TITLE: Fibrin sealants in soft-tissue surgery of the head and neck: a systematic review and meta-analysis of randomised controlled trials

SHORT TITLE: Fibrin sealants in head and neck surgery

Bajwa MS1,2, Tudur-Smith C3, Shaw RJ1,2, Schache AG1,2

1. Department of Molecular and Clinical Cancer Medicine, Northwest Cancer Research Centre, University of Liverpool, Liverpool, UK
2. Regional Maxillofacial Unit, Aintree University Hospital, Liverpool, UK
3. University of Liverpool, Department of Biostatistics, Liverpool UK

CORRESPONDING AUTHOR: Mr. Mandeep S Bajwa

 Academic Clinical Fellow

 Regional Maxillofacial Unit

 Aintree University Hospital

 Longmore Lane, Fazakerly

 Liverpool L9 7AL

 Email: msbajwa@doctors.org.uk

 Tel: 07950 583792

ABSTRACT

BACKGROUND: Fibrin sealants (FS) are commercially available products used in surgical wounds as adjuncts to haemostasis and closure of dead space. The role of FS in soft-tissue head and neck surgery has not been established.

OBJECTIVES: To assess if FS improves wound related outcomes in patients undergoing soft-tissue surgery of the head and neck anatomical region that would commonly require a drain.

TYPE OF REVIEW: Systematic review and meta-analysis of randomised controlled trials (RCTs)

SEARCH STRATEGY: MEDLINE (1946 – 2016), EMBASE (1974 – 2016), PubMed (2016), CENTRAL (2016), ClinicalTrials.gov (2016), WHO International Clinical Trials Registry and Platform (2016), Research Gate (2016).

EVALUATION METHOD: Two independent reviewers screened and selected studies. Included studies were assessed for risk of bias and data extracted using a predetermined data collection form.

RESULTS: Of the 421 studies that were screened 11 RCTs met the inclusion criteria. There were 2 RCTs on thyroidectomy, 3 on ‘surgery involving neck dissection’ (central or lateral), 5 on rhytidectomy and 1 on parotidectomy. There was a tendency for FS to reduce ‘mean total drainage volume’ (mean difference -26.86ml, 95%CI -43.41 to -10.31, I2=97%, p=0.001). Sub-group analysis of thyroidectomy (mean difference -36.36ml, 95%CI -72.82 to 0.10, I2=79%, p=0.05), ‘surgery involving neck dissection’ (mean difference -33.21ml, 95%CI -70.01 to 3.59, I2=94%, p=0.08) and rhytidectomy (mean difference -13.79ml, 95%CI -17.57 to -10.01, I2=0%, p<0.00001) concurred with the overall analysis. There was a suggestion that FS may reduce ‘mean retention time of drains’ by 1.24 days (95%CI -3.32 to 0.85, I2=99%, p=0.25) and ‘hospital length of stay’ by 2.09 days (95% CI -5.18 to 0.99, I2=97%, p=0.18) but this was not statistically significant. There was also a suggestion that FS may protect against adverse events (RR 0.69, 95%CI 0.35 to 1.38, I2=0%, p=0.29) and haematoma/seroma formation (RR 0.49, 95%CI 0.22 to 1.07, I2=0%, p=0.07).

CONCLUSIONS: There was considerable heterogeneity within the RCTs included in this study thus restricting definitive conclusions. FS has however shown a definite benefit in rhytidectomy and potential benefit in other soft-tissue head and neck surgical procedures. Further pragmatic trials are required particularly in the field of lateral neck dissection.

INTRODUCTION

Fibrin sealants (FS) are commercially available and US Food and Drug Administration (FDA) approved products that have been extensively investigated in recent years within several areas of surgery.1 However results have been variable and often unduly influenced by poor study design. FS is applied to the raw surfaces of the surgical wound prior to closure and considered to be an adjunct to haemostasis. The mechanism of action is derived from the final stages of the clotting cascade where thrombin cleaves fibrinogen to form a fibrin clot. This clot can seal small vessels and close dead space by adhering the wound surfaces, both essential steps in healing after surgery. The potential clinical advantages to patients and healthcare organisations are significant and include reducing the rate of postoperative complications (e.g. haematoma or seroma formation and infection) and reducing surgical wound drainage thereby avoiding the need for, or minimising the retention time of surgical drains.

In a systematic review and meta-analysis of wound drains after thyroid surgery, Woods et al showed that drains were not routinely required and indeed, increased infection rate, post-operative pain and length of hospital admission.2 Despite this evidence some surgeons are still reluctant to change their practice of using drains. If the application of FS to thyroid wounds reduced the drainage volume and/or facilitated the earlier removal of drains, this would further substantiate the findings of Woods et al.2 In doing so it may also provide significant benefit to both the patient, in terms of reduced complications and improved recovery, and to the health care provider, through reduced length of stay and improved efficiency of care delivery.

To date there are three published systematic reviews on the use of tissue adhesives (not necessarily FS) in soft-tissue surgery of the head and neck region looking specifically at rhytidectomy and tonsillectomy.3-5 The most recent systematic review on the use of tissue adhesives in rhytidectomy by Killion et al showed that their application significantly reduced the rate of haematoma formation and reduced the volume of surgical drainage. Since Killion et al published their study in 2015 no further relevant randomised controlled trials (RCT) have been published.4 Sproat et al5 published their systematic review on the use of tissue adhesives in tonsillectomy wounds in 2016 and found that they did not significantly reduce the rate of post-operative pain or bleeding. The authors commented on the fact that most studies were of low quality and were underpowered to detect statistical significance even when pooled in the meta-analysis.5 There are currently no systematic reviews on the use of FS that encompass the entirety of soft-tissue head and neck surgery or even look specifically at thyroid surgery, parotid surgery or neck dissection. To this end we sought to conduct a systematic review of RCTs to answer the following questions regarding the application of FS in patients undergoing soft-tissue surgery of the head and neck region that would commonly require a surgical drain compared to a non-exposed control group:

1. Does FS reduce the volume of wound drainage?
2. Does FS reduce the time of surgical drain retention?
3. Does FS reduce the time to discharge or time to being declared surgically fit for discharge?
4. Does FS reduce the rate of clinically significant adverse events (AEs) defined as Clavien-Dindo6 grade II or worse, or the rate of haematoma/seroma formation?
5. Does FS reduce post-operative pain?
6. Does FS allow a quicker return to normal function as documented by patient reported outcome measures?
7. Is FS considered to be an acceptable intervention by patients?
8. Is FS a cost-effective intervention?

METHODS

A review protocol was established and prospectively registered on the ‘PROSPERO: International Prospective Register of Systematic Reviews’ website.7 This study was written in accordance with the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA) guidelines.8

All published RCTs comparing FS to non-exposed controls, published during any year and written in any language including adult patients of any gender or ethnicity having soft-tissue surgery of the head and neck anatomical region that would commonly require the placement of a surgical drain were included. RCTs that included patients having FS applied to bone, cartilage, dental, ocular, middle ear or intra-cranial tissues were excluded except if the FS was used to close the soft tissue dead space created to access underlying structures.

The following databases were searched: EMBASE (1974 to July 2016); MEDLINE (1946 to October 2016); PubMed (start of records to November 2016); Cochrane Library and Central Register of Controlled Trials (October 2016); ClinicalTrials.gov (October 2016); World Health Organisation International Clinical Trials Registry Platform (October 2016). The website “Research Gate” was also searched for unpublished work, conference presentations or posters (October 2016). The search strategy using MeSH terms was as follows: (“head and neck neoplasms” or “otorhinolaryngologic diseases” or “otorhinolaryngologic surgical procedures” or “oral surgical procedures” or “dermatologic surgical procedures” or “cervicoplasty” or “rhinoplasty” or “lymph node excision” or “salivary gland” or “stomatognathic diseases” or “craniocerebral trauma” or “neck injuries”) and (“controlled clinical trials” or “systematic review” or “meta-analysis” or “randomised controlled trial as topic”) and (“fibrin tissue adhesive”). The search was limited to humans.

The study selection process was carried out by uploading the search results from all databases to “EPPI-Reviewer 4: software for systematic reviews” (Social Science Research Unit, University of London). This software also facilitated the removal of duplicate studies. Two reviewers (MSB & AGS) selected studies by screening the title and abstract and then repeating the process using full-text versions of studies that cleared the first stage of screening. Studies were excluded if it transpired that they were based on excluded surgical procedures (as previously mentioned), did not specifically use FS or were not the correct study design. All resultant studies that cleared the second round of screening were included in the systematic review and meta-analysis. If there was any conflict in the two authors applying the inclusion and exclusion criteria a third author was consulted (RJS).

Data was collected in keeping with the guidance published in the “Cochrane Handbook for Systematic Reviews of Interventions” version 5.1.0. The quality assessment was carried out using the Cochrane Collaboration’s tool for assessing risk of bias which can be found in the handbook.9 This was also performed independently by two reviewers assessing: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias. Each source of bias was reported as low risk, uncertain or high risk. Clearly blinding of the surgeon poses challenges in the study design so in terms of performance bias, un-blinding the surgeon at the point of wound closure was considered to be the minimum acceptable standard.

The primary outcomes of interest in this review were ‘volume of drainage’ and ‘time of drain retention.’ Secondary outcomes were ‘time to hospital discharge’ or ‘being declared surgically fit for discharge,’ ‘wound complications or adverse events,’ ‘post-operative pain,’ ‘time to return to normal function using patient reported outcome measures,’ ‘patient acceptability to FS’ and ‘cost analysis.’ Data was collected using a spreadsheet with predetermined column headings for each data entry and was trialled on the first two studies. Where important information was lacking formal requests were made to the corresponding authors. In order to standardise the severity of complications the Clavien-Dindo classification was used.6 Only complications of grade II (e.g. requiring antibiotics for a wound infection) or worse were considered significant.

Statistical Analysis

Data was analysed using RevMan version 5.3.5 software (Cochrane Collaboration). For each trial the difference in means and 95% confidence interval were calculated for continuous outcomes and the risk ratio and 95% confidence interval calculated for dichotomous outcomes. Individual trial effects were combined using a random effects inverse variance weighted method for continuous outcomes and Mantel-Haenszel method for dichotomous outcomes. The degree of heterogeneity was assessed using the I2 statistic and sensitivity analyses assuming a fixed treatment effect undertaken for comparison. If authors chose to present their continuous data as median and interquartile range (IQR) then it was assumed the data was skewed. The authors were approached for the actual mean and standard deviation (SD). If there was no response and the degree of skewness was minimal then it was considered appropriate to estimate the mean and SD for the purposes of meta-analysis, accepting the limitations of this approach.10 The mean and SD was also estimated if the authors did not respond and presented their data as median with minimum and maximum values.11 If adequate data permitted, the following subgroup analyses had been planned to compare the surgical procedure performed (e.g. thyroidectomy); the type and volume of fibrin adhesive used; use of harmonic scalpel or similar thermo-coagulation device for haemostasis; type of post-operative drainage (e.g. active versus passive, open versus closed); the maximum volume of drain output over 24 hours that was considered safe to remove the drain.

RESULTS

A total of 421 articles were identified after duplicates were removed from the various searches. Of these 11 studies were included in the final review and meta-analysis. A total of 522 patients were randomised across these 11 studies, including 180 patients in rhytidectomy trials that were ‘split-patient’ controlled trials (i.e. rhytidectomies were bilateral procedures and patients were randomised according to whether the right or left side received FS). Figure 1 provides details of the screening processes in the form of a PRISMA diagram. Table 1 provides the details of the included articles. Two trials looked at the use of FS in thyroidectomy (hemi- and total),12, 13 2 at total thyroidectomy with some form of neck dissection (Kim et al14 included patients having central neck dissection whereas Vidal-Perez et al15 included patients having central and lateral neck dissections), 1 at lateral neck dissection,16 1 at parotidectomy17 and 5 at rhytidectomy.18-22 Only 6 of the included studies12, 14-16, 18, 19 reported a sample size calculation and only 3 of these reached the planned sample size. Inclusion and exclusion criteria were broadly similar among all studies with all trials only including healthy adult patients and excluding patients who had previous surgery to the area, were anticoagulated or had a bleeding/clotting disorder.

Table 2 provides details of the risk of bias assessment. The overall quality of trials varied and many did not report complete methodological information to carry out a full assessment of risk of bias. In cases of incomplete information, authors were approached by email however only one responded. Key findings were that while random sequence generation was mostly adequately performed, such attempts at reducing selection bias were incomplete due to the lack of adequate reporting of allocation concealment. None of the 5 trials in which patients dropped out after randomisation performed an ‘Intention-to-treat’ analysis. They were considered at high risk of attrition bias if the number of dropouts were unequal between the two groups of patients.12, 16-19 Four trials pre-registered their protocol on ClinicalTrials.gov so that a comparison between the planned outcomes and reported outcomes could be made and assessment of reporting bias possible.12, 14, 18, 19 Several trials were industry funded but only the trials by Hester et al included authors who were employed by or were stockholders in the manufacturer (Baxter Healthcare).18, 19

Primary Outcomes

With regards to wound drainage all trials used a closed suction drain of varying calibre apart from Lee et al. who did not use any drains for rhytidectomy but rather applied a pressure bandage for 3 days.20 Figure 2 shows the forest plot for all trials that provided enough data to perform meta-analysis on ‘mean total drainage volume’. Similar surgical procedures are grouped together to enable sub-group analysis. Hornig et al12 presented their data as median and IQR, the skewness was thought to be minimal and therefore the mean and SD was estimated.10 Vidal-Perez et al presented their data as median with minimum and maximum values and the mean and SD was estimated.11 The meta-analysis showed substantial statistical heterogeneity in all the sub-groups (thyroidectomy I2 = 79%; surgery involving neck dissection I2 = 94%) apart from in rhytidectomy (I2 = 0%). There was a clear tendency for reduced ‘mean total drainage volume’ with FS in the overall analysis with a mean difference of 26.86ml (95% CI -43.41 to -10.31, p < 0.00001). Although this was statistically significant, the result needs to be interpreted with caution due to the substantial statistical and clinical heterogeneity of the studies (I2 = 97%). The individual sub-group analysis concurs with the overall analysis, however for surgery involving neck dissection, the difference was not quite statistically significant (p = 0.08). The sub-group analysis of rhytidectomy shows a clear statistically significant benefit of FS reducing drainage volume with no statistical heterogeneity. The study by Maharaj et al was not included in the meta-analysis because they did not provide the standard deviation of the mean nor provide enough information to estimate it. The trial did however find that the mean total drainage volume in superficial and total parotidectomies was 41.3ml in the FS arm compared to control that was 65.3ml. This was a statistically significant difference (p = 0.02).17

Figure 3A shows the meta-analysis on the retention time of drains (days). This analysis includes 4 studies that looked at different surgical procedures and had different protocols for drain removal. Hornig et al removed the drain once it produced <10ml/8hrs; Huang et al <10ml/24hrs; Kim et al <20ml/24hrs; Vidal-Perez et al <20ml/24hrs. The overall analysis shows a tendency for FS to reduce the mean retention time of drains by 1.24 days (I2 = 99%, 95%CI -3.32 to 0.85, p = 0.25) however there is substantial statistical heterogeneity and the difference is not statistically significant. This heterogeneity is primarily because the study by Vidal-Perez et al15 very strongly favours the use of FS compared to the other studies. Studies involving rhytidectomy were not included because all drains were removed at approximately 24 hours. Maharaj et al17 found that, for patients having parotidectomy, the FS group retained the drain for 25.6 hours and the control 30.4 hours; this study was excluded from meta-analysis because it did not provide the SD or p value other than to say it was not significant.

Secondary Outcomes

Figure 3B show the meta-analysis on ‘hospital length of stay’ in days. Overall there was a tendency for FS to reduce hospital stay by 2.09 days (I2 = 97%, 95% CI -5.18 to 0.99, p = 0.18) however this was not statistically significant and there was substantial statistical heterogeneity. Again Maharaj et al was not included in the analysis because of missing information; they found that the mean time to discharge for patient having parotidectomy was 1.4 days in the FS group and 1.6 days in the control group, again this was not statistically significant (p value not provided).

Figure 4A shows the meta-analysis of AEs (Clavien-Dindo grade II or worse). This includes all surgical complications that required treatment within 30 days of the procedure and included haematoma/seroma formation that required invasive treatment, nerve palsies that required intervention, wound infections and ICU admission. There were no deaths reported in any study and there were no adverse reactions to FS (e.g. aprotinin sensitivity or surgical emphysema) reported. The meta-analysis shows that there was no statistical heterogeneity between trials (I2 = 0%) and suggested that FS may be protective against developing a significant AE with a risk ratio of 0.69 but the 95% CI (0.35 to 1.38) includes values of risk ratio that could indicate harmful effect of either FS or standard and so this result is inconclusive. Figure 4B shows the forest plot of a further analysis on the rate of haematoma/seroma requiring an intervention (e.g. aspiration or return to theatre). Again there was no statistical heterogeneity (I2 = 0%) and FS showed a tendency to reduce the risk of developing a haematoma or seroma with a risk ratio of 0.49 (95% CI 0.22 – 1.07). The effect of FS in reducing the rate of haematoma or seroma was not quite statistically significant (p = 0.07).

Post-operative pain was reported in 3 studies that found no significant difference between FS and control.15, 16, 18 All studies reported pain using visual analogue scales (VAS); only Vidal-Perez et al presented the data as a mean with SD, however they failed to specify at what point in the patient’s pathway the VAS was measured. The other 2 studies presented the VAS in a bar graph format with no additional information. Unfortunately due to the poor reporting of post-operative pain meta-analysis was not possible, however individually, no study found a statistically significant difference between the FS group and control. No trials assessed if FS improved the recovery of function using patient reported outcome measures. In terms of FS being acceptable to patients, only the trial by Huang et al reporting difficulties in recruitment.16 Finally, Vidal-Perez et al was the only study to attempt a cost analysis. They found that the cost per patient in their institution was 377.72 Euro for the FS group and 1133.16 Euro for the control group. This was a significant difference (p < 0.05) and was primarily driven by the increased ‘hospital length of stay’ in the control group.

DISCUSSION

This systematic review identified 11 RCTs that assessed the effect of FS on patients having soft-tissue surgery to the head and neck anatomical region. These studies were very heterogeneous in their quality, design and reporting making meta-analysis difficult to interpret and provide conclusive answers to the questions set out in the introduction. Whilst benefit from the inclusion of FS was a consistently apparent finding in all trials, this did not always translate into a difference in clinical outcome. Each operative sub-group is discussed in turn.

Thyroidectomy (Hemi- and Total)

There was substantial statistical heterogeneity in the sub-group analysis of thyroidectomy studies (I2 = 79%) in terms of ‘mean total drainage volume’. This heterogeneity may have been because the differences in cut-off volume for drain removal (10ml/8hr for Hornig et al and 10ml/24hr for Uwiera et al) and the mean and SD was estimated for the study by Hornig et al.10, 12 The ‘mean total drainage volume’ for thyroidectomy was significantly reduced by 36.36ml in the FS arm compared to control (95% CI -72.82 to 0.10, p = 0.05) however this is tempered by the high statistical heterogeneity. Hornig et al12 and Uwiera et al13 reported a “mean total drainage volume” ranging from approximately 70 – 120ml, this is contradictory to the meta-analysis by Woods et al2 who demonstrated that not using drains was safe and may even be beneficial i.e. one would expect 70 – 120ml in the anterior neck to be clinically obvious and needing aspiration/evacuation. It is unclear if this disparity is simply due to the stimulating effect of a closed suction drain in the wound. As Woods et al2 have shown that drains are not routinely required in thyroid surgery it is difficult to argue the case for using FS. The current meta-analysis shows that FS has potential benefits in reducing drainage volume but this has not translated into a significant difference in clinical outcome (both in the pooled and individual study analysis). The findings of this study offer little to change the practice of surgeons who already perform drainless surgery other than to say FS is safe to use. More evidence is required on the use of FS in patients who are at higher risk of complications (e.g. patients on anticoagulation).

Surgery Involving Neck Dissection (Central or Lateral)

Overall FS had a tendency towards being beneficial in ‘surgery that involved a neck dissection’ in terms of reducing the ‘mean total drainage volume’ by 33.21ml (I2 = 94%, 95% CI -70.01 to 3.59, p = 0.08). It is difficult to draw any conclusions regarding the clinical impact of this reduction in drainage volume because the result was not statistically significant and there was substantial statistical heterogeneity. This heterogeneity can be explained by the fact that the 3 studies included in this analysis incorporated different surgical procedures. Huang et al16 just looked at lateral neck dissection, Kim et al14 just looked at total thyroidectomy with central neck dissection and Vidal-Perez et al15 looked at total thyroidectomy with central and lateral neck dissection. The degree of heterogeneity is compounded by the fact that Vidal-Perez et al15 showed a significantly greater benefit of using FS compared to the other studies. Similar effects of this study on the heterogeneity of meta-analysis can be seen in ‘retention time of drains’ and ‘hospital length of stay’ (Figure 3). It is possible that the estimation of mean and SD along with the subtle variation in drain removal protocol may have had a small part to play. Another explanation could be that FS is of greater benefit to patients who have a lateral neck dissection. Of all the procedures included in this review, lateral neck dissection is the most extensive and creates the greatest potential dead space. The surgery commonly involves large muscle belly exposure with dissection around large calibre vessels and carries with it, risks of major complication due in part to the proximity to the airway. Huang et al16 did not show such a marked benefit from using FS, however their study was vastly underpowered due to problems with recruitment. The premise that FS is of greater benefit in patients having lateral neck dissection is supported by two non-randomised studies that both showed a clear benefit of using tissue adhesives (FS or autologous platelet and plasma adhesives). This is both in terms of total wound drainage and retention time of drains.23, 24

Rhytidectomy & Parotidectomy

The evidence for the use of FS in parotidectomy and rhytidectomy seems more clear-cut. The meta-analysis shows that FS has a definite benefit in reducing wound drainage in rhytidectomy trials by approximately 13ml (p < 0.00001); this benefit also translates to a reduced rate of haematoma/seroma formation. The findings of this study agree with the findings of Killion et al4, despite some differences in inclusion criteria of studies and statistical method, and support the use of FS in rhytidectomy.

Unfortunately the trial by Maharaj et al17 on the use of FS in parotidectomies only provided enough data to include it in the meta-analysis on AEs and haematoma/seroma formation. If we analyse their results in isolation, they do support the use of FS in terms of reducing ‘mean total drainage volume’ and ‘haematoma/seroma’ formation. This is supported by the findings of Conboy and Brown who performed 21 parotidectomies using FS without a drain in a day surgery setting and reported no wound complications and found a health economic benefit.25 There is a need to substantiate these findings with a well-designed RCT comparing FS with no drain to standard of care with a drain. Having a third arm of this trial where patients are deprived of both FS and a drain is possible but may be controversial in terms of patient safety unless additional measures are taken e.g. pressure bandages are applied.

It is important to clarify that only Woods et al has provided robust evidence for the omission of surgical drains in thyroidectomy. Lee et al used pressure bandages instead of surgical drains in both arms of their study on rhytidectomy; however not all head and neck procedures are amenable to the use of pressure bandages. Conboy and Brown provide evidence through a small case series that surgical drains can be omitted in parotidectomy so long as FS is used. Therefore any future trials comparing FS to standard of care without a drain need careful consideration with regards to patient safety, especially if the procedure in question is not amenable to pressure dressings e.g. lateral neck dissection.

Care should be taken when interpreting the numerical value of pooled mean differences shown in Figure 3 with regards to ‘retention time of drains’ (-1.24 days 95% CI -3.32 to 0.85) and ‘hospital length of stay’ (-2.09 days 95% CI -5.18 to 0.99). This is because of the substantial statistical heterogeneity and because the analysis was performed over different surgical procedures that may not be directly comparable. Instead it is more appropriate to look at the ‘relative’ effect of FS on these outcomes. Overall it is fair to say that the relative effect of FS is beneficial however not statistically significant.

The meta-analysis on AEs (Clavien-Dindo grade II or worse) demonstrated that FS is safe for use in the head and neck anatomical region and may have a protective benefit albeit not to a statistically significant level (I = 0%, RR 0.69, p = 0.29). The analysis on ‘haematoma/seroma formation that required invasive treatment’ showed that FS had a tendency for greater benefit (I2 = 0%, RR 0.49, p = 0.07) but it was mainly the rhytidectomy and parotidectomy trials that contributed to this result. There were surprisingly few significant complications reported in the ‘surgery involving neck dissection’ studies. This can be explained by the fact that the studies excluded patients who were at high risk of complications (e.g. previous surgery, radiotherapy, bleeding disorders or anticoagulation).

To summarise the key findings of this study, each of the questions posed in the introduction has been addressed.

1. Overall FS has been shown to reduce the mean total volume drained (-26.86ml, 95% CI -43.41 to -10.31, P = 0.001, I2 = 97%), however there is substantial statistical heterogeneity (Figure 2). Within the sub-group analyses ‘thyroidectomy’ and ‘surgery involving neck dissection’ suffered from wide confidence intervals that just crossed the line of no effect. The evidence to support the use of FS in reducing the in mean total volume drained is stronger in the sub-group analysis of ‘rhytidectomy’.
2. There was a tendency for FS to reduce the retention time of drains however this was not statistically significant. Most studies found that this reduction was less than 0.5 days and so did not translate to a clinically significant outcome. One study found that FS reduced the time of drain retention by 3.75 days which is clinically significant15, however no other study reproduced this outcome leading to the substantial statistical heterogeneity (I2 = 99%) as shown in Figure 3A.
3. Again, there was a tendency for FS to reduce the hospital length of stay but this was not statistically significant and hampered by substantial statistical heterogeneity (Figure 3B).
4. There was a tendency for FS to reduce the rate of clinically significant AEs defined as Clavien-Dindo6 grade II or worse (Figure 4A) albeit not to a statistically significant level. The evidence for FS reducing the rate of haematoma or seroma was stronger (Figure 4B). It is important to note that many studies had no complications in either arm because they made a conscious decision to exclude patients at increased risk of complications.
5. Meta-analysis of post-operative pain was not possible due to the differing ways that studies reported it. Of the 3 studies that did report pain, none found that FS made a statistically significant difference.
6. None of the studies in this review looked at the effects of FS on health related quality of life and whether it expedited the return to normal function.
7. All studies apart from 1 found that FS was an acceptable intervention for patients. This study reported difficulties in recruitment but did not explain why patients were averse to participation.
8. No studies performed detailed cost analyses. One study reported a crude cost-benefit analysis and found FS resulted in a saving of 755 Euro per patient driven by reduced hospital length of stay.

In conclusion this systematic review has found that the evidence for the use of FS in soft-tissue head and neck surgery is encouraging but its interpretation is hampered by heterogeneous, sometimes poor, methodology and reporting of trials. As such the ability for robust conclusions to be drawn from meta-analyses are necessarily limited. All the trials included in this systematic review excluded patients who were at increased risk of developing complications. Given that we are faced with an ageing population who may have multiple co-morbidities, future trials should include these patients so that our understanding of the role of FS in head and neck surgery may improve. It is clear that further clinical trials incorporating robust methodology are needed, this particularly the case with regards to lateral neck dissection where there is a paucity of randomised data and where the potential for greatest benefit exists, through avoidance of severe complications and reduction in hospital length of stay.

CONFLICT OF INTEREST

None declared

FUNDING

Self-funded

KEY POINTS

1. FS has been shown to reduce the ‘mean total volume of wound drainage’ in soft-tissue surgery of the head and neck, however not all studies have shown that this results in significantly earlier drain removal or hospital discharge.
2. The meta-analysis has shown a clear benefit of using FS in rhytidectomy in terms of reducing ‘mean total drainage volume’ and reducing ‘haematoma/seroma formation’.
3. FS is unlikely to change the practice of surgeons who carry out thyroidectomy without using a drain.
4. There is a suggestion that lateral neck dissection may benefit significantly from using FS but there is substantial statistical heterogeneity of data and very few patients randomised so far.
5. There is a need for more pragmatic RCTs that include patients at higher risk of complications so that we may understand the effects of FS in this growing population.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year | Surgery | Country | Planned sample size | Number randomised | No. of drop-outs | Reasons for drop-outs | Intention to treat analysis | Intervention | Control |
| Hester et al18 (phase II) | 2013 | Rhytidectomy | USA | 40 | 46 | 1 | Unclear | No | Artiss FS | No FS |
| Hester et al19(phase III) | 2013 | Rhytidectomy | USA | 75 | 75 | 4 | Screening failure, voluntary withdrawal  | No | Artiss FS | No FS |
| Hornig et al12 | 2016 | Thyroidectomy | USA | 110 | 70 | 15 | Voluntary withdrawal, deviation from protocol  | No | Evicel FS  | Saline Placebo |
| Huang et al16 | 2016 | Lateral Neck Dissection | Taiwan | 134 | 18  | 3 | Neck wound communicated with upper aerodigestive tract, poor drain function | No | Tissucol FS | No FS |
| Kim et al14 | 2012 | Thyroidectomy and central neck dissection | South Korea | 72 | 78 | 0 | - | - | Berplast P FS | No FS |
| Lee et al20 | 2009 | Rhytidecomy | USA | - | 9 | 0 | - | - | Crosseal FS | No FS |
| Maharaj et al17 | 2006 | Parotidectomy | Canada | - | 60 | 10 | Incomplete data or loss to follow-up | No | Tisseel FS | No FS |
| Marchac et al21 | 2005 | Rhytidecomy | France | - | 30 | 0 | - | - | Tisseel FS | No FS |
| Oliver et al22 | 2001 | Rhytidecomy | UK | - | 20 | 0 | - | - | Beriplast P FS  | No FS |
| Uwiera et al13 | 2005 | Thyroidectomy | Canada | - | 56 | 0 | - | - | Tisseel FS | No FS |
| Vidal-Perez et al15 | 2016 | Thyroidectomy and neck dissection | Spain | 60 | 60 | 0 | - | - | Tissucol FS | No FS |

Table 1. Summary of included trials. Pts = Patients, FS = Fibrin sealant.

Table 2. Risk of bias assessment of included trials. Green = low risk of bias, yellow = uncertainty, red = high risk of bias. A brief description of why the study was categorised to a particular risk of bias is provided. FS = fibrin sealant, ITT = Intention to treat analysis

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Random Sequence Generation | Allocation Concealment | Blinding of Participants & Personnel | Blinding of Outcome Assessment | Incomplete Outcome Data | Selective Reporting | Conflict of Interest |
| Hester et al (2013)18 | Predefined randomisation sequence | No data  | Surgeon knew allocation prior to wound closure | Independent investigators | No ITT. But only one patient dropped out (equal for both groups) | Registered ClinicalTrials.gov | Industry funded; 2 authors employees &/or stockholders of Manufacturer |
| [Hester et al (2013)](file://C:\Users\cat1\Documents\mdrive\MRC%20HUB\richard%20shaw\Cochrane%20Review\SR%20papers\Hester-%20Randomized,%20Controlled,%20Phase%203%20Study%20to%20Evaluate%20the%20Safety%20and%20Efficacy%20of%20Fibrin%20Sealant%20VH%20S:D%204%20s-apr%20(Artiss)%20to%20Improve%20Tissue%20Adherence%20in%20Subjects%20Undergoing%20Rhytidectomy.pdf)19  | Predefined randomisation sequence | No data | Surgeon knew allocation prior to wound closure | Not clear if investigators were different to surgeon | No ITT. But only four patients dropped out (equal for both groups) | Registered ClinicalTrials.gov | Industry funded; 2 authors employees &/or stockholders of Manufacturer |
| Hornig et al (2016)12 | Computer generated random sequence | Allocation never revealed to surgeon as study staff closed the wound | Placebo control | Blinded assessors | No ITT and uncertainty about equality in both groups | Registered ClinicalTrials.gov | Industry funded |
| [Huang et al (2016)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CHuang-%20The%20impact%20of%20tissue%20glue%20in%20wound%20healing%20of%20head%20and%20neck%20patients%20undergoing%20neck%20dissection.pdf)16 | Computer generated random sequence | No data | Surgeon knew allocation prior to wound closure | Blinded assessors | No ITT and uncertainty about equality in both groups | Pre-registered trial protocol not found | None declared |
| [Kim et al (2012)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CKim-%20Efficacy%20of%20Fibrin%20Sealant%20for%20Drainage%20Reduction%20in%20Total%20Thyroidectomy%20with%20Bilateral%20Central%20Neck%20Dissection.pdf)14 | Computer generated random sequence | Allocation concealed until the point of use in theatre | Patients blinded and surgeon blinded up to the point of use | Blinded assessors | No drop-outs | Registered ClinicalTrials.gov | None declared |
| [Lee et al (2009)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CLee-%20Efficacy%20of%20Crosseal%20Fibrin%20Sealant%20%28Human%29%20in%20Rhytidectomy.pdf)20 | Random drawing of which side got FS e.g. flipping coin | No data | Surgeon knew allocation prior to wound closure | Blinded assessors | No drop-outs | Pre-registered trial protocol not found | Industry funded |
| [Maharaj et al (2006)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CMaharaj-%20Tisseel%20to%20Reduce%20Postparotidectomy%20Wound%20Drainage-%20Randomized%2C%20Prospective%2C%20Controlled%20Trial.pdf)17 | Sealed envelope | Envelope sealed until point of use | Patients blinded and surgeon blinded up to the point of use | Blinded assessors | No ITT and unequal drop-outs among groups | Pre-registered trial protocol not found | None declared |
| [Marchac et al (2005)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CMarchac-%20Early%20Postoperative%20Efficacy%20of%20Fibrin%20Glue%20in%20Face%20Lifts-%20A%20Prospective%20Randomized%20Trial.pdf)21 | Not clear that patients were consecutive and method of randomisation was dubious | No data | Not clear when surgeon was un-blinded | Surgeon assessed outcome | No drop-outs | Pre-registered trial protocol not found | None declared |
| [Oliver et al (2001)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5COliver-%20A%20prospective%2C%20randomized%2C%20double-blind%20trial%20of%20the%20use%20of%20fibrin%20sealant%20for%20face%20lifts..pdf)22 | Random drawing of which side got FS e.g. flipping coin | No data  | Surgeon knew allocation prior to wound closure  | Blinded assessors | No drop-outs | Pre-registered trial protocol not found | Industry funded |
| [Uwiera et al (2005)](file:///C%3A%5CUsers%5Ccat1%5CDocuments%5Cmdrive%5CMRC%20HUB%5Crichard%20shaw%5CCochrane%20Review%5CSR%20papers%5CUwiera-%20Tisseel%20and%20Its%20Effects%20on%20Wound%20Drainage%20Post-Thyroidectomy-%20Prospective%2C%20Randomized%2C%20Blinded%2C%20Controlled%20Study.pdf)13 | Block Randomisation | No data  | Not clear when surgeon was un-blinded | Blinded assessors | No drop-outs | Pre-registered trial protocol not found | None declared |
| Vidal-Perez et al (2016)15 | Sealed envelope | Envelope sealed until point of use | Patients blinded and surgeon blinded up to the point of use | Blinded assessors | No drop-outs | Pre-registered trial protocol not found | None declared |