which all 170 patients served as their own control [35–37, 39]. Four studies examined thyroidectomy, two studies examined salivary gland surgery (parotidectomy), two studies examined neck dissection, and two studies examined thyroidectomy combined with neck dissection. All studies examined at least two of the listed outcomes. No studies, however, investigated the rate of blood transfusion. Patient characteristics were relatively uniform overall except for studies relating to rhytidectomy procedures where most of the study cohort were female [35–37, 39].

Review findings

A summary of key findings with pooled results is listed in Table 3. Eight studies suggested that surgical drains were removed slightly earlier in the fibrin sealant group compared to control group (MD − 0.49 days, 95% CI − 0.68 to − 0.29, $p=0$) (Fig. 2). This was statistically significant, however, contained substantial statistical heterogeneity ($I^2=92\%$). The rate of postoperative wound complications, including hematoma, seroma, infection, and wound dehiscence, showed a statistically significant reduction in the fibrin sealant group compared to the control group with minimal statistical heterogeneity among the nine included studies (RR 0.64, 95% CI 0.45 to 0.92, $p=0.015$, $I^2=12\%$) (Fig. 3).

Compared to those receiving placebo or usual care, there was a small and statistically significant reduction in total drain volume output (mL) in those receiving fibrin sealant (MD − 16.54, 95% CI − 18.56 to − 14.52, $p=0$). However, this result contained moderate to high statistical heterogeneity ($I^2=59\%$) (Fig. 4). Similarly, the length of hospital stay (days) appeared significantly reduced in the fibrin sealant group compare to controls (MD − 0.84, 95% CI − 1.11 to − 0.57, $p=0$), yet the seven included studies were impacted by substantial statistical heterogeneity ($I^2=93\%$) (Fig. 5). It was suggested that the rate of surgical management of postoperative hematoma was reduced with fibrin sealant use; however, this result was not statistically significant (Fig. 6). There were no deaths nor allergic reactions to fibrin sealant reported in any study. The meta-analysis suggests a harmful effect of either fibrin sealant or placebo/usual care (RR 1.06, 95% CI 0.61 to 1.85); however, this result was not statistically significant ($p=0.835$); it contained moderate statistical

Table 3 Summary of pooled mean differences and relative risks of included studies

Outcome	No. of studies	Effect measure, fixed effects (95% CI)	*P*-value	χ^2	I^2
Time to surgical drain removal postoperatively (days)	8 (8 RCTs)	MD − 0.49 (− 0.68 to − 0.29)	0	92.04	92
Rate of wound complications (incl. hematoma, seroma, infection, wound dehiscence)	9 (8 RCTs, 1 quasi-experimental)	RR 0.64 (0.45 to 0.92)	0.015	9.04	12
Total drain volume output (mL)	13 (12 RCTs, 1 quasi-experimental)	MD − 16.54 (− 18.56 to − 14.52)	0	29.21	59
Length of hospital stay (days)	7 (7 RCTs)	MD − 0.84 (− 1.11 to − 0.57)	0	88.69	93
Rate of surgical management for postoperative hematoma	4 (3 RCTs, 1 quasi-experimental)	RR 0.28 (0.06 to 1.33)	0.11	2.28	0
Rate of adverse events	4 (4 RCTs)	RR 1.06 (0.61 to 1.85)	0.835	5.67	47

Negative MDs indicate reduction of outcome measure in the intervention group relative to the control group

MD mean difference, *RR* relative risk, *RCT* randomized controlled trial, *CI* confidence interval

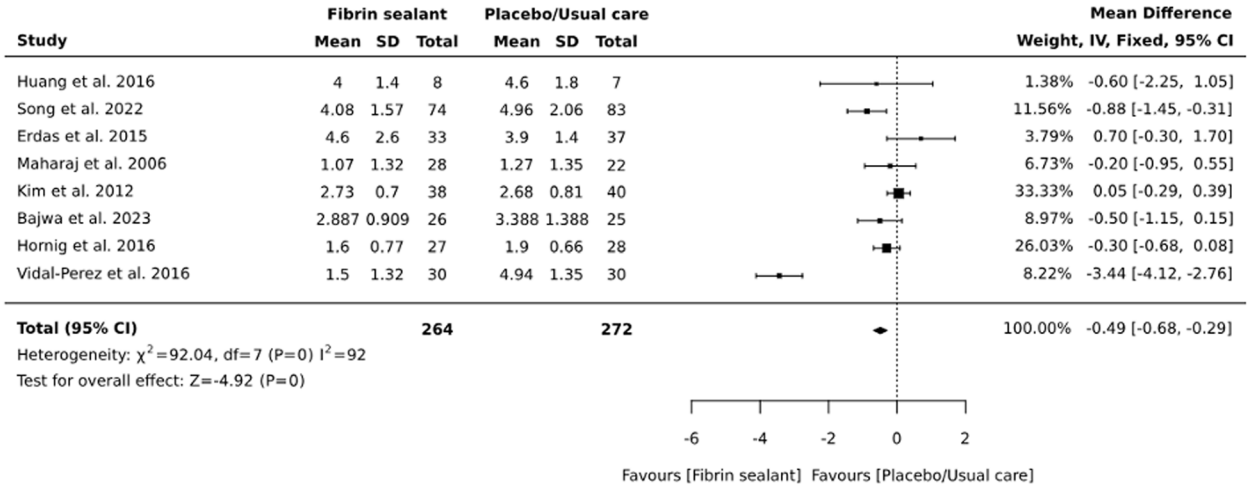

Fig. 2 The effect of fibrin sealant compared with placebo or usual care on time to removal of surgical drain (days) postoperatively

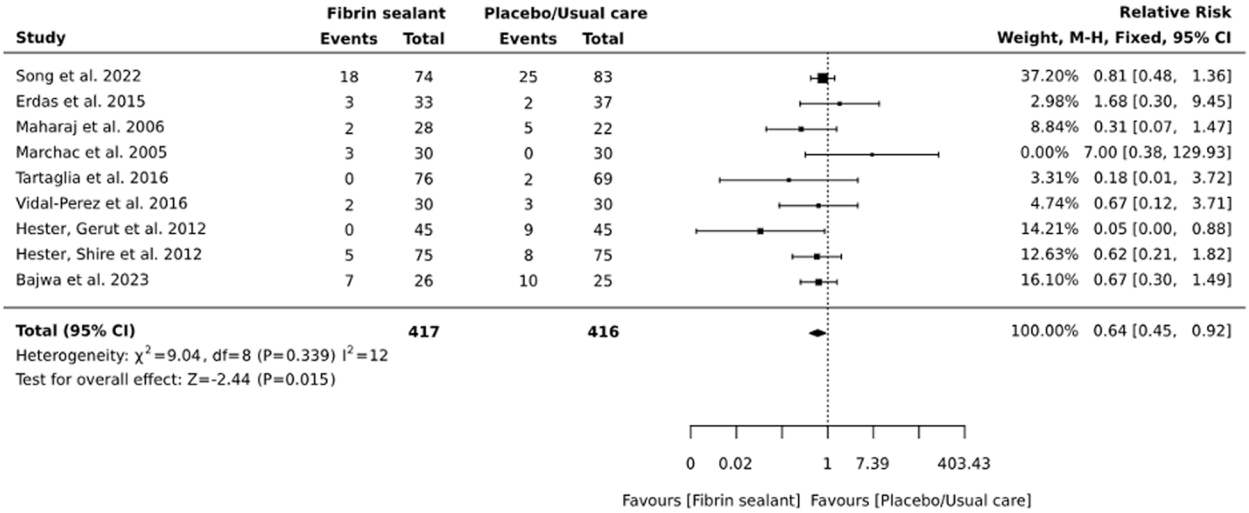

Fig. 3 The effect of fibrin sealant compared with placebo or usual care on the rate of wound complications (including hematoma, seroma, infection, and wound dehiscence) within the first 6 weeks postoperatively

heterogeneity ($I^2 = 47\%$), and the four included studies were of low to moderate methodological quality (Fig. 7, Table 1). In addition, some adverse events reported by studies were later deemed unrelated to the intervention [35, 36]. Three studies could not be included the meta-analysis for this outcome due to having zero events in both groups [30, 31, 34]. None of the fourteen included studies investigated the rate of blood transfusion nor commented on this outcome measure.

Subgroup analysis was performed for the type of surgery to investigate the impact on effect measures and heterogeneity for total drain volume output, length of stay, and time to drain removal (Appendix V). For total drain volume output (mL), statistical heterogeneity was diminished upon subgrouping for thyroidectomy, rhytidectomy, and salivary gland surgeries ($I^2 = 4\%$, 0, 0 respectively), and effect measures remained statistically significant. Statistical heterogeneity for length of hospital stay (days) also subsided upon analysis of studies examining salivary gland surgery only ($I^2 = 0$), but not for thyroidectomy surgery ($I^2 = 82\%$). Time to drain removal (days) in the salivary gland surgery subgroup had a reduced, yet still moderate level of statistical heterogeneity compared to all included studies ($I^2 = 50\%$ vs 92%). There was no statistically significant difference on the rate of wound complications between fibrin sealant and control groups in rhytidectomy procedures ($p = 0.072$, $I^2 = 66\%$). However, it was noted that the

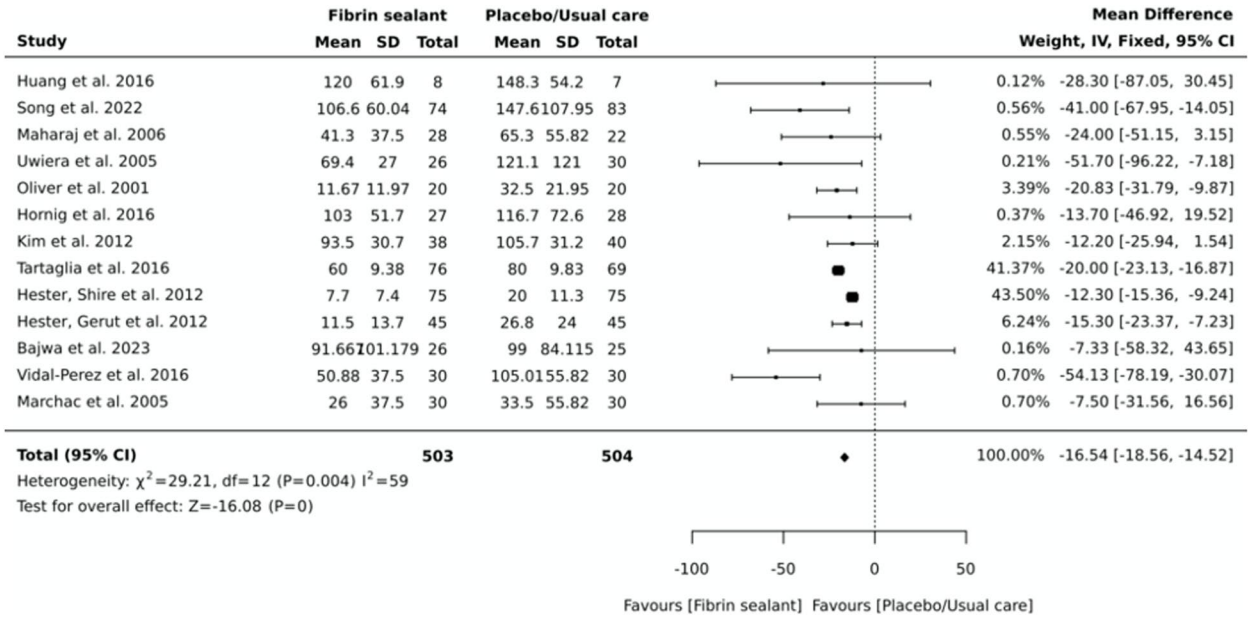

Fig. 4 The effect of fibrin sealant compared with placebo or usual care on total drain volume output (mL)

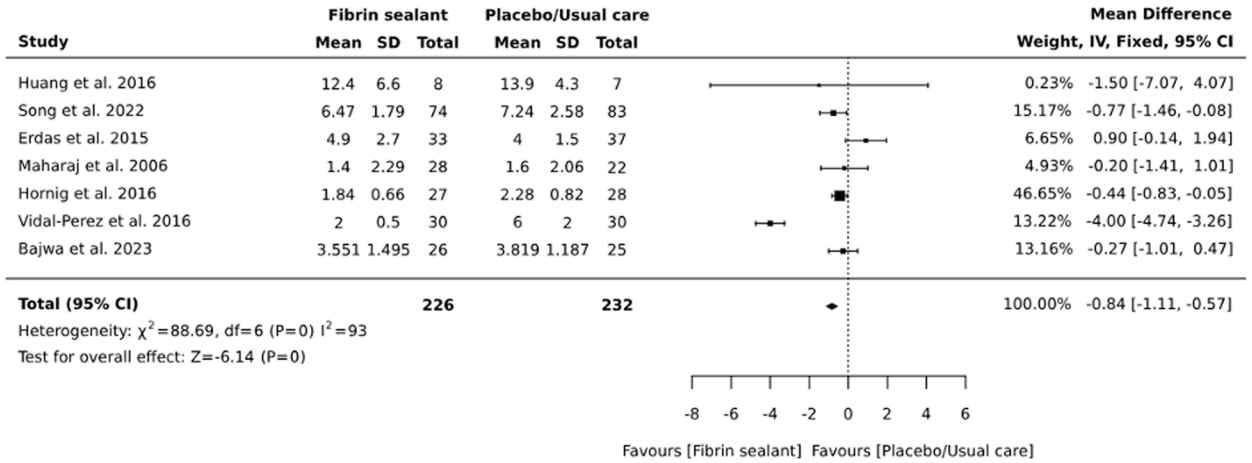

Fig. 5 The effect of fibrin sealant compared with placebo or usual care on length of hospital stay (days)

number of studies in each subgroup was small, ranging between two to three studies.

Application of a random effects model was performed to test the assumption of within and between study variability (Appendix V). Similar results were yielded for rate of wound complications, drain volume output, rate of surgical management of hematoma, and rate of adverse events. Conversely, results for time to removal of surgical drain and length of hospital stay were statistically non-significant, contradicting findings from the fixed effects model.

Sensitivity analyses found that the exclusion of studies involving patients with coagulopathy or on anticoagulant or antiplatelet medication yielded similar results for time to removal of surgical drain and rate of wound complications (Appendix V).

The exclusion of seven studies that required imputation for missing values or conversion of data showed no major change in the results for drain volume output. There was a reduction in the length of hospital stay (MD – 1.67 days) on exclusion of three studies; however, substantial statistical heterogeneity persisted. Statistical heterogeneity

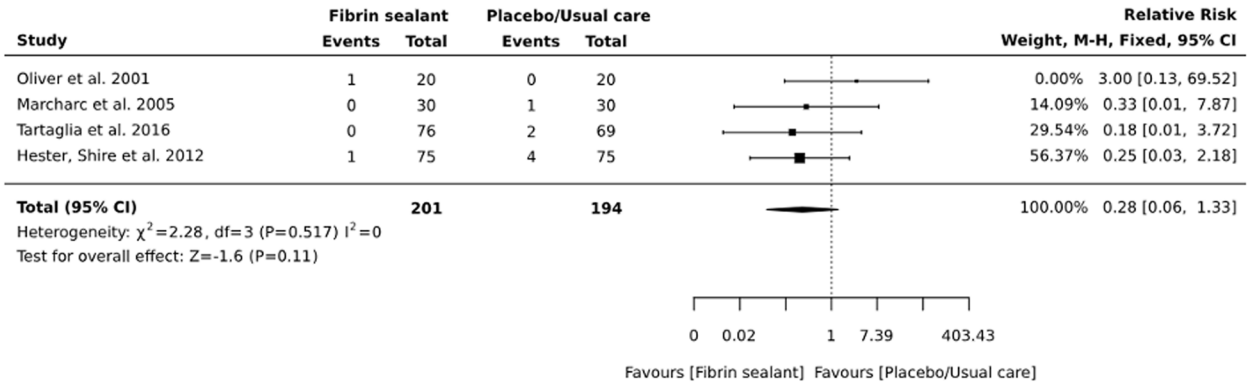

Fig. 6 The effect of fibrin sealant compared with placebo or usual care on rate of surgical management for postoperative hematoma

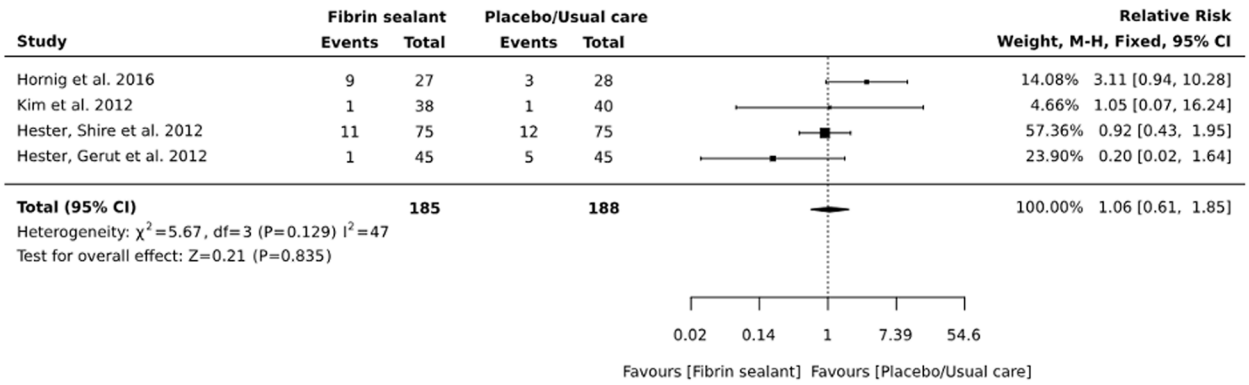

Fig. 7 The effect of fibrin sealant compared with placebo or usual care on rate of adverse events

was slightly reduced on the exclusion of four studies that evaluated time to removal of surgical drain (I^2 72% from 92%); however, it yielded a statistically non-significant result which differs from the pooled result of all studies.

A funnel plot consisting of nine studies showed a symmetrical, inverted funnel on visual inspection, suggesting low risk of publication bias (Fig. 8). However, two studies were not presented on the funnel plot due to zero events in both groups. Given the low number of studies, the power of the test is likely low, and therefore we cannot exclude the risk of publication bias.

Certainty of evidence was generally very low to low for all outcomes due to imprecision, inconsistency, and bias related to participant retention, outcome assessment, and allocation concealment. The Summary of Findings table illustrates key results alongside certainty of evidence (Appendix VI).

Discussion

This review included 14 studies that evaluated the effectiveness of fibrin sealants in patients undergoing head and neck surgery. Although results appeared to reject the null hypothesis, significant clinical and methodological heterogeneity impacted the interpretation of findings.

There was almost a 12-h reduction in the time to removal of surgical drains postoperatively in the fibrin sealant group compared to controls. This is clinically significant as it directly relates to improved patient comfort, mobility, and length of hospital stay. Patients often must remain in hospital for monitoring if drain output remains high; therefore, prompt removal of the drain when deemed safe facilitates earlier discharge planning. As it is uncommon for patients to be discharged in the middle of the night, a difference of 12 h in drain time may dictate whether a patient requires an overnight hospital stay too. Despite this statistically significant result, there was substantial heterogeneity among the eight included RCTs. On sensitivity analysis, statistical significance diminished on the application of a random effects model, and removal of studies involving imputed or converted data. The heterogeneity may be explained by the vast differences in thresholds for drain removal between studies (Appendix IV). For example, [40] removed the drainage tube when output was < 10 ml/24 h compared with [41]

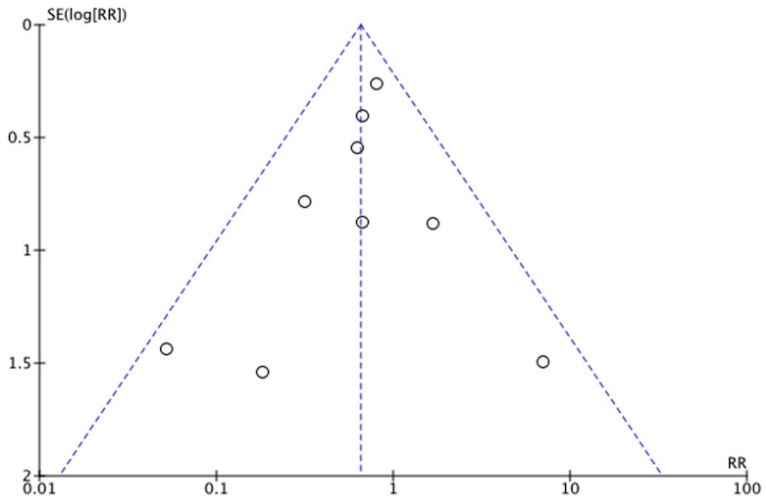

Fig. 8 Funnel plot for publication bias

who removed the drain when output was < 10 ml for 2 consecutive days. In addition, both studies by Hester and colleagues [35, 36] stated drain removal was at the surgeon's discretion. This issue of substantial clinical heterogeneity was also present in a previous systematic review; however, their findings were not statistically significant which may be due to having a smaller number of included studies (4 RCTs) compared to this meta-analysis (8 RCTs) [19].

Among nine studies, the use of fibrin sealant showed promising results on reducing the rate of wound complications, including hematoma, seroma, infection, and dehiscence. However, there was no statistically significant difference when subgrouped for rhytidectomy. This may be explained by the nature of rhytidectomy procedures which do not usually involve deep dissection into internal structures of the head and neck. There was also no statistically significant reduction in the rate of surgical management of postoperative hematoma. This could be explained by the small event numbers in this outcome due to the exclusion of patients with coagulation disorders or medications affecting bleeding tendency in at least two of the four included studies. The previous systematic review also failed to show statistical significance on the rate of hematoma and seroma formation requiring invasive treatment [19]. Nevertheless, this modest reduction in the rate of wound complications related to fibrin sealant use is a clinically significant finding due to its correlation with improved patient outcomes and reduced healthcare burden.

A statistically significant reduction in length of hospital stay by 0.84 days was demonstrated in this meta-analysis. This is a significant improvement for both patients and healthcare providers. Substantial statistical heterogeneity was present; however, this was also seen in a previous review which lacked statistical significance (MD − 2.09 days, 95% CI − 5.18 to 0.99, I^2 97%, $p = 0.18$) [19]. This difference may be explained by their meta-analysis containing 3 RCTs involving thyroidectomy and neck dissection only compared to our review which included 7 RCTs. The persistence of statistical heterogeneity in both systematic reviews relate to the numerous variables that contribute to the duration of a patient's inpatient admission, including patient factors, surgery type, and complications. In addition, time to removal of surgical drains is often a rate-limiting factor in the discharge planning progress. This issue did not change on subgrouping for thyroidectomy studies. However, when subgrouped for parotidectomy surgeries only, statistical heterogeneity diminished, and there was statistically significant decrease in length of hospital stay in the fibrin sealant group compared with controls.

The mean difference in total drain volume output (− 16.54 mL) was slightly lower than in the previous systematic review (− 26.86 mL) [19]. This could be due to the addition of a fourth rhytidectomy RCT in our review as drain output volumes from this type of surgery are generally low. Based on subgrouping, statistical heterogeneity was likely due to the comparison of diverse surgical procedures as each type covers different anatomy with various levels of tissue manipulation. Although statistical heterogeneity was circumvented by subgrouping for thyroidectomy and rhytidectomy procedures, effect measures remained small. It is unlikely that this small difference in the fibrin sealant group would significantly impact on the immediate safety of patients. However, it may determine the timing of drain removal based on the hospital or surgeon's

protocol (i.e., remove drain when < 20 ml/24 h). As a result, this may facilitate earlier discharge and reduce the risk of hospital-associated complications such as infections.

Four studies evaluating the rate of adverse events associated with fibrin sealant use did not produce statistically significant results. However, the 95% CI (0.61 to 1.85) suggested a harmful effect in either the fibrin sealant group or placebo/usual care group. This finding aligns with results from a previous systematic review [19]. Selective outcome reporting is a likely cause for the inconsistency of this outcome data. Many studies did not report on adverse events, and if reported, it was unclear if all or some events were included. Some adverse events were also later deemed unrelated to the intervention, but still reported in the final study results [35, 36].

Upon exclusion of studies that required imputation for missing data or converting of data, results were no longer statistically significant for time to removal of drain. For drain volume output, there was a very small decrease in mean difference (− 16.08 m from − 16.54 mL). Conversely, there was a large increase in the mean difference for length of hospital stay following exclusion of imputed data (− 1.67 days from − 0.84 days). These inconsistencies reflect possible assumptions introduced into the meta-analysis and calls for caution when interpreting these findings.

Based on the critical appraisal of the methodological quality of the included studies, the risk of selection bias was low to moderate due to the lack of information regarding allocation concealment in several studies. There was a high risk of bias related to the administration of the intervention due to lack of blinding across all studies. Blinding of the surgeon administrating fibrin sealant or placebo is challenging, and often not possible, in the hospital setting. Some studies have attempted to address this issue by introducing a third person in the study to administer the product intra-operatively; however, it was not feasible to blind these individuals either [38, 43]. There was moderate risk of bias related to the assessment and measurements of outcomes, predominantly due to concerns regarding blinding of outcome evaluators and reliability of outcome measurements. The risk of bias relating to participant retention was low to moderate as several studies did not perform intention-to-treat analyses, and multiple studies did not describe differences between groups where there was incomplete follow-up. Two studies utilized inappropriate *t*-tests for statistical analysis which may have resulted in a significant difference between the groups which do not actually exist [23, 34].

Limitations

Several limitations were identified during this systematic review and meta-analysis. The low methodological quality of some included studies significantly impacts the generalizability of the results. The GRADE results further emphasize limitations in certainty of the evidence. Studies with poor methodological rigor, such as inadequate allocation concealment, lack of blinding, and incomplete outcome reporting, introduce biases that can distort the true effect of fibrin sealants. These biases undermine the reliability of the findings, making it challenging to draw definitive conclusions.

Heterogeneity was a significant issue due to various aspects of study design and implementation (see Appendix IV). Head and neck surgery includes diverse procedures with anatomical and technical differences, influencing complication risks and the effectiveness of fibrin sealants. Different drain removal thresholds led to discrepancies in timing and outcomes. Patient inclusion and exclusion criteria varied, with some studies excluding those with coagulation disorders or on anticoagulant therapy, affecting baseline risk profiles and generalizability. Inconsistencies in outcome definitions and measurements, variations in randomization, blinding, and adverse event reporting further contributed to heterogeneity. Differences in fibrin sealant type, dosage, and application technique also impacted effectiveness. Additionally, varying sample sizes led to imprecise estimates and limited the ability to detect significant differences.

There was a small number of studies available for analysis, and many studies had small sample sizes. Two studies were terminated early due to insufficient recruitment [38, 40]. Some data sets contained zero events which could not be imputed into the meta-analysis. Although there exist statistical methods to address "zero cells," this was not pursued due to the risk of biasing study estimates towards no difference or introducing a directional bias in the intervention effect [27]. Furthermore, no studies included the outcome of blood transfusion. Information on this outcome may provide further evidence on the effectiveness of fibrin sealants in reducing bleeding and blood transfusion requirements. The risk of publication bias was evaluated using a funnel plot; however, this test was underpowered due to the low number of included studies which limits the ability to detect real asymmetry. Therefore, while this review suggests potential benefits of fibrin sealants, quality issues within the studies caution against broad application of these results without further high-quality, standardized research.

Conclusions

This review has demonstrated with low certainty that fibrin sealant use is associated with a statistically significant reduction in wound complications, including hematoma, seroma, infection, and wound dehiscence, in patients undergoing soft tissue surgery of the head and neck. There was also a reduction in time to surgical drain removal and length of hospital stay; however, these results contained significant heterogeneity. Fibrin sealants showed a small reduction in total drain volume output which may have indirect significance to clinical practice. There was a lack of sufficient evidence to comment on the impact of fibrin sealant use on the rate of surgical management of postoperative hematoma and the rate of adverse events. Further robust research in this area is recommended to strengthen methodological quality, address issues of clinical and methodological heterogeneity, and clarify the degree of certainty related to the use of fibrin sealants in head and neck surgery. Given the clinical promise indicated by this review, future research on the cost-effectiveness of fibrin sealants is needed to guide clinical practice and decision-making.

Recommendations for practice

The results from this study facilitate evidence-based decision-making regarding the use of fibrin sealant in head and neck surgery. We recommend the use of fibrin sealants in this specific setting for a modest reduction in the risk of wound complications, including hematoma, seroma, dehiscence, and infection. Incorporating fibrin sealants into surgical protocols may enhance patient care in alignment with this outcome. As the evidence is unclear for the other outcomes studied, surgeons are recommended to consider the risks and benefits of fibrin sealant use for each patient and surgical procedure. Surgeons might consider applying fibrin sealants more routinely in procedures with higher complication risks, such as thyroidectomies or extensive neck dissections. Furthermore, standardized protocols for drain management, including lower volume thresholds for removal, could be adopted to capitalize on the reduced drain output and reduced rate of hematoma/seroma associated with fibrin sealants, thereby expediting patient discharge and optimizing bed utilization. Implementing these changes can lead to improved patient recovery experiences, decreased healthcare costs, and better overall efficiency in surgical departments. These recommendations are based on a comprehensive review of the literature (Grade B, JBI Grades of Recommendation) [45].

Recommendations for research

There is a pressing need for high-quality studies with robust designs and adequate blinding to better understand the effectiveness of fibrin sealants in head and neck surgery. This includes addressing the differences in study designs, drain removal protocols, and outcome measurements which all contribute to statistical heterogeneity. Researchers should plan for allocation concealment and clearly describe methods used to assess outcomes particularly for wound complications. Implementing an intention-to-treat analysis and ensuring blinding of study personnel are also recommended. Where possible, statistical results should be presented as values that can be included in future meta-analyses. Additionally, research on the cost-effectiveness of fibrin sealants is essential to assess whether the financial investment translates to overall healthcare savings by reducing hospital stays, readmissions, and other complications. Such analysis helps in making informed decisions about adopting fibrin sealants in clinical practice, ensuring that resources are allocated efficiently and patient outcomes are optimized. The results from this systematic review enable reserachers to build upon these findings as new studies arise.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-024-02634-w.

Supplementary Material 1.

Acknowledgements

The authors acknowledge and thank Dr Thomas Sullivan from the South Australian Health & Medical Research Institute for assisting with statistics, and Ms Vikki Langton (Librarian) for guidance and feedback in developing a search strategy.

Authors' contributions

Conceptualization: MN; writing (original draft preparation): MN; writing (review and editing): LT; independent second reviewer: CL; supervision: AF, CL. All authors have read and approved the published version of the manuscript.

Funding

The authors declare no funding in the role of content development.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Data extracted from included studies can be found in the appendix. Template data collection form is available from the priori protocol. The JBI critical appraisal forms used are publicly available in the JBI Manual for Evidence Synthesis.

Declarations

Ethics approval and consent to participate

This study is a systematic review of current literature; therefore, no ethical approval was required.

Consent for publication

Not applicable.

Competing interests
This review is to contribute towards a Master of Clinical Science degree for the first author, MN. CL is the Associate Professor at the School of Public Health (The University of Adelaide) with a research field in JBI.

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Received: 3 March 2024 Accepted: 8 August 2024
Published online: 28 September 2024

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