Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Health and Economic Advantages Associated With the Use of TachoSil: An Update of Systematic Review

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Background: The international scientific literature is systematically analyzed in this review over a period of nearly 10 years with respect to the use of the active hemostat and surgical sealant patch TachoSil, considering its economic effects. It`s an update of the first review published in 2014.

Methods: A PubMed systematic literature review was done from Nov 2013 up to December 2022. Based on the criteria used to select, the papers were grouped in terms of study design, surgery type, reduction in the time to hemostasis, shorter hospital stay, fewer number of post-operative complications, and the impact of TachoSil to operative procedures.

Results: Medical evidence of TachoSil is well documented, in different clinical studies and for several indications. In this second review 18 scientific papers were screened. In total data from 3.375 patients were analyzed, of whom 1.748 were treated with TachoSil. Nine of the 18 papers (50%) were classified as randomized clinical trials (RCTs). The time required for hemostasis following the administration of TachoSil was significantly shorter than that observed with other surgical treatment techniques, with a median time of up to four minutes. The reduction in post-operative complications was evaluated in 15 studies that were conducted on patients in a variety of surgical specialties. When using TachoSil the hospitalization duration was briefer, as observed in the past review.

Conclusion: The second analysis of scientific papers demonstrates that TachoSil plays a supporting role in surgical procedures, enhancing hemostasis and facilitating tissue sealing when conventional techniques are inadequate.This approach has been linked to a reduction in post-operative complications, length of hospital stay, and consequently, hospital cost.

Keywords: TachoSil, hemostasis, length of hospitalization, postoperative complications, economic evaluation

Introduction

Surgical bleeding is a significant cause of morbidity and mortality in patients.[1] It is a normal physiological response to tissue damage and may result from either topical or systemic medical or surgical interventions.[1] The process of hemostasis is initiated: The vascular bed begins to leak, and it is followed by clotting. This involves the formation of a clot, which is then broken down by fibrinolysis. Several factors contribute to this process.[2,3] Surgeons have various pharmacological agents and instruments to control bleeding, including traditional methods like pressure and tourniquets, as well as advanced techniques such as compressive bandages, ligatures, sutures, clippings, and electrocautery (monopolar, bipolar), ultrasonic, radiofrequency, or laser instruments.[4]

Over the past century, there has been a remarkable amount of progress in the field of topical hemostats, which can be broadly classified into four main categories: fibrin sealants, gelatin-based products, oxidized cellulose, and collagen products.[5] Therefore, proximal vessel hemostasis is not dependent on thrombus formation; rather, it is caused by collagen

Received: 2 August 2024
Accepted: 26 February 2025
Published: 1 March 2025

and elastin fusing to form the intima, which results in the formation of permanent scar tissue.[6] These systems can be broadly classified into three categories: hemostatic dressings, surgical sealants, and blood-derived local hemostatic agents. 1

Hemostats are medical devices derived from plants (polysaccharides, cellulose), animals (collagen, gelatin), and minerals (zeolite). They work through chemical and/or mechanical mechanisms, promoting platelet aggregation and supporting the coagulation cascade. Surgical sealants, also medical devices, may be synthetic or semi-synthetic and polymerize in the presence of water, interacting with the coagulation cascade mechanically.[3] The introduction of local hemostatic products identified as topical drugs of human or animal origin is a more recent phenomenon.[7,8] Passive mechanical products without coagulation factors include Surgicel, TissuFleece, and Spongostan, while passive non-mechanical sealants like CoSeal and BioGlue also lack coagulation factors. Active non-mechanical products with coagulation factors include Floseal and Surgiflo, and active fibrin sealants include Beriplast and Tisseel. TachoSil is a bioactive product combining coagulation factors, sealing, and mechanical support.

All these substances work through the coagulation cascade, providing either a metabolic hemostatic effect or acting as mechanical agents to form a seal. While they have similar clinical indications, some products focus on hemostasis, while others aid in sealing and enhance suture efficacy.[3] TachoSil, for example, is an equine-derived collagen patch coated with human fibrinogen and thrombin. It is used in both adults and children (from one month old) to improve hemostasis, promote tissue sealing, and support suturing in vascular surgery when standard techniques are inadequate. It is also indicated in adults for supportive sealing of the dura mater to prevent postoperative cerebrospinal leakage following neurosurgical procedures.[9] It is a prescribing product that does not require special storage (temperature below 25°C) and is ready for use, unlike other drugs.[9]

The efficacy of these products is often called into question due to methodological flaws and a lack of rigorous scientific investigation, as evidenced by the literature.[10] In general, the available studies are uncontrolled and conducted in a limited number of surgical areas.[11] These products are widely used in a variety of clinical scenarios. However, their use is generally off-label. In addition, research and evaluation of their potential economic impact on healthcare systems is even more limited, challenging decision makers (ie, physicians and pharmacists) to make cost-effective decisions in a context of increasing sustainability of spending.[11]

In the initial systematic review of the literature in Pubmed up to Nov 2013, the selection criteria included reduction of time to hemostasis, shorter hospital stay and fewer post-surgery complications. This resulted in the screening of twenty-four scientific papers.[11] In the first report, 11 of 15 studies (54%) were randomized controlled trials with 2116 patients, 1,055 of whom were treated with TachoSil. In surgeries on liver, heart, and kidney patients, TachoSil reduced bleeding time significantly (1–4 minutes) compared to other techniques. Additionally, 13 of the 15 studies showed a significant reduction in post-operative complications with TachoSil. The reduction in hospital stay for TachoSil patients ranged from 2.01 to 13.58 days, with a significant difference favoring the patch in 8 studies.[11] In the update of the systematic review Colombo 2014 a second systematic review of the literature indexed in PubMed was done starting from November 2013 up to December 2022.[11] The selection criteria were the same. Two additional articles are of older date.[12,13] They could not be disregarded to ensure the completeness and coherence of this research.

Methods

The objective of this second review is to conduct a comprehensive analysis of the international scientific literature pertaining to the utilization of TachoSil in hemostasis in hemostasis and as a surgical sealant, with a particular focus on its economic impact. A systematic review of the principal literature databases, including PubMed, was thus conducted over a 10-year period, beginning in 2013.[10,14] Papers were selected if they contained clinical data demonstrating a clear effect on the utilization of healthcare system resources (National Health Service [NHS], healthcare funds, or insurance), if TachoSil was to be compared with other options (common suturing techniques, medical devices, surgical sealants, or other hemostatic products) to enhance postoperative hemostasis, the consequences on hospitalization, and changes in postoperative complications, and finally, if they addressed any economic considerations. Abstracts and posters were not considered, as they were considered lacking sufficient information.

The key words used in the search (crossed all together in different order) were as follows: “TachoSil” and “pharmacoeconomics”, “hemostatic agents”, “haemostasis”, “hemostasis”, “bleeding”, “sealant”, “lungs”, “fibrinogen”, “randomized trial”, “cost-effectiveness”. The papers were selected if they contained clinical data demonstrating a clear

impact on healthcare resource utilization, including the National Health Service (NHS), healthcare funds, or insurance. TachoSil was compared with other surgical options, including standard suturing techniques, medical devices, surgical sealants, and other hemostatic products, to improve postoperative hemostasis and analyzed for impact on length of hospital stay and postoperative complications.

Results

The findings of the research study are presented in Figure 1. Out of 1.585 singled-out potential papers, 1.566 were excluded because they did not contain references about TachoSil, were not pertinent with the aim of the review or were about animal research (Figure 1).

After an exhaustive search, a total of 18 scientific papers were identified for inclusion in this research project.[12,13,15–30] Out of these, 6 papers (30%) were classified as randomized clinical trials (RCTs), 1 paper is an meta-analysis of 6 RCTs, 1 paper (0,6%) was categorized as cohort studies, 3 papers (17%) were classified as case studies. They were performed in several countries all over the world and included TachoSil in many different fields of surgery to demonstrate medical evidence. The selection of these papers was based on predetermined criteria, and they were further grouped into three main categories based on the specific outcomes they investigated. These categories were as follows: 1) the impact on the reduction of the time to achieve hemostasis 2) change in the length of hospital stay, 3) the decrease in postoperative complications, and 4) the impact of TachoSil on operative procedures. It should be noted that all of these parameters have the potential to modify the patient NHS costs. Moreover, the papers were carefully tabulated, explicitly indicating the surgical specialties and the sealant agents utilized for comparison, particularly when comparing with TachoSil. The inclusion criteria specified that articles published prior to 2013 should be excluded. However, there were two exceptions to this rule, as outlined in references.[12,13] These two articles were deemed exceptional due to their valuable and relevant information, which could not be disregarded to ensure the completeness and coherence of this research (Table 1).

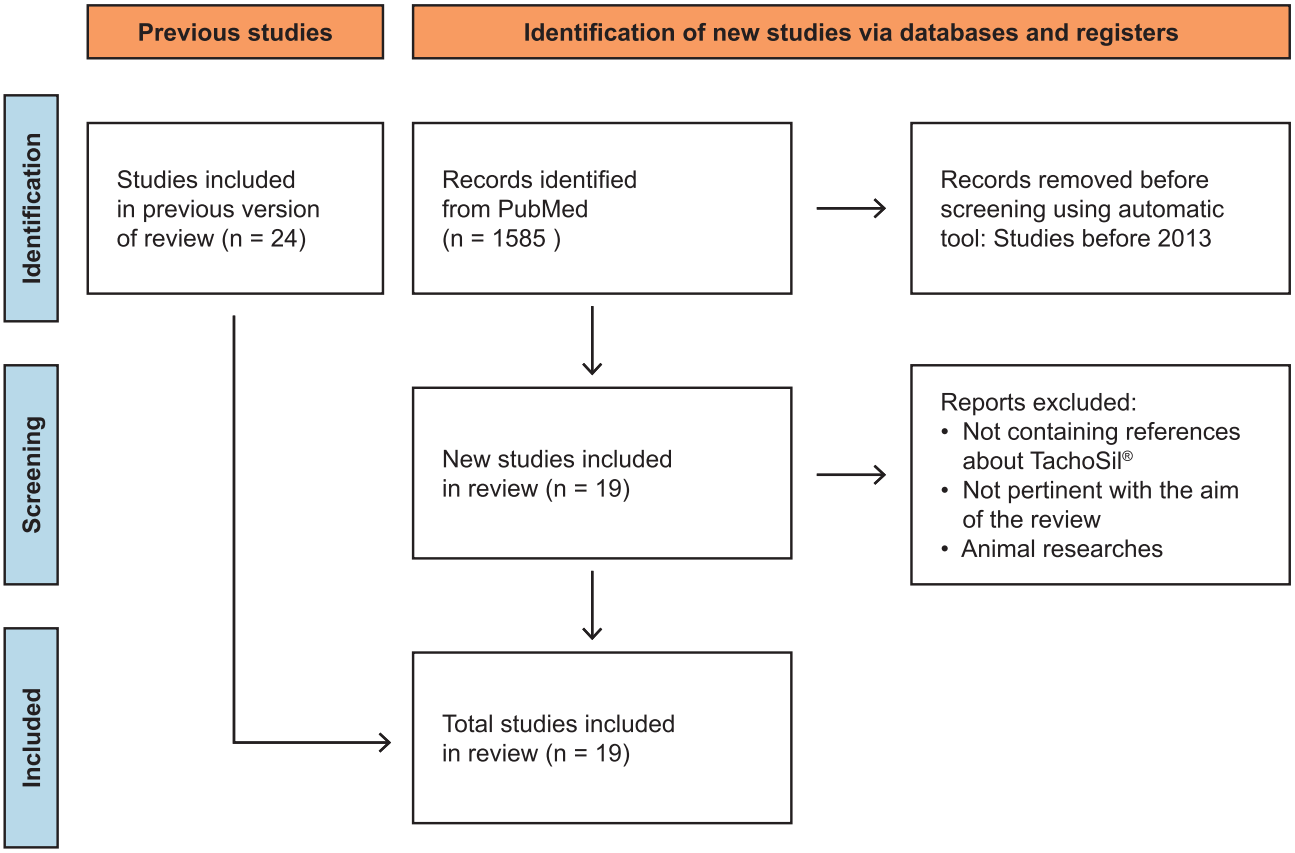

Figure 1 Flow diagram of the selection process to identify studies to be included.

https://doi.org/10.2147/TCRM.S476650

Table 1 List of Articles Included in the Study Along With Their Summarized Information

Author	Countries	Design	Surgery	Sealant Agents	Outcome variables
Caretta et al 2022[15]	Switzerland and Italy	Cohort study and systematic review of the literature	Neurosurgery (craniotomie)	TachoSil vs without additional TachoSil	- POC
Mungroop et al 2021[16]		RCT and meta-analysis (3 studies)	Abdominal Surgery (pancreatectomy)	TachoSil vs Standard treatment	- LHS - POC
Zhou et al 2019[17]	Italy	Meta-analysis of 6 RCTs	Lung surgery (lobectomy)	TachoSil vs Standard techniques	- POAL - POC - LHS
Grimm et al 2018[18]	Austria	RCT	Gynecology lymphadenectomy (Pelvic for cervical or	TachoSil vs without additional TachoSil	- POC
Baggio et al 2018[19]	Italy	RCT	Gynecology (inguinofemoral lymphadenectomy for vulvar cancer)	TachoSil vs without additional TachoSil	- POC
Schindl et al 2018[20]	Austria	RCT	Abdominal Surgery (pancreatoduodenectomy)	TachoSil vs without additional TachoSil	- LHS - POC
Glineur et al 2018[21]	Belgium, Latvia, Germany, USA	RCT	Cardiovascular surgery (different open procedures)	TachoSil vs Veriset	- TTH - POC
Pelizzo et al 2018[22]	Italy	Case report	Lung surgery (pneumothorax)	TachoSil	- POC
Fontana et al 2018[23]	Italy	Systematic literature search and retrospective observational study	Abdominal surgery (e.g. Liver resection, pancreatectomy, colorectal resection, sleeve gastrectomy, cholecystectomy)	TachoSil	- TTH
Kawasaki et al 2017[24]	Japan	RCT	Hepatic surgery (liver resection)	TachoSil and TachoComb	- TTH - POC
Tonyali et al 2017[25]	Turkey	Retrospective clinical study	Urology (kidney resection)	TachoSil vs Floseal	- OT - IOIT - LHS - POC
Filosso et al 2016[26]	Italy	Case study	Lung surgery (chest wall and spinal surgical resection)	TachoSil	- TTH - POC
Watanabe et al 2016[27]	Japan	Case series	Neurosurgery (anterior lumbar fusion surgery)	TachoSil	- TTH
Moench et al 2014[28]	Germany	RCT	Hepatic surgery (liver resection)	TachoSil vs Sangustop	- TTH - POC
Antonelli et al 2014[29]	Italy	Observational multicentric study	Urology (partial nephrectomy)	TachoSil vs FloSeal vs no hemostatic agents	- POC
Öllinger et al 2013[30]	Austria, Germany and Belgium	RCT	Hepatic surgery (liver resection)	Tachosil vs Veriset	- TTH - POC - LHS

(*Continued*)

Table 1 (Continued).

Author	Countries	Design	Surgery	Sealant Agents	Outcome variables
Marta et al 2010[12]	Austria, Italy, Denmark, Germany and Hungary	RCT	Lung surgery (pulmonary lobectomy)	TachoSil vs Standard surgical technique	- POAL - POC
Siemer et al 2007[13]	Germany, Austria, Denmark and Belgium	Open randomized prospective multinational parallel group trial	Urology (kidney resection)	TachoSil vs Standard suture techniques	- TTH

Abbreviations: RCT, Randomized clinical trial; LHS, Length of hospital stay; POC, Postoperative complications; TTH, Time to hemostasis; POAL, Postoperative air leakage; OT, Operation time, IOIT, intraoperative ischemia time.

Reduction in Time to Hemostasis

A total of seven selected papers were subjected to analysis with the objective of determining the reduction in time to hemostasis when TachoSil or other sealant agents were utilized. Three randomized controlled trials were conducted on patients undergoing hepatic, renal, or cardiac surgery. A total of 869 patients were included in the study, 508 were treated with TachoSil. The discrepancies in the time required for hemostasis reached statistical significance in three of the papers[13,21,30] (Table 2).

Table 2 Time to Hemostasis Reduction: TachoSil Versus Other Standard Techniques

Authors	Countries	Design	Surgery	Sealant Agents	Patient Numbers	Time to Hemostasis (min)	Statistical Difference (*p*-value)
Siemer et al 2007[13]	Germany, Austria, Denmark and Belgium	Open, randomised, prospective, multicenter and multinational, parallel group trial	Urology	TachoSil vs Standard suture techniques	92 vs 92	5.3 vs 9.3	$p < 0.0001$
Fontana et al 2018[23]	Italy	Systematic literature search and retrospective observational study	Abdominal surgery	TachoSil	308 (no comparator)	No information	–
Kawasaki et al 2017[24]	Japan	Randomized, double-blind, non-inferiority trial	Hepatic surgery	TachoSil and TachoComb	54 and 54	5 vs 5	$p = 1.0$
Moench et al 2014[28]	Germany	RCT	Hepatic surgery	TachoSil vs Sangustop	65 vs 61	2.2 vs 3.4	n.s.
Öllinger et al 2013[30]	Austria, Germany and Belgium	RCT	Hepatic surgery	TachoSil vs Veriset	18 vs 32	3 vs 1	$p < 0.001$
Glineur et al 2018[21]	Belgium, Latvia, Germany, USA	RCT	Cardiovasc ular surgery	TachoSil vs Veriset	45 vs 45	1.5 vs 3	$p < 0.0001$
Filosso et al 2016[26]	Italy	Case study	Lung surgery	TachoSil	3 (no comparator)	No information	–
Watanabe et al 2016[27]	Japan	Case series	Neurosurg ery	TachoSil	6 (no comparator)	34 ± 12	–

Abbreviation: RCT, Randomized clinical trial.

https://doi.org/10.2147/TCRM.S476650

Nephron-Sparing Surgery (NSS)

The time required for hemostasis was significantly shorter with TachoSil than with standard suturing techniques (mean: 5.3 vs 9.5 minutes; $p < 0.0001$). Hemostasis was achieved within 10 minutes in 92% of TachoSil patients and in 67% of patients in the standard of care group ($p < 0.0001$). The application of the patch demonstrated superior efficacy to standard suturing in controlling intraoperative hemorrhage.[13]

Abdominal Surgery

The median time to hemostasis was 1.0 minutes for the Veriset patch and 3.0 minutes for TachoSil ($p < 0.001$). Bleeding severity did not influence time to hemostasis in patients undergoing hepatic surgery.[30] For bleeding sites with a surface area of 100 cm^2, The Veriset patch exhibited a markedly accelerated onset of hemostasis in comparison to TachoSil (hemostasis: 1.0 min vs 4.0 min; $p = 0.033$). The Veriset patch demonstrated a 94% success rate (95% CI 77.8–98.9) in achieving hemostasis within three minutes, whereas the TachoSil group exhibited a 71% success rate (12/17 patients) (95% CI 46.0–88.0) ($p = 0.034$). The Veriset hemostatic patch demonstrated significantly faster hemostasis in patients undergoing hepatic resection, regardless of bleeding severity or surface area, compared to TachoSil. In all participants with hepatic surgery, hemostasis was achieved within five minutes of the application of the study treatment, with TachoComb (54/54, 100%) and TachoSil (54/54, 100%) exhibiting comparable efficacy [22]. The response rate was identical across all study groups ($p = 1.0$). Another study compared the efficacy a collagen hemostat with a carrier-bound fibrin sealant after liver resection [26]. A total of 53 out of 61 TachoSil patients (86.9%) achieved complete hemostasis within three minutes after the application of the hemostat, compared to 52 out of 65 Sangustop patients (80.0%) ($p = 0.3453$) exhibiting hemostasis five minutes after the administration of the hemostatic agents was 93% in the TachoSil cohort and 95% in the in the Sangustop cohort ($p=0.7114$). The median time to hemostasis was reduced by approximately one minute after the application of COLL (2.2 minutes) in comparison to CBFS (3.4 minutes). A retrospective observational study showed the effective option of TachoSil in helping to control bleeding in hemostasis in abdominal surgery.[23],308 patients in hepatic surgery, after elective and emergency splenectomy, colorectal and bariatric surgery. Most frequently used was the fibrin patch in the gallbladder bed after cholecystectomy.

Cardiovascular Surgery

The time to hemostasis (median) (target bleeding site, TBS) was 3.0 minutes in patients treated with TachoSil and 1.5 minutes in patients treated with the Veriset hemostatic patch ($p < 0.0001$), indicating a statistically significant difference between the two groups.[21] For the TachoSil group, 92% achieved hemostasis within 3 minutes at all treated bleeding sites, compared to 88% with the Veriset hemostatic patch. So, proportion of patients achieving hemostasis at all treated sites at 3 minutes between the two treatment groups was similar. No notable discrepancy was observed between the two treatment groups with respect to any of the surgical procedures or TBS characteristics.

Thoracic Surgery

In three instances, evidence of diffuse bleeding was observed on the resected surface of the spine. This was effectively managed using traditional hemostatic aids, including[16] hot swabbing and electrocautery, followed by placement of large-sized TachoSil.[26] All chest drainages were removed on the second and third postoperative days. There were no radiological signs of hemothorax or hematoma at the postoperative chest X-ray, which demonstrated the efficacy the procedure in controlling diffuse bleeding following chest wall resection.

Neurosurgery

Patients who underwent anterior lumbar fusion surgery and had sustained vessel injuries were treated with TachoSil.[27] Result: The time required to achieve hemostasis with the sealant matrix was observed to fall within a range of 10 to 60 minutes, with an average time of 34 ± 12 minutes (mean ± SD).

A Reduction in the Length of Hospitalization

The length of hospital stay was reported in six of the selected papers (one-third of the total number of studies screened), which were conducted on patients undergoing liver surgery, pancreatic interventions, kidney surgery, and lung surgery.

These selected papers include in total nine randomized controlled trials,[12,16,17,20,30] and one retrospective clinical study.[25] These studies included in total 412 patients, 385 of these were treated with TachoSil. (Table 3) The results of the studies are quite different and depend on the intervention and indication (pelvic lymphadenectomy, pancreatectomy, pancreatoduodenectomy, laparoscopic nephron-sparing surgery, lung surgery). This variability should be considered when interpreting the outcomes of each study, as the effectiveness of adjunctive hemostatic agents may vary across different surgical procedures and patient populations. For instance, while TachoSil demonstrated a reduction in the length of hospitalization in certain procedures, the results were not consistent across all types of surgery. This discrepancy highlights the importance of considering the specific surgical context when evaluating the efficacy of hemostats. The studies included in this review cover a wide range of surgeries, and the observed outcomes depend heavily on factors such as the type of procedure, the presence of complications, and the particular characteristics of the patient cohort.

After kidney resection the mean duration of hospitalization was determined to be longer (3.2 ± 0.5 days) without use of adjuvant hemostatic agent (AHA) in comparison to the application of TachoSil (2.9 ± 0.7 days) and the use of Floseal (2.8 ± 0.7 days). In the TachoSil group the mean duration of hospitalization was shorter (although not significantly) in comparison to the no AHA group. A significant difference was observed between the Floseal and no AHA groups ($p = 0.043$).[25]

Regarding pancreatoduodenectomy, the multicenter randomized study was unable to demonstrate that the utilization of fibrin-coated collagen exerts a protective influence on the prevalence and severity of postoperative pancreatic fistula. Furthermore, no notable discrepancies were observed in secondary endpoints, such as postoperative complications, time to drain removal, and hospitalization, in patients undergoing pancreatoduodenectomy with pancreatojejunostomy.[20] A further study demonstrated that the hospital stay was shorter in the fibrin patch group. It may be posited that this shorter hospital stay can be attributed to the lower reoperation rate.[16]

In hepatic surgery, there were no statistically significant differences observed in the length of ICU stay ($p = 0.67$) or hospitalization ($p = 0.301$) following the application of the Veriset patch or TachoSil. The mean standard deviation (SD) durations of ICU stay and hospitalization were 2.8 ± 6.3 and days 15.2 ± 9.2 days, respectively, in patients treated with the Veriset patch, and 2.2 ± 2.1 days and 18.5 ± 12.0 days, respectively, in patients in the TachoSil group.[30]

Table 3 Reduction of Duration of Hospitalization: TachoSil Versus Standard Techniques

Authors	Countries	Design	Surgery	Sealant Agents	Patient Numbers	Hospital Stay (days) (min)	Statistical Difference (*p*-value)
Tonyali et al 2017[25]	Turkey	Retrospective clinical study	Urology	TachoSil vs Floseal	25 vs 36	2.9 ± 0.7 vs 2.8 ± 0.7	$p = 0.043$
Mungroop et al 2021[16]	Nether- land	RCT and meta-analysis (3 studies)	Abdominal surgery	TachoSil vs Standard treatment	125 vs 122[§]	7 (5–9) vs 8 (6–11)	$p = 0.025$[#]
Schindl et al 2018[20]	Austria	RCT	Abdominal surgery	TachoSil vs without additional patch	71 vs 71	22.1 (2.2) vs 18.2 (0.9)	$p = 0.810$
Öllinger et al 2013[30]	Austria, Germany and Belgium	RCT	Hepatic surgery	TachoSil vs Veriset	18 vs 32	18.5 ± 12.0 vs 15.2 ± 9.2	$p = 0.301$
Zhou et al 2019[17]	Italy	Meta-analysis of 6 RCTs	Lung surgery	TachoSil vs Standard techniques	465 vs 456[$]	−1,89 (MD)	$p < 0.0001$
Marta et al 2010[12]	Austria, Italy, Denmark, Germany and Hungary	RCT	Lung surgery	TachoSil vs Standard surgical technique	148 vs 151[$]	8 (1–36) vs 9 (4–28)	$p = 0.35$

Notes: #, Mann–Whitney-*U*-test, $, patients are also part of Zhou et al 2019 [15], §, patients from the RCT, not from the meta-analysis.
Abbreviation: RCT, Randomized clinical trial.

In lung surgery, alveolar air leakage is associated with an increased risk of postoperative morbidity, prolonged hospital stays, and greater healthcare costs. A recent study compared the efficacy of TachoSil in treating grade 1 and 2 air leakage after elective pulmonary lobectomy with that of standard surgical treatment, including resuturing, stapling, and no further treatment. The results demonstrated that TachoSil treatment resulted in clinical intra- and postoperative advantages.[12] And patients treated with the active hemostat and surgical sealant patch had a reduced length of stay at the hospital: 8 days (1—36) vs 9 days (4—28) days; p = 0.35.[12]

A meta-analysis of six randomized controlled trials (RCTs) was conducted to investigate the efficacy of TachoSil in reducing the incidence of air leakage following pulmonary surgery and in shortening the duration of hospitalization.[17] The study reported the duration of hospital stay. The TachoSil group had a shorter hospital stay than the standard surgical treatment group,7 with a mean difference of −1.89 days (95% CI: −2.42 to −1.35 days; p < 0.0001). In the subgroup analysis, a significant difference was identified. Therefore, TachoSil resulted in a decreased in-hospital cost, with a potential cost- saving benefit that may outweigh the additional cost of the patch.[17]

Decrease in Postoperative Complications

The incidence of postoperative complications was evaluated in 15 studies conducted on patients undergoing kidney, gynecological, abdominal, cardiovascular, thoracic, or cranial surgery. Eight studies (53%) analyzed were randomized controlled trials.[16–21,28,30] A total of 2,850 patients were included in the 15 studies, of whom 1,274 were treated with TachoSil (Table 4). Postoperative complications may include air leaks (in patients who have undergone lung surgery), intra-abdominal infections, asymptomatic lymphocele, pericardial complications, postoperative fistulas, and other complications. The literature reviewed for this study suggests that TachoSil may be an effective intervention to mitigate intraoperative complications and postoperative air leaks, as well as other postoperative complications, although statistical significance was only observed in certain instances (Table 4). A reduction in complications leads to hospitalization, which has economic benefits (Table 4).

Urology

The incidence of postoperative complications did not differ between the AHA, Floseal- and TachoSil group (p = 0.876) after kidney resection. Furthermore, the TachoSil group did not experience any significant postoperative bleeding or late complications.[25] Other data concerning partial kidney resection analyzed the postoperative complications. The incidence of postoperative bleeding complications necessitating transfusions (Clavien grade 2) or reintervention (Clavien grade 3) within a 30-day postoperative period was evaluated. No significant differences were observed regarding complications in general, surgical complications necessitating transfusions (Clavien grade 2), or reinterventions (Clavien 3).[29]

Gynecology

The intraoperative application of collagen-fibrin patches to the pelvic side walls does not reduce the incidence of symptomatic lymphoceles in women with gynecologic malignancies undergoing pelvic lymphadenectomy.[18] A total of 42 lymphoceles (727.4%) and 8 symptomatic lymphoceles (5.2%) were observed. Symptomatic lymphoceles observed in the TachoSil group were 5/68 (7.4%) and 3/85 (3.5%) women in the control group (p = 0.47). The incidence of asymptomatic lymphoceles was 16 cases (23.5%) in the patch group and 18 cases (1.2%) in the control group (p = 0.85). The overall prevalence of lymphoceles was 42 cases among 153 women who underwent pelvic lymphadenectomy with adequate follow-up, as documented in the medical records. In conclusion, the findings indicate that active fibrin-collagen patches are ineffective in preventing symptomatic lymphoceles in women undergoing pelvic lymphadenectomy when used in a clinical setting analogous to that of the trial.[18] In patients undergoing bilateral inguinofemoral lymphadenectomy for vulvar cancer and treated with supportive agents, the overall complication rate was 53% (10/19) in the TachoSil arm and 47% (9/19) and in the in the TachoSil arm and 47% (9/19) in the control group (p = 0.74).[19] The overall prevalence of grade 2 lymphedema was 21.1% in the group treated with a sealant patch and 10.1% in the control group (p = 0.76).

Table 4 Reduction in Postoperative Complications: TachoSil Versus Other Standard techniques[31]

Authors	Countries	Design	Surgery	Sealant Agents	Patient Number	Postoperative Complications (n, %)	Statistical Difference (*p*-value))
Tonyali et al 2017[25]	Turkey	Retrospective clinical study	Urology	TachoSil vs Floseal	25 vs 36	≤ Clavien 2: 5 (20%) vs 5 (13.8%) > Clavien 2: 0 vs 1 (2.7%)	$p = 0.876$
Antonelli et al 2014[29]	Italy	Observational multicentric study	Urology	TachoSil vs FloSeal vs no hem- ostatic agents	66 vs 66 vs 66	Clavien 2: 3 (4,5%) vs 4 (6,1%) vs 8 (12,1%) Clavien 3: 0 (0%) vs 2 (3,0%) vs 1 (1,5%)	–
Grimm et al 2018[18]	Austria	RCT	Gyne- cology	TachoSil vs without addition-nal patch	75 vs 89	21 (30,9%) vs 21 (24,7%)	–
Baggio et al 2018[19]	Italy	RCT	Gyne- cology	TachoSil vs without addition-nal patch	19 vs 19	10 vs 9	$p = 0.74$
Schindl et al 2018[20]	Austria	RCT	Abdominal surgery	TachoSil vs without addition- nal patch	71 vs 70	54 vs 50	$p = 0.839$
Mungroop et al 2021[16]	Netherland	RCT and meta- analysis (3 studies)	Abdominal surgery	TachoSil vs Standard treatment	125 vs 122[§]	25 vs 29	$p = 0.539$
Kawasaki et al 2017[24]	Japan	Randomized, double-blind, non-inferiority trial	Hepatic surgery	TachoSil and TachoComb	55 and 56	–	–
Moench et al 2014[28]	Germany	RCT	Hepatic surgery	TachoSil vs Sangustop	16 vs 23		
Öllinger et al 2013[30]	Austria, Germany and Belgium	RCT	Hepatic surgery	TachoSil vs Veriset	18 vs 32	6 vs 16	–

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https://doi.org/10.2147/TCRM.S476650

https://doi.org/10.2147/TCRM.S476650

Table 4 (Continued).

Authors	Countries	Design	Surgery	Sealant Agents	Patient Number	Postoperative Complications (n, %)	Statistical Difference (*p*-value))
Glineur et al 2018[21]	12 countries in Europe	RCT	Cardiovas-cular surgery	TachoSil vs Veriset™	45 vs 45	0#	–
Zhou et al 2019[17]	Italy	Meta-analysis of 5 RCTs	Lung surgery	TachoSil vs Standard tech- niques	postop. air leak: day 1: 452 vs 445 day 2: 422 vs 415 day 3: 50 vs 50 air leak duration: 63 vs 61	post air leak: day 1: 196 vs 237 day 2: 107 vs 137 day 3: 8 vs 21 air leak duration: MD −3,32	[7] $p = 0.21$ [7] $p = 0.87$ [7] $p = 0.83$ [7] $p = 0.16$
Pelizzo et al 2018[22]	Italy	Case report	Lung surgery	TachoSil	1	–	–
Filosso et al 2016[26]	Italy	Case study	Lung surgery	TachoSil	3	–	–
Marta et al 2010[12]	Austria, Italy, Denmark, Germany and Hungary	Randomised, parallel-group trial	Lung surgery	TachoSil vs Standard surgical tech-nique	148 vs 151[$]	68% vs 42%	$p = 0.022$
Caretta et al 2022[15]	Switzer- land and Italy	Single-centre comparative cohort study and systematic review of the literature	Neuro-surgery	TachoSil vs without additio- nal patch	310 vs 352	24 vs 28	$p = 0.960$

Notes: #, reoperation for bleeding complications up to 5 days post-surgery, none of the AEs in either treatment groups were device-related; $, patients mentioned are also part of Zhou et al 2019 [15], §, patients mentioned are from the RCT, not from the meta-analysis.
Abbreviation: RCT, Randomized clinical trial.

Abdominal Surgery

The incidence of clinically significant findings related to drainage was higher in the Veriset patch group (5 patients, 16%) than in the TachoSil group (1 patient, 6%) among those who underwent hepatic surgery.6 Patients treated with the Veriset patch showed instances of biloma (n = 2), hematoma (n = 1), intra-abdominal abscess (n = 1) and inferior vena cava occlusion with multiorgan failure (n = 1). The patient who had been treated with TachoSil subsequently experienced a recurrence of bleeding.[30] Between patients in the patch group and the control group who underwent pancreatoduodenectomy with pancreatojejunostomy notable discrepancies were observed in postoperative complications. They were classified according to the Clavien-Dindo system, with severity assessed based on the presence and extent of a postoperative pancreatic fistula, the concentration of amylase in drain fluid, the time until drain removal, and the time until fistula closure.[16,20] In elective liver resection, a total of 21 serious complications were observed in 16 TachoSil patients (26%), while 29 serious complications occurred in 23 Sangustop patients (35%). Most of these complications can be attributed to the surgical procedure itself, the underlying disease, or the preoperative health status of the patient. The most prevalent significant postoperative complications were bilomas (present in 3.2% of patients treated with TachoSil and 4.6% of those treated with Sangustop), biliary leaks (present in 3.2% of patients treated with TachoSil and 3.1% of those treated with Sangustop), and intra-abdominal collections (present in 3.2% of patients treated with TachoSil and 3.1% of those treated with Sangustop). The remaining complications included fluid collection (3.2% in TachoSil and 3.1% in Sangustop), and wound infection or dehiscence (1.6% in TachoSil and 4.6% in Sangustop).[28] A postoperative pancreatic fistula was observed in 54 patients (22.2%) who underwent distal pancreatectomy. Among those who received a patch, 25 of 125 patients (20.0%) developed this complication, while 29 of 122 patients in the control group (23.8%) experienced it (p = 0.539).[16]

Cardiovascular Surgery

Patients experienced serious adverse events (AEs) up to 30 days post-surgery, with 22.2% of those in the TachoSil group and 27.3% of those in the Veriset group experiencing such events. It is notable that none of the AEs in either treatment group were device related. Furthermore, within five days post-surgery, no patients required a reoperation for bleeding complications[21] five days following surgery, no patients required reoperation for bleeding complications.[21]

Lung Surgery

A reduction in air leakage was observed following pulmonary lobectomy when TachoSil was used in comparison to conventional techniques.[12] In the TachoSil group the percentage of patients without air leakage as a postoperative complication was higher at all time points up until day 17, at which point air leakage occurred in only three patients in each treatment group. The superior efficacy of the sealant matrix in sealing air pathways was confirmed by a Log rank test, which demonstrated a significant between-group difference in the duration of postoperative air leakage (p = 0.030. The TachoSil group also exhibited a more pronounced reduction in intraoperative air leakage intensity (p=0.042) and a markedly shorter time of postoperative air leakage (p = 0.014) compared to the control group. With TachoSil the[4] time until chest drain removal was 4 days (median), in the standard group 5 days (p = 0.054). A total of 39 patients (26%) (sealant patch) and 50 patients (33%) (standard of care) experienced postoperative complications, with the most prevalent conditions are cardiac arrhythmia, atelectasis, and pneumonia.[12] A meta-analysis of six RCTs examining the incidence of postoperative air leakage following pulmonary surgery revealed a reduction in the prevalence of chest tube duration, and the time of hospital stays.[17] The administration of TachoSil did not result in an elevated risk of postoperative complications, including postoperative air leak and duration, the timing for the removal of the chest tube and the occurrence of postoperative morbidity. These findings suggest that TachoSil may be a safe and effective method for the prevention of postoperative air leak.[17] Additionally, two case studies/case reports demonstrated that the utilization of TachoSil and its hemostatic properties can facilitate the reduction of postoperative complications.[22,26]

Neurosurgery

Postoperative complications associated with cerebrospinal fluid (CSF) leakage occurred in 24 (7.74%) (with) and 28 (7.95%) (without TachoSil) procedures (p = 0.960).[15] The results of the multivariate analysis indicated that there were no statistically significant differences between the incidence of complications between the two groups (aOR 0.97, 95% CI 0.53–1.80, p = 0.930). Furthermore, no notable discrepancies were observed in the postoperative functional, disability, or neurological scores.

Table 5 Influence of Application of TachoSil on Operation Time (OT) and Intra-Operative Ischemia Time (IOT)

Author	Country	Design	Surgery	Sealant Agents	Patient Number	OT and IOT	Statistical Difference (*p*-value)
Tonyali et al 2017[25]	Turkey	Retrospective clinical study	Urology	TachoSil vs Floseal	25 vs 36	OT: 137.4 ± 42.4 min vs 120.9 min ± 23.1* min IOT: 23.1 ± 6.3 min vs 21.3 ± 4.3 min	OT: $p = 0.004$ IOT: $p = 0.101$

Abbreviations: RCT, Randomized clinical trial; OT, Operation time, IOIT, Intraoperative ischemia time.

Impact of TachoSil on Surgical Procedures

A single study has examined the additional outcome of the use of adjuvant hemostatic agents (AHAs) in comparison to the absence of AHAs, with the objective of reducing the operation time (OT) and the intraoperative ischemia time (IOT).[25] The mean duration of surgery was found to be significantly shorter with Floseal (120.9 ± 23.1 minutes) compared to the no AHA group (156.6 ± 34.4 minutes). Additionally, with TachoSil the duration (mean) of surgery was also lower (though not significantly so) than in the no AHA group. A direct comparison of Floseal and TachoSil revealed that Floseal exhibited a superior mean duration of surgery. The[10] mean ischemia time was longest in the group without AHAs (24.3 ± 4 minutes) and shortest in the Floseal group (21.3 ± 4.3 minutes). The use of AHAs, such as Floseal and TachoSil, resulted in a shorter warm ischemia time (not significant) compared to the use of AHAs alone. Floseal demonstrated superior efficacy compared to TachoSil (Table 5).

Discussion

Summary

In the present analysis, new data and confirmations have been identified, primarily concerning hemostasis time and postoperative complications. Only to a limited extent there are explicit outputs regarding hospitalization length. The information obtained from this study has shown homogeneity across different therapeutic areas, thus allowing for a more comprehensive assessment of TachoSil's effectiveness. The results are a supplement to the initial review from 2013 [11]. In this review data from in total 3.375 patients were analyzed, 1.748 were treated with TachoSil. The initial review encompassed a total of 337 patients, of whom 1,055 were treated with TachoSil.[11] The update provided further important insights and further substantiated existing statements.

Limitations

However, the review has a primary limitation concerning the lack of complete data from each included study, and furthermore, the studies exhibit varying structures. And not all the studies were RCTs. The economic endpoint was not a primary focus of the studies. Pharmacoeconomic simulation models were not employed. The inclusion of such models could assist decision-makers in identifying the critical factors for selecting the optimal topical hemostatic agent and surgical sealant.

Additionally, it could facilitate the formulation of prospective economic evaluations and the accurate quantification of treatment costs for clinicians.[32]

The objective of this study is to present a comprehensive and accurate synthesis of the existing research on this sealant, with the aim of providing a unified and scientifically sound basis for evaluating its efficacy. Information comparing TachoSil with standard treatments or other sealants in terms of hemostasis time is available in eight of the considered studies).[13,21,23,24,26–28,30] It is crucial to emphasize that hemostatic efficacy is commonly evaluated at 3 minutes for TachoSil; therefore, data interpretation must be standardized and consider this parameter. For example, in the 2018 study by Glineur et al[21] which compared the hemostatic efficacy of TachoSil to Veriset, TTH values of 3.0 and 1.5 minutes were observed, respectively. Although Veriset may appear to achieve hemostasis more rapidly, a closer analysis suggests that TachoSil demonstrates a comparable rate of success in controlling bleeding within the first three

minutes, with a success rate of 91.1% compared to Veriset's 87.8%. While these results are similar, further investigation is needed to determine whether TachoSil may offer a slight advantage in this regard. Six of the included studies[12,16,17,20,25,30] provide information on the impact of using TachoSil on hospitalization duration which results briefer, as observed in the past review.[11]

The third outcome of this research focuses on postoperative complications, mentioned in 15 of the selected works.[12,15–22,24–26,28–30] Two studies specifically address the time and duration of air leaks after pulmonary surgeries,[17,21] where TachoSil appears to contribute positively to faster resolution. This is a crucial point, as alveolar air leak is one of the most prevalent complications following, for instance, video-assisted thoracoscopic surgery (VATS) lobectomy. The clinical and economic impact of air leaks after major pulmonary resection is well documented and significant.[33] A reduction in the number of surgical procedures has been demonstrated to result in a shorter length of hospital stay, postoperative complications, and a reduction in related costs.[33] Only one study[25] provides information on the duration of the surgical operation and the impact of sealant use on both intraoperative ischemia and surgical duration and this is an important information that was not found and evaluated in past. The information obtained from this review includes both quantitative data (numeric data) and qualitative data (comparisons and comments from observational analyses). Consequently, the results were evaluated non-uniformly across the selected studies, and their evaluation should take this aspect into account. Another new aspect pertains to the study by Schindl et al 2018[18], where the utilization of a double sheet of TachoSil in pancreatic surgery is discussed. This is important to take under consideration because it has an impact on costs besides the health outcome on the patient. Despite these variations, the beneficial impact of TachoSil in medical practice can be confirmed and appreciated.

Conclusion

We affirm the conclusions drawn in the initial review conducted in 2013 regarding all outcomes.[11] This suggests that the use of TachoSil may improve hemostasis and aerostasis times and could help contain or avoid some postoperative complications, leading to a potential reduction in hospitalization duration when compared to no adjunctive product use. However, when compared to other adjunctive products such as Floseal and Veriset, the benefits of TachoSil may vary depending on the study.

Data Sharing Statement

All data generated or analyzed during this review are included in this published article.

Acknowledgment

This research was supported by Corza Medical Switzerland. The authors alone are responsible for the views expressed.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

This research was supported by Corza Medical Switzerland. The authors are employees of independent research organizations and maintained independent scientific control over this study, including data analysis and final interpretation of the results. The authors declare that they have no conflict of interest.

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