

2.11 Haemostatics

Human thrombin + Calcium chloride + Fibrinogen + Tranexamic acid

บัญชี

รูปแบบ sterile sol

เงื่อนไข

1. ใช้สำหรับภาวะเลือดออกจากรูปเหตุ การถอนฟัน การผ่าตัดผู้ป่วยที่มีภาวะเลือดออกแล้วหยุดยาก เช่น hemophilia, thrombocytopenia, platelet dysfunction, von Willebrand's disease และ congenital factor VII deficiency เป็นต้น

2. ใช้กับผู้ป่วยที่ได้รับการผ่าตัดซึ่งไม่สามารถห้ามเลือดด้วยวิธีปกติได้ เช่น การผ่าตัดตับ การผ่าตัดหัวใจ การผ่าตัดปอด เป็นต้น

Human thrombin + Calcium chloride + Fibrinogen (Fibringluraas®)

รูปแบบ sterile sol

ไม่เลือกไว้ในบัญชียาหลักแห่งชาติ เหตุผล เห็นควรให้พัฒนาศักยภาพในการผลิต fibrin glue / fibrin sealant โดยสภาวิชาชีพไทย เพื่อให้พึ่งพาตนเองได้อย่างยั่งยืน

1. ข้อมูลโดยสรุป

Fibrin glue หรือ fibrin sealant ประกอบด้วยสองส่วนหลัก คือ fibrinogen และ thrombin ซึ่งบรรจุแยกกัน และอาจมีส่วนประกอบอื่นๆ เช่น calcium ion หรือ aprotinin ขณะใช้ สารทั้งสองจะทำปฏิกิริยาเป็นกาวเหนียวเพื่ออุดบริเวณที่เลือดออก เช่น กรณีทำหัตถการ เป็นต้น⁽¹⁾

Fibrin glue ที่ผลิตโดยสภาวิชาชีพประกอบด้วย Human thrombin + Calcium chloride + Fibrinogen + Tranexamic acid ในขณะที่ผลิตภัณฑ์ซึ่งภาคเอกชนเสนอ (Fibringluraas®) มีส่วนประกอบคล้ายกันแต่ไม่มี tranexamic acid (ดูหัวข้อ 2.1 หน้า 2)

สำหรับประโยชน์ในการใช้มีข้อมูลทั้งกรณีที่ได้ประโยชน์จากการใช้ยา⁽²⁻⁵⁾ และมีบางการศึกษาที่ไม่พบประโยชน์จากการใช้ยา⁽⁶⁻⁸⁾ แม้ว่า fibrin glue ของสภาวิชาชีพไม่มี [การศึกษาทางคลินิก](#) เช่นเดียวกับผลิตภัณฑ์ของภาคเอกชน อย่างไรก็ตาม ประสพการณ์จากแพทย์ผู้ใช้ได้ชี้แจงว่า มีประสิทธิภาพในการหยุดเลือดจากหัตถการเช่นกัน

นอกจากนี้ ค่าใช้จ่ายด้านยาจาก fibrin glue ของสภาวิชาชีพยังต่ำกว่าผลิตภัณฑ์ของภาคเอกชน (ดูหัวข้อ 2.1 หน้า 2) คณะทำงานประสานผลการพิจารณาในบัญชียาหลักแห่งชาติ ในการประชุมครั้งที่ 7/2555 (4 เมษายน 2555) เห็นว่า สภาวิชาชีพควรพัฒนาศักยภาพการผลิตให้เพียงพอต่อความต้องการใช้ยา เพื่อให้เกิดการพึ่งพาตนเองได้อย่างยั่งยืน จึงคงรายการยาไว้ตามเดิมโดยไม่เพิ่มรายการยาจากภาคเอกชนไว้ในบัญชี และคณะอนุกรรมการพัฒนาบัญชียาหลักแห่งชาติเห็นชอบตามเหตุผลดังกล่าว

2. รายละเอียดข้อมูลเชิงวิชาการ

2.1 ความแตกต่างระหว่าง Fibrin glue, Fibrin sealant ซึ่งผลิตโดย สภากาชาด และ Fibringluraas®

หัวข้อเปรียบเทียบ	สภากาชาด	Fibringluraas® (2C 4/49)
ราคาต่อชุด (บาท)	100 – 2,200	8,000 (ม.ค. – มี.ค. 2555)
แหล่งที่มาของวัตถุดิบ	คนไทย	คนจีน
ส่วนประกอบ		1 ชุด (แยกกันระหว่าง fibrinogen และ thrombin)
- Human thrombin	มี	1000 IU
- Calcium chloride	มี	CaCl ₂ *2H ₂ O In process 180 mg Diluent 0.294 mg (2 mL of ~ 40 mmol/L)
- Fibrinogen	มี	100 – 180 mg
- Tranexamic acid	มี	ไม่มี
Clinical study	N/A	Clinical study report on efficacy and safety of fibrin sealant (human) in the treatment of selected surgical bleeding Methods: stratification, randomization, parallel control and self-control, N = 413 (100 pairs in group-control study, 60 pairs in self-control study, 153 cases in opening study) Type of surgery: general, liver, thoracic, cardiovascular, burn Results: Efficacy Group control study (test group vs control group) - bleeding time 115.0 ± 79.8 s VS 273.1 ± 153.8 s; p < .01 - quantities of bleeding 5.15 ± 5.5 g VS 14.6 ± 12.8 g; p < .01 Self control study (test group vs control group) - bleeding time 32.1 ± 18.6 s VS 93.8 ± 77.2 s; p < .01 - quantities of bleeding 3.3 ± 3.2 g VS 5.7 ± 4.9 g; p < .01 Safety: no adverse reaction, no infection (HBsAg, Anti-HCV, Anti-HIV, Anti-syphilis negative)

2.2 ข้อมูล practice guidelines จากฐานข้อมูลต่างๆ

จากการสืบค้นฐานข้อมูลต่างๆ ด้วยคำสำคัญ fibrin glue หรือ fibrin sealant หรือ fibrin tissue adhesive เมื่อวันที่ 22 สิงหาคม 2554 พบผลลัพธ์ดังนี้

1) NICE guidance⁽⁹⁾

ไม่พบผลลัพธ์

2) NHS evidence⁽¹⁰⁾

กำหนด types of information เป็น guidelines พบผลลัพธ์ ดังนี้

- Fibrin sealant 28 ผลลัพธ์
- Fibrin glue 15 ผลลัพธ์
- Fibrin tissue adhesive 24 ผลลัพธ์

โดยผลลัพธ์ทั้งหมด นำมาประเมินเฉพาะ practice guidelines ที่กล่าวถึง fibrin glue หรือ fibrin sealant ที่เกี่ยวข้องกับเหลือ ผลลัพธ์ สรุปได้ดังนี้

2.1) National Institute for Health and Clinical Excellence 2007⁽⁶⁾

ข้อมูลด้านความปลอดภัยของการใช้ fibrin glue ใน anal fistula พบว่าไม่มีข้อบกพร่องใด อย่างไรก็ตามหลักฐานด้านประสิทธิภาพในขณะนี้อาจยังไม่เพียงพอที่จะสนับสนุนการใช้ยาในวงกว้าง

Closure of anal fistula using a suturable bioprosthesis plug

1 Guidance

1.1 Current evidence suggests that there are no major safety concerns associated with the closure of anal fistula (fistula in ano) using a suturable bioprosthesis plug. However, evidence on the efficacy of the procedure is not adequate for it to be used without special arrangements for consent and for audit or research...

2 The procedure

2.1 Indications

2.1.4 Less invasive techniques, developed with the aim of minimising the risk of incontinence, include injection of fibrin glue (a solution of fibrinogen and thrombin) and use of a bioprosthesis plug.

2.3 Efficacy

2.3.1 In a non-randomised controlled trial with a mean follow-up of 14 weeks, 13% (2/15) of patients treated with a bioprosthesis plug had persistent drainage and/or a patent secondary opening at the end of follow-up, compared with 60% (6/10) of patients treated with fibrin glue ($p < 0.05$)...

2.4 Safety

2.4.1 No safety outcomes were reported in any of the four studies identified.

2.4.2 The Specialist Advisers did not consider there to be any major safety concerns.

2.2) Williams, *et al.*, 2007⁽²⁾

ข้อแนะนำในการรักษา anal fistula พบว่า anal fistula ไม่ว่าจะชนิด simple หรือ complex อาจใช้ track debridement และ fibrin glue injection ในการรักษาได้ (level of evidence III, B)

III Evidence obtained from well-designed nonexperimental descriptive studies, such as comparative studies, correlation studies and case studies

B Evidence of type IIa, IIb or III and generally consistent findings

Fibrin glue

Findings

Simple anal fistulas may be treated by track debridement and fibrin glue injection (level III, grade B).

Recommendations

Complex anal fistulas may be treated by track debridement and fibrin glue injection (level III, grade B).

Results

There are 18 studies in the literature including two RCTs [203,204] and 13 prospective non-randomized [200, 205–214] trials. The remaining three were retrospective [215–217]. Healing rates ranging from 60% to 70% have been

reported [203,205,209,210,212,214,216]. Risk factors for failure include Crohn's disease, rectovaginal fistula, HIV infection and a short fistula track.

Most studies have used commercially available fibrin glue products (Tisseel, Viguard and Beriplast). Two used autologous fibrin alone and two a combination of commercial and autologous preparations. There was no difference in the healing rates according to the type of fibrin preparation employed. Thus Cintron et al. [205] in comparing Tisseel, Viguard and autologous glue preparations in 79 fistulas found no difference in the healing rates.

Several studies have compared healing rates of simple and complex fistulas although the definition of complex is somewhat arbitrary because of lack of a standardized classification. Healing rates vary from 14% to 60% [205,212,214] with success reported in more than 50% in a recent multicentre prospective study [216]. Continence rates have not been reported.

While early studies have reported high rates of cure [210,214], the long-term results have been less successful, with reported recurrence rates of up to 100% [202]. The factors responsible for this include the variability of study design, the duration and accuracy of follow-up, mixed indications for surgery and lack of uniformity of operative technique. Assessment of fibrin glue should include MRI after treatment which can identify any residual sepsis. This has been found to correlate to early failure or delayed recurrence [202,218]. Thus Buchanan et al. [212] treated 22 patients with fibrin glue with initial success in 77%. By 16 months, however, only three (14%) remained healed. Failure was predicted by evidence of persistent sepsis in the track on a posttreatment MRI scan. Thus any study of fibrin glue (or the fibrin plug; see below) should include MRI as part of the assessment.

2.3) Royal College of Obstetricians and Gynecologists⁽⁷⁾

ไม่แนะนำให้ใช้ fibrin sealant เป็นประจำใน second-trimester oligohydramnios ที่เกิดจากเยื่อหุ้มแตก เนื่องจากคลอดก่อนกำหนด (level of evidence III, B)

Preterm prelabour rupture of membranes

8. Use of fibrin glue

What is the role of fibrin glue in the sealing of chorioamniotic membranes to prevent pulmonary hypoplasia?

Fibrin sealants are not recommended as routine treatment for second-trimester oligohydramnios caused by PPROM.

There are publications involving small patient numbers with midtrimester PPROM describing transvaginal or transabdominal injection of fibrin into the amniotic fluid with the aim of sealing the membranes.^{57–59} The 'amniopatch' resulted in an increase in amniotic fluid volume in some cases.

Larger studies are needed when examining neonatal outcome before this treatment can be recommended as routine practice.

Level of evidence III, B

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

B Requires the availability of well controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)

2.4) Whiteford, et al., 2005⁽³⁾

ข้อแนะนำในการรักษา anal fistula พบว่า anal fistula ไม่ว่าจะชนิด simple หรือ complex อาจใช้ track debridement และ fibrin glue injection ในการรักษาได้ (level of evidence IV, B)

III - Well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies

B - Evidence of Type II, III, or IV and generally consistent findings

Treatment of a Simple Fistula-in-Ano

2. *Simple anal fistulas may be treated with track debridement and fibrin glue injection. Level of Evidence:*

Class IV; Grade of Recommendation: B. Fibrin glue is an easy and repeatable treatment for fistula-in-ano with relatively few side effects and little to no risk of fecal incontinence. Successful healing rates from 60 to 70 percent can be achieved.²⁰⁻²⁶

Risk factors for failure include Crohn's disease, rectovaginal fistula, human immunodeficiency virus, and short fistula length.

Treatment of a Complex Fistula-in-Ano

1. *Guideline: Complex anal fistulas may be treated with debridement and fibrin glue injection. Level of*

Evidence: IV; Grade: B. As with simple fistula-in-ano, fibrin glue is an easy, repeatable treatment for a complex fistula-in-ano. Using this technique, healing rates from 14 to 60 percent have been achieved in small studies.²⁰⁻²² Incontinence rates, however, although theoretically low, have not generally been reported.

2.5) Better Blood Transfusion Network 2010⁽⁴⁾

กรณีที่ใช้ fibrin glue ได้อย่างมีประสิทธิภาพ

- Cardiac surgery
- Vascular surgery
- Tonsillectomy

กรณีที่สามารถใช้ fibrin glue ได้

- Orthopaedic surgery
- Lung resection ในผู้ป่วยบางราย

Topical surgical sealants factsheet

4. Research Based Evidence of Uses in Specific Surgical Specialties

- Autologous platelet gel and fibrin sealants may be effective in reducing peri-operative blood loss in orthopaedic surgery¹
- Routine usage of surgical adhesives and glues in patients having lung resections cannot yet be recommended however they may be useful in selected situations²
- Fibrin sealants are safe and effective for use as an adjunct to haemostasis in patients undergoing cardiac surgery³
- Fibrin sealants are mostly used in vascular surgery to control anastigmatic bleeding⁴
- In tonsillectomies fibrin sealants/glues have been shown to be effective both as a haemostatic agent but also in reducing pain following a tonsillectomy⁵

A paper from 2006 evaluating the differences between fibrin sealants is referenced⁶

5. References

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5. Vaiman M, Eviatar E, Shlamkovich N, Segal S. Effect of modern fibrin glue on bleeding after tonsillectomy and adenoidectomy *Annals of Otolaryngology, Rhinology & Laryngology* 112(5) 410-4.

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2.6) Gibson, et al., 2004⁽⁵⁾

Fibrin glue มีประสิทธิภาพในการลดเลือดออกจากแนวเย็บแผลผ่าตัด ในผู้ป่วยที่ผ่าตัดหัวใจ

Transfusion guidelines for neonates and older children

6. Transfusion support for cardiac surgery, ECMO and acquired coagulopathies

6.1.5. Coagulation components for cardiac surgery

Topical thrombin/fibrin glues are effective in reducing suture line bleeding. If products incorporating aprotinin are used then it should be borne in mind that these patients may mount an immune response similar to those receiving intravenous aprotinin, which may cause reactions at the time of subsequent exposure.

2.7) British Society for Haematology⁽¹¹⁾

ยาหรือวิธีที่เกี่ยวข้องในการรักษา สำหรับการจัดการในผู้ป่วยที่ได้รับต้านการแข็งตัวของเลือดและจำเป็นต้องได้รับการผ่าตัดทางทันตกรรม แนะนำให้ใช้ oxidised cellulose (Surgicel) (grade B, level IIb) หรือ tranexamic acid mouthwashes (grade A, level Ib)

CLASSIFICATION OF EVIDENCE LEVELS (AHCPR)

1. a. Evidence obtained from meta-analysis of randomised controlled trials.
b. Evidence obtained from at least one randomised controlled trial
2. a. Evidence obtained from at least one well-designed controlled study without randomisation.
b. Evidence obtained from at least one other type of well-designed quasi-experimental study. *
3. Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
4. Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

STRENGTH OF RECOMMENDATION:

A. Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing specific recommendation. (*Evidence levels Ia, Ib*).

B. Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (*Evidence levels IIa, IIb, III*).

C. Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (*Evidence level IV*).

Guidelines for the management of patients on oral anticoagulants requiring dental surgery

Summary of key recommendations

1. The risk of significant bleeding in patients on oral anticoagulants and with a stable INR in the therapeutic range 2-4 (i.e. <4) is very small and the risk of thrombosis may be increased in patients in whom oral anticoagulants are temporarily discontinued. Oral anticoagulants should not be discontinued in the majority of patients requiring out-patient dental surgery including dental extraction (grade A level Ib).
2. Recommendations: For patients stably anticoagulated on warfarin (INR 2-4) and who are prescribed a single dose of antibiotics as prophylaxis against endocarditis, there is no necessity to alter their anticoagulant regimen (grade C, level IV).
3. The risk of bleeding may be minimised by:
 - a. The use of oxidised cellulose (Surgicel) or collagen sponges and sutures (grade B, level IIb).
 - b. 5% tranexamic acid mouthwashes used four times a day for 2 days (grade A, level Ib). Tranexamic acid is not readily available in most primary care dental practices.
4. For patients who are stably anticoagulated on warfarin, a check INR is recommended 72 hours prior to dental surgery (grade A, level Ib)
5. Patients taking warfarin should not be prescribed non-selective NSAIDs and COX-2 inhibitors as analgesia following dental surgery (grade B, level III).

...

6. Local haemostatic measures.

...

Blinder et al (13) in a study of 150 patients undergoing dental extractions and without interruption of their anticoagulants, randomised patients to one of three groups: group 1 (50 patients mean INR 2.38) who were treated with gelatin sponges and sutures; group 2 (50 patients mean INR 2.7) who were treated with gelatin sponges sutures and tranexamic acid mouthwashes and group 3 (50 patients mean INR 2.19) who received fibrin glue, gelatin sponges and sutures. 13 patients (8.6%) developed post-operative bleeding: 3 in group 1, 6 in group 2 and 4 in group 3. The use of gelatin sponges and sutures provided adequate haemostasis for dental extraction without interruption of anticoagulants. Tranexamic acid mouthwashes or fibrin glue offered no benefit over resorbable gelatin sponges plus suturing.

...

In a study of 26 patients undergoing dental extraction with an INR of 2.0-4.2, the sockets were packed with a resorbable oxycellulose dressing ('Surgicel') and sutured with a resorbable suture [20]. A second group of patients (INR 2.1-4.1) received local packing of the sockets with a fibrin adhesive ('Beriplast'). Only 1 patient in the second group had significant postoperative haemorrhage. The authors concluded that fibrin adhesive is as effective as oxycellulose dressing in preventing postextraction haemorrhage in patients receiving oral anticoagulants.

...

A further study randomised 49 patients (undergoing 152 dental extractions) to either tranexamic acid (4.8% four times a day for 7 days) (26 patients: mean INR 3.0 range 2.3-4.0) or autologous fibrin glue (23 patients: mean INR 3.1 range 2.1-4.0) (19). 2 cases of post-operative bleeding were noted in the group that received autologous fibrin glue but both cases had elevated INRs (5.9/7.9) at the time of surgery. Tranexamic acid was found to be a more cost-effective alternative.

...

3) BMJ clinical evidence

ไม่พบ clinical practice guidelines ที่เกี่ยวข้อง อย่างไรก็ตาม พบ systematic review 1 ผลลัพธ์ ซึ่งผู้ประพันธ์ ได้สรุปไว้ว่า การให้ fibrin glue ไม่ได้มีประโยชน์มากกว่าการไม่ใช้ fibrin glue ในผู้ป่วยมะเร็งตับอ่อนหรือตับอ่อน

อักเสบที่รับการผ่าตัด⁽⁸⁾ (low-quality evidence: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.)

QUESTION What are the effects of interventions to prevent pancreatic leak after pancreaticoduodenectomy in people with pancreatic cancer considered suitable for complete tumour resection?

OPTION FIBRIN GLUE.

Symptom severity

Compared with no glue Fibrin glue may be no more effective at preventing pancreatic leak in people who have had pancreatic surgery for neoplasms or inflammatory disease (low-quality evidence).

For **GRADE evaluation of interventions for pancreatic cancer**, see table, p 33 .

Benefits: We found one RCT comparing fibrin glue versus no glue after a variety of types of pancreatic surgery for pancreatic neoplasms or inflammatory disease. [20] It found no significant difference in pancreatic fistula between fibrin glue and no glue (see table 8, p 22).

Harms: The RCT reported that "no complication could be directly related to the [fibrin] glue". [20] As fibrin glue aims to reduce adverse effects of pancreaticoduodenectomy, all other outcomes are discussed in the benefits section above.

Comment: Clinical guide:

The mortality associated with pancreaticoduodenectomy is less than 5% in high-volume specialist centres. However, morbidity ranges from 30% to 60%. [18] One of the major complications and causes of death after pancreaticoduodenectomy is leakage from the residual pancreatic stump. As a result, numerous attempts, both pharmacological and technical, have been made to prevent pancreatic stump-related complications.

4) Pubmed

ใช้คำสำคัญ ("Fibrin Tissue Adhesive"[Mesh]) AND "Practice Guideline" [Publication Type] ไม่พบข้อมูล

วิธีการสืบค้นข้อมูลจาก Pubmed

Fibrin Tissue Adhesive

An autologous or commercial tissue adhesive containing FIBRINOGEN and THROMBIN. The commercial product is a two component system from human plasma that contains more than fibrinogen and thrombin. The first component contains highly concentrated fibrinogen, FACTOR VIII, fibronectin, and traces of other plasma proteins. The second component contains thrombin, calcium chloride, and antifibrinolytic agents such as APROTININ. Mixing of the two components promotes BLOOD CLOTTING and the formation and cross-linking of fibrin. The tissue adhesive is used for tissue sealing, HEMOSTASIS, and WOUND HEALING.

Entry Terms:

- Adhesive, Fibrin Tissue
- Tissue Adhesive, Fibrin
- Fibrin Adhesive
- Adhesive, Fibrin
- **Fibrin Glue**
- Glue, Fibrin
- Fibrinogen Adhesive
- Adhesive, Fibrinogen
- Fibrin Sealant System
- Sealant System, Fibrin
- Autologous **Fibrin Tissue Adhesive**
- **Fibrin Sealant**
- Sealant, Fibrin
- Crosseal
- Fibrin Klebe System Immuno
- Transglutine
- Fibrin Sealant, Human
- Human Fibrin Sealant

- Sealant, Human Fibrin
- Tisseel
- Tissel
- Tissucol
- Beriplast
- Fibrin Seal
- Seal, Fibrin

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