



## Topic Exploration Report <sup>1</sup>

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

- Determine the quantity of evidence available for a technology of interest.
- Identify any gaps in the evidence.
- Inform decisions on topics that warrant fuller assessment by Health Technology Wales (HTW).

Topic exploration report number	TER534
Topic	Fibrin sealants for intraoperative bleeding
Summary of findings	<p>Fibrin sealants, including glues and patches, can be used in a wide variety of surgeries as both a means to control bleeding or to seal wounds.</p> <p>We identified two sets of guidelines covering fibrin sealant use during emergency surgery and obstetric or gynaecological surgery. Both recommend that fibrin sealants could be used as adjuncts to conventional methods, including surgical techniques, to control intraoperative bleeding but should not replace surgical techniques, where appropriate.</p> <p>Two health technology assessments looking at specific fibrin glue products (Vivostat and Vistaseal) found that there was a lack of evidence on their effectiveness and did not recommend them for routine use.</p> <p>Seven systematic reviews reporting intraoperative outcomes for the use of fibrin sealants during various types of surgery were identified. Generally, fibrin sealants were non-inferior to controls for all outcomes. However, comparators were quite varied, including surgical techniques (e.g. clipping), manual compression, and other topical haemostats.</p> <p>There was limited economic evidence and results varied from dominated to cost saving. No analyses considered the UK perspective.</p> <p>Results were reported from various types of surgery and these are unlikely to be generalisable across procedures. There is also uncertainty around which comparators match standard care in Wales.</p>

<sup>1</sup> [Cyfieithu dogfennau HTW wedi'u cyhoeddi o'r Saesneg i'r Gymraeg](#)  
Translation of published technical HTW documents from English into Welsh

## Introduction and aims

Intraoperative bleeding during surgical procedures can be a serious issue that requires quick resolution. This is usually done via conventional methods including applying mechanical pressure, techniques such as suturing, clipping or cautery, or interventional radiology. If intraoperative bleeding persists despite these methods, or if conventional methods are not suitable due to the location of bleeding or risks to surrounding tissue, adjunctive measures can be used to control bleeding.

Fibrin sealants, including glues and patches, are one type of adjunctive measure to control bleeding. They work by combining fibrinogen and thrombin, which then forms a fibrin clot at the site of application, mimicking the final stages of the blood clotting cascade. These can be used in a wide variety of surgeries as both haemostats to control bleeding or to seal wounds.

Examples of fibrin glues include Vistaseal/Veraseal, Tisseel/Tissucol, and Evicel. These are all made from human fibrinogen and thrombin, though some contain other active ingredients as well. Vivostat and Cryoseal are examples of fibrin glues that are made from a sample of a patient's own blood using a processing machine onsite. This process takes between 20 minutes and one hour to prepare the fibrin sealant. Tachosil and EVARREST are examples of fibrin patches, both comprised of human fibrinogen and thrombin, but the backing of the patch is made from equine collagen or oxidised regenerated cellulose and polyglactin 910, respectively. These patches are bioresorbable and can be left in place after treatment.

Health Technology Wales researchers searched for evidence on the clinical and cost effectiveness of fibrin sealants for the control of intraoperative bleeding.

## Evidence overview

### Guidelines

One guideline on the use of topical haemostatic agents during obstetric or gynaecological surgery was identified that commented on the use of fibrin sealants. The American College of Obstetricians and Gynecologists (ACOG) recommends that 'when bleeding is more active or in the presence of coagulopathy, biologically active agents such as topical thrombin and fibrin sealants may be considered' (ACOG 2020). However, ACOG also state that surgical techniques for controlling intraoperative bleeding should be attempted before the use of haemostatic agents, but these can be used in situations where surgical techniques are not safe.

Chiara et al. (2018) carried out a systematic review of the use of topical haemostats during trauma or emergency surgery and reported recommendations made by a panel of experts after reviewing the evidence. The meeting was run by the Italian Society of Emergency Surgery and Trauma, endorsed by the World Society of Emergency Surgery, and included representatives of medical technology companies. In agreement with ACOG, the panel recommended that haemostats are not a substitute for surgical techniques to control bleeding. They also recommend that fibrin sealants, in glue or patch form, are effective in the presence of spontaneous or drug-induced coagulation disorders but that the indications of various haemostatic agents are different and that knowledge is required of the different agents to ensure their appropriate selection during specific scenarios.

### Health technology assessments

Two health technology assessments (HTAs) of fibrin sealants were identified, one on Vivostat and one on Vistaseal.

## Evidence overview

Vivostat was assessed in the HTA conducted by the Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT) and they found that there was little evidence for the clinical or cost effectiveness of this product (CEDIT 2015). There was a lack of studies comparing Vivostat to other fibrin sealants and the organisation recommended it should only be used for research purposes.

Vistaseal was compared to other available fibrin sealants (Tisseel and Evicel) in an HTA by the Institut National d'Excellence en Santé et en Services Sociaux (INESSS 2022). Using evidence from four randomised controlled trials (RCTs) and one network meta-analysis, Vistaseal was considered to be effective at controlling intraoperative bleeding during vascular surgery, liver resection, and soft tissue surgery. The safety of the product was judged to be similar to other fibrin sealants. It was noted by experts that fibrin sealants are mostly used as tissue glues, rather than haemostatic agents, in Québec and that there was a lack of evidence of Vistaseal's haemostatic effectiveness and comparison to other fibrin sealants. INESSS did not recommend adding Vistaseal to its list of approved blood system products.

### Secondary evidence

Seven systematic reviews on the use of fibrin sealants during various types of surgery, reporting intraoperative outcomes, were identified. A total of 51 studies, which are relevant to this report, were included in the reviews, reporting data from 10,612 participants. The majority of these studies, 33 out of 51, were RCTs. Across all relevant studies included in the systematic reviews, 2 investigated Vistaseal/Veraseal, 4 Tisseel/Tissucol, 2 Evicel, 5 Tachosil, 4 Vivostat, 1 Cryoseal, 28 included unspecified fibrin sealant products, and 5 included fibrin sealant products not available in the UK. Only two of the systematic reviews stated where included studies were conducted and three studies included in these reviews were conducted in the UK.

Intraoperative blood loss was found to be significantly reduced with fibrin sealants in the following surgery types: cardiovascular (versus other haemostats and conventional treatment), minimally invasive benign gynaecological (versus bipolar energy), and myomectomy (versus placebo or no treatment) (Daud et al. 2020, Ito et al. 2018, Kongnyuy and Wiysonge 2014). However, there was no significant difference in the total blood loss during knee surgery or in the amount of intraoperative blood loss during hip arthroplasty, compared to no treatment/placebo/unclearly reported comparators (Yang et al. 2015, Zhao et al. 2018). Zhao et al. (2018) did report that there is a significant reduction in postoperative blood loss when using fibrin sealants compared with placebo treatment. Yang et al. (2015) also reported a significant decrease in haemoglobin reduction with the use of fibrin sealants and Ito et al. (2018) found a decrease in postoperative haemoglobin reduction as well.

The time to achieve haemostasis was reported in four systematic reviews. Daud et al. (2020) found that this was significantly reduced in those receiving a fibrin sealant during cardiovascular surgery compared to manual compression, swabs, or gelatine sponges, and Groenewold et al. (2011) found that fibrin sealants led to quicker haemostasis than thrombin or placebo treatment during skin grafting. Fibrin sealants also reduced time to haemostasis compared to bipolar energy during minimally invasive benign gynaecological surgery (Ito et al. 2018). Danker III et al. (2021) compared the proportion of patients achieving haemostasis, within four minutes, with different fibrin sealant products to manual compression during peripheral vascular surgery. They found that Vistaseal, Evicel and Tisseel were all more likely to achieve haemostasis by four minutes than manual compression.

Yang et al. (2015) and Zhao et al. (2018) both found that fibrin sealants led to decreased need for blood transfusion during knee and hip surgery, respectively, compared to no

## Evidence overview

treatment/placebo/unclearly reported comparators, despite also finding no significant difference in amount of blood lost. No difference was found in the need for transfusion compared to no treatment during myomectomy (Kongnyuy and Wiysonge 2014). However, it is unclear whether these referred to intra- or postoperative need for transfusion. Daud et al. (2020) reported the need for postoperative transfusion after cardiovascular surgery and found no significant difference between fibrin sealants and other haemostats or conventional treatment.

Adverse events and complications were discussed in five of the systematic reviews. Danker III et al. (2021) state that the overall rates of adverse events during cardiovascular surgery were 15 to 83%, but the proportion of events possibly related to fibrin sealants, specifically, was much lower at 0 to 2%. There was no significant difference in the rate of postoperative complications when comparing use of fibrin sealant to bipolar energy during myomectomy procedures (Ito et al. 2018). Zhao et al. (2018) also found no significant difference in the rates of complications and adverse events when comparing fibrin sealant use to placebo treatment during hip arthroplasty. However, the incidence of complications was found to be significantly lower (odds ratio 0.56 [95% confidence interval 0.38 to 0.83]) when using fibrin sealants for knee surgery (Yang et al. 2015). Kongnyuy and Wiysonge (2014) stated that there was insufficient evidence on adverse events during myomectomy.

Other perioperative or postoperative outcomes were also reported in some studies, including a reduction in operative time when fibrin sealants were used during laparoscopic myomectomy (Ito et al. 2018) and a reduction in the length of hospital stay when they were used during knee surgery (Yang et al. 2015). Daud et al. (2020) reported that there was no significant difference in rates of re-operation due to bleeding or 30-day mortality rates.

### Economic evidence

Four economic analyses were identified, however, three of these were reported as conference abstracts. Economic data was also considered in two of the systematic reviews.

Jamous et al. (2014) reported a cost analysis of a fibrin sealant patch during elective liver surgery in a conference abstract. Using a German hospital perspective, they state that the use of EVARREST fibrin patch may be cost saving over standard of care when factors such as hospital stay, proportion of patients using ventilator, and mean ventilator hours are also considered. They estimated a cost saving of €458 per patient. In another conference abstract, Danker III et al. (2019) suggest that the use of Vistaseal during various surgeries could lead to avoiding \$57,500 to \$159,100 in additional treatment costs in a hypothetical cohort of 10,000 patients compared to standard of care (manual compression or Surgicel). The perspective used in this analysis is not stated. The third conference abstract presented a cost analysis of Veraseal from an Italian hospital perspective. Mantuano et al. (2020) found that Veraseal reduced additional haemostatic usage compared to standard of care (manual compression or Surgicel) and, based on an annual cohort of 8,000 patients, could lead to cost savings of €67,649, €22,558 and €26,500 in liver, peripheral vascular, and soft tissue surgeries, respectively. The latter two abstracts were very similar and were both presented by employees of the manufacturer of Vistaseal/Veraseal.

Merchán-Galvis et al. (2022) performed a quality of life and cost-effectiveness analysis of topical tranexamic acid and fibrin glue during femur fracture surgery. They found that there was no significant difference between the two interventions in changes in quality of life, but that fibrin glue was dominated by tranexamic acid in the cost-effectiveness analysis. Tranexamic acid was also more cost-effective than usual haemostasis methods.

## Evidence overview

The systematic review by Kongnyuy and Wiysonge (2014) found that there were insufficient data to assess the costs of haemostatic interventions during myomectomy. Daud et al. (2020) reported one study in their systematic review that performed an economic evaluation in a Spanish setting. This study estimated that the cost of the fibrin sealant CryoSeal was €822 per patient and that it was only 21% likely to be cost-effective at a willingness to pay threshold of €10,000.

## Areas of uncertainty

- There is variety in the components of different fibrin sealant products.
- Evidence was available in a wide variety of surgical procedures, which will have varying risks and difficulties associated with intraoperative bleeding. It is unlikely that results can be generalised across procedures.
- Comparators vary across studies, and it is uncertain whether any of these match the current standard of care in NHS Wales.
- There is a lack of evidence comparing fibrin sealants to interventional radiology, which is increasingly being used to control severe intraoperative bleeding.
- There is a lack of clarity around whether the need for blood transfusion was reported as intraoperative or postoperative in some studies.
- Most of the systematic reviews did not state the settings of included studies, and only three studies were conducted in the UK where this was reported.
- No economic evidence was identified in a UK setting.

## Literature search results

### Health technology assessments and guidance

ACOG. (2020). Topical Hemostatic Agents at Time of Obstetric and Gynecologic Surgery. Committee Opinion Number 812. American College of Obstetricians and Gynecologists. Available at: <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/10/topical-hemostatic-agents-at-time-of-obstetric-and-gynecologic-surgery> [Accessed 22 February 2024].

CEDIT. (2015). Vivostat fibrin sealant. Comité d'Evaluation et de Diffusion des Innovations Technologiques. Available at: <http://cedit.aphp.fr/vivostat-fibrin-sealant/> [Accessed 22 February 2024].

Chiara O, Cimbanassi S, Bellanova G, et al. (2018). A systematic review on the use of topical hemostats in trauma and emergency surgery. *BMC Surg*. 18(1): 68. doi: <https://doi.org/10.1186/s12893-018-0398-z>

INESSS. (2022). Vistaseal – Intraoperative bleeding. Institut National d'Excellence en Santé et en Services Sociaux. Available at: <https://www.inesss.qc.ca/publications/repertoire-des-publications/publication/evaluation-sur-vistasealmc-saignement-peroperatoire.html> [Accessed 22 February 2024].

### Evidence reviews and economic evaluations

Danker III W, Ferko N, Hogan A. (2019). PBI23 A cost analysis of hemostatic surgical resources associated with a novel fibrin sealant compared to standard of care across surgery types. *Value in Health*. 22: S421. doi: <https://doi.org/10.1016/j.jval.2019.09.127>

Danker III W, DeAnglis A, Ferko N, et al. (2021). Comparison of fibrin sealants in peripheral vascular surgery: A systematic review and network meta-analysis. *Ann Med Surg (Lond)*. 61: 161-8. doi: <https://doi.org/10.1016/j.amsu.2020.12.003>

Daud A, Kaur B, McClure GR, et al. (2020). Fibrin and Thrombin Sealants in Vascular and Cardiac Surgery: A Systematic Review and Meta-analysis. *Eur J Vasc Endovasc Surg*. 60(3): 469-78. doi: <https://doi.org/10.1016/j.ejvs.2020.05.016>

Groenewold MD, Gribnau AJ, Ubbink DT. (2011). Topical haemostatic agents for skin wounds: a systematic review. *BMC Surgery*. 11(1): 15. doi: <https://doi.org/10.1186/1471-2482-11-15>

Ito TE, Martin AL, Henderson EF, et al. (2018). Systematic Review of Topical Hemostatic Agent Use in Minimally Invasive Gynecologic Surgery. *Jsls*. 22(4). doi: <https://doi.org/10.4293/jsls.2018.00070>

Jamous N, Corral M, Hollmann S, et al. (2014). Cost analysis of a fibrin sealant patch for parenchymal bleeding during elective hepatic surgery: A germany hospital perspective. *Value in Health*. 17(3): A36. doi: <https://doi.org/10.1016/j.jval.2014.03.219>

Kongnyuy EJ, Wiysonge CS. (2014). Interventions to reduce haemorrhage during myomectomy for fibroids. *Cochrane Database Syst Rev*. 2014(8): Cd005355. doi: <https://doi.org/10.1002/14651858.CD005355.pub5>

Mantuano M, Paragò V, Vrouchou P, et al. (2020). PSU8 A Cost Analysis of Hemostatic Surgical Resources Associated with Veraseal Compared to Standard of Care in Italy. *Value in Health*. 23: S739. doi: <https://doi.org/10.1016/j.jval.2020.08.1994>

Merchán-Galvis A, Posso M, Canovas E, et al. (2022). Quality of life and cost-effectiveness analysis of topical tranexamic acid and fibrin glue in femur fracture surgery. *BMC Musculoskelet Disord*. 23(1): 827. doi: <https://doi.org/10.1186/s12891-022-05775-y>

Yang TQ, Geng XL, Ding MC, et al. (2015). The efficacy of fibrin sealant in knee surgery: A meta-analysis. Orthop Traumatol Surg Res. 101(3): 331-9. doi: <https://doi.org/10.1016/j.otsr.2014.07.035>

Zhao Z, Ma X, Ma J, et al. (2018). A Systematic Review and Meta-analysis of the Topical Administration of Fibrin Sealant in Total Hip Arthroplasty. Scientific Reports. 8(1): 78. doi: <https://doi.org/10.1038/s41598-017-16779-3>

<b>Date of search</b>	22 February 2024
<b>Concepts used</b>	Vistaseal, Veraseal, fibrin glue, fibrin sealant, intraoperative, surg*



## Proposed research question and evidence selection criteria (if selected)

<b>Proposed Research question</b>	<b>What is the clinical effectiveness and cost effectiveness of fibrin sealants for controlling intraoperative bleeding?</b>
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	<b>Inclusion criteria</b>	<b>Exclusion criteria</b>
<b>Population</b>	Patients undergoing surgery with intraoperative bleeding not controlled by conventional methods	
<b>Intervention</b>	Fibrin sealants, fibrin glues, fibrin patches	
<b>Comparison/ Comparators</b>	No treatment Other topical haemostats Placebo	
<b>Outcome measures</b>	Time to haemostasis Estimated blood loss Need for blood transfusion Adverse events Health-related quality of life Resource use/economic outcomes	

<b>Proposed speciality</b>	<b>Blood and immune system</b>
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