B. Braun Closure Technologies

Clinical Evidence for Lyostypt®

Biosurgicals

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SHARING EXPERTISE

Clinical Evidence for Lyostypt®

Rationale

Hemostasis in peripheral vascular surgery is made more difficult by the need for direct arterial and arterial graft suturing as well as by systemic anticoagulation to prevent thrombosis during periods of vascular occlusion. Polytetrafluorethylene (PTFE) is one of the most frequently used graft materials for vascular replacement or bypass in the case when no autologous venous grafts are available (1). However, the insufficient elasticity of PTFE and its porosity promote the development of suture hole bleeding (2, 3) which can cause considerable loss of blood and prolongation of operations due to additional suturing with danger of iatrogenic stenosis (2).

There are several medical risk factors that potentially affect bleeding time and hemostasis, such as hypertension, chronic liver disease, or renal failure (4). The problem of bleeding from suture holes remains a serious drawback to the use of PTFE. Suture line bleeding in arterial surgery is primarily controlled with a precise surgical technique, including the use of fine suture material and needles (5). To facilitate the control of residual bleeding after suturing of arterial operative sites, various topical hemostatic aids are in use. Traditionally, the problem of suture hole bleeding is managed by compression with surgical swabs and reversal heparin. Other attempts to control suture hole bleeding have also been used with various success, such as ethylcyanoacyrlate glue (6), different forms of collagen (7-10), oxidized cellulose (9, 11), gelatine sponge (9), or fibrin (12, 13). Another approach to topical hemostasis is the use of an agent that enhances or accelerates the formation of an autogenous thrombus, such as topical thrombin, which can be used in conjunction with scaffolding-type agents (14, 15). Preclinical data strongly suggest that hemostats made of collagen have a stronger hemostatic effect than hemostats made of oxidized cellulose (9, 16, 17, 18, 19, 20); (figure 1). In vitro experiments also showed that the cell growth was not affected by collagen in contrast to oxidized cellulose (figure 2).

In general, the ideal hemostat should be easy to use with good risk-benefit and cost-benefit ratios. Such an agent should be easily applied in a controlled fashion, highly predictable in creating hemostasis, non-toxic and must not have an adverse affect on anastomotic patency. Furthermore, increased anastomotic strength would also be beneficial.

Rationale

Fig.1: Bleeding time and blood loss from a standard wound at the liver edge of healthy rats after application of different hemostatic agents (33).

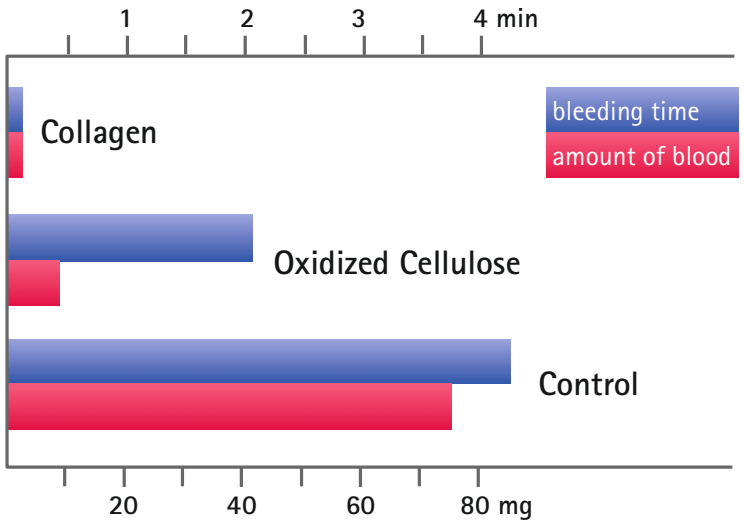
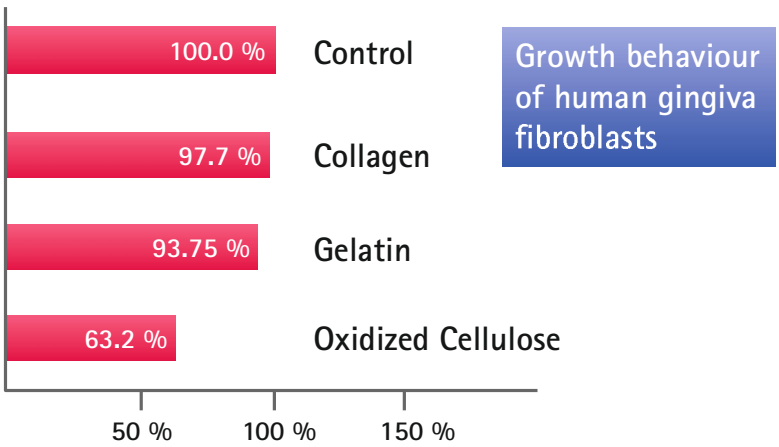


Fig. 2: Cell growth of human fibroblasts on various hemostatic products (24).



Lyostypt® is an absorbable wet-stable collagen compress made of collagen fibrils of bovine origin. Collagen leads to thrombocyte adhesion and to activation of coagulation factor XIII. The structure of Lyostypt® offers a great framework for adhesion of platelets and thus provides an additional impetus to clotting. Lyostypt® achieves hemostasis very swiftly, it can be removed easily, it can be applied endoscopically, and it can be combined with fibrin glue and antibiotics (16, 21).
Collagen hemostats showed low tissue reaction, fast resorption and good biocompatibility (15). Lyostypt® is γ-sterilized and available in rectangular fleeces of various sizes. The Lyostypt® fleece has been designed to remain, in general, at the site of application, but can be removed after bleeding has stopped. Absorption takes place within 3 weeks as a result of phagocytosis and enzymatic degradation. The rate of absorption also depends on the amount of Lyostypt®.

Lyostypt® collagen hemostatic fleece is indicated for capillary bleedings, parenchymal haemorrhages, oozing wound haemorrhages, for the local hemostasis in hemodialysis and as a supportive method for other techniques in hemostasis.

Lyostypt® should not be applied to infected areas. It should not be employed in connection with cemented endoprostheses since this would reduce the adhesive capacity of the bone cement. It should not be used in patients with known hypersensitivity to proteins of bovine origin.

Hemostats of collagen and oxidized cellulose origin have been in clinical use for many years (7-11), but no direct clinical comparison of their hemostatic performance has been published so far. Therefore, a randomized clinical trial evaluating the hemostatic effect of Lyostypt® versus Surgicel® (Johnson & Johnson) in suture hole bleeding after arterial bypass anastomoses was conducted by B. Braun (22, 23).

Clinical Evidence

In vitro analysis of different hemostatic devices.

The aim of the investigation performed by **Wachol-Drewek et al. (16)** was to compare the in vitro drug delivery of sponges containing gentamicin with that of collagen implants of various structures immersed in different antibiotic solutions.

Collagen derived from bovine skin was suspended in water for injections containing gentamicin at the required concentration and homogenized. Two collagen implants of various structures and a gelatine sponge were compared with this material. Lyostypt®, a collagen sponge consisting of absorbable native collagen fibrils of bovine origin, which is normally used for hemostasis, was investigated. Furthermore Osteovit®, a collagen sponge consisting of porous collagen structure of bovine origin whose antigens, fats, minerals, enzymes and non-collagenous components have been removed was used. The third product used was the gelatine sponge Gelita®, a hemostatic agent made of pure gelatine, whose rapid hemostatic effect is due to the great uptake ability of the gelatine sponge and the specific effect of gelatine. Any collagen-like structure is absent from this gelatine sponge. To stabilize the sponge structure, the material is chemically cross-linked. This method has the result that the gelatine sponge has the lowest density and the highest liquid absorption capacity.
The two different collagen implants (Lyostypt®, Osteovit®) and the gelatine sponge (Gelita®) were placed in five different antibiotic solutions until complete saturation occurred. The following antibiotics were chosen: gentamicin sulphate, cefotaxim, fusidic acid, clindamycin, and vancomycin, respectively.

The antibiotic delivery by the collagen implants and the lyophilized sponge containing gentamicin is completed after a maximum of four days. The amount of antibiotic delivered depends upon the type of implant and the antibiotic agent. After only 24 hours 90 % of the drug has diffused out of the implants. All antibiotic agents have been released completely by all implants by four days. In the case of fusidic acid and vancomycin antibiotic release is only detectable for two days after the start.

The authors conclude that an implant that has a protective effect against wound infections over a required period of 24 - 48 hours, all materials described are suitable.

Heidemann (24) analysed the biological tolerance of three different hemostats (collagen fleece, oxidized cellulose and gelatine sponge).
These products were tested on cultured human gingiva fibroblasts. The hemostats were mixed with the culture medium in different concentration and incubated on the cells for five days, thereafter the cells were fixed and analysed.

None of these products induced the proliferation of the cells. The use of oxidized cellulose resulted in reduced proliferation of the cells in comparison of untreated cells and cells which have been treated with collagen or gelatine, respectively (figure 2). The treatment with oxidized cellulose induced already at low concentration a modification of the cell shape and the mutations of the nucleus. Alteration in cell morphology was observed with gelatine dependent on the concentration. In contrast, only a few modified cells occurred after treatment with collagen and only in the highest concentrations.

The results indicate that materials with a good biocompatibility should be chosen to stop different kinds of bleedings and that hemostats based on microfibrillar collagen are very suitable because they fulfill this criterion.

Animal studies comparing the efficacy of hemostats composed of microfibrillar collagen with other hemostatic products (table 1).

Takács et al. (25) compared the hemostatic effect of different agents (Sangustop®, Tachosil®, Surgicel®) in liver surgery. A standardized liver resection was performed in pigs and the bleeding was stopped by the application of the different products. The time to hemostasis was measured. Tissue examples were taken from the liver and histologically analysed after 21 days.

In total 60 pigs were treated; 20 with each device. The bleeding time for Sangustop®, Tachosil® and Surgicel® were 140 ±88 sec., 243 ±140 sec. ($p= 0.005$ vs Sangustop®), and 352 ±70 sec. ($p< 0.001$ vs Sangustop®) respectively. In the Sangustop® group only one device layer was needed in 14 of 20 pigs to stop the bleeding. In contrast, pigs treated with Tachosil® or Surgicel® required two or three device layers to achieve hemostasis. The histological analysis showed that the treatment with Surgicel® led to more fibrosis in comparison to Sangustop®. Significantly more inflammation was seen with Tachosil® compared to Sangustop® or Surgicel®.
The data showed that the hemostatic effect of Sangustop® (collagen) is significantly better than that of Surgicel® (oxidized cellulose) and Tachosil® (collagen coated with fibrin and thrombin).

Haußmann et al. (26) evaluated the hemostatic effect of 4 different products used for local hemostasis in liver surgery.

In healthy and with CCl_4 venomed rats a standardized liver resection was performed. The blood loss and the time to hemostasis was analysed, after the application of various products. As hemostatic agent, Clauden powder, collagen-powder, oxidized cellulose, and thrombin were used. The application of all products resulted in a fast hemostasis and a low blood loss. Hemostasis was achieved most-rapidely after application of collagen.

Thus, it was concluded that the collagen based product was the most effective agent for hemostasis.

The purpose of the study performed by **Ünlü et al. (27)** was to investigate the use of fibrin glue, gelatine and collagen for the reduction of suture hole bleeding in rabbit vascular grafts in comparison to untreated controls.

In total, 28 rabbits were operated by one surgeon. Midline incision in the fascia was performed. Blood flow to the aorta was interrupted using surgical clamps. A 1 cm incision was made in the abdominal aortic wall of each animal. This incision was covered with a polytetrafluoroethylene patch sutured with polypropylene. Thereafter, the clamps were released to ensure blood spilled from the suture holes. Fibrin glue (FG), collagen (C) and gelatine-resorcinol formaldehyde (CRF) were applied to cover the suture holes in the different groups but nothing was used in the control group. Time to hemostasis and blood loss were measured and compared in the different groups.

The mean blood loss was significantly lower in the Fibrin, Gelatine and Collagen treated group when compared with the control group. The volume of blood lost in the Fibrin group was significantly lower than that of the Collagen group and gelatine group. Fibrin reduced significantly the time to hemostasis and the volume of blood loss compared to other groups.

Clinical Evidence

Ereth et al. (28) evaluated the safety and efficacy of commonly used agents for hemostasis in neurosurgical techniques.

A brain defect was performed in 228 rats and microfibrillar collagen, oxidized cellulose, gelatine matrix and no treatment were tested for their hemostatic effect. Time to hemostasis was measured. The foreign reaction was investigated in the animals after scarification at different time points up to 28 days. All hemostats induced hemostasis within one minute and therefore, performed better than the untreated control. Residual material of gelatine, oxidized collagen and microfibrillar collagen was seen till 14 days after surgery.
The authors concluded that all hemostatic agents were efficient in controlling bleeding in the majority of standardized neurological lesions.

In an in vitro test six common hemostatic agents were analysed by **Wagner et al. (18)** for their utility.
Three different types of collagen sponges, microfibrillar collagen, gelatine foam and oxidized cellulose were studied for their ability to mediate platelet aggregation, deposition and activation and to initiate gross clot formation.
Agents composed of microfibrillar collagen were the most effective inducers of platelet aggregation and induced more rapidly clot formation than the other used products. The authors presented an overall activity ranking of the materials used: collagen foam > gelatine > oxidized regenerated cellulose.

Table 1: Animal studies comparing collagen based hemostats versus other hemostatic agents.

Study	Year	Animal
Takacs et al.	2010	Pigs
Haußmann et al.	1974	Rat
Ünlü et al.	2002	Rabbit
Ereth et al.	2008	Rat
Wagner et al.	1996	ND
Voormolen et al.	1987	Rabbit
Rybock et al.	1977	Canine

Voormolen et al. (19) conducted an experimental study in rabbits in which cerebral lesions were made and filled with oxidized regenerated cellulose and collagen fleece. Bleeding time was measured in 26 animals. Results showed statistically significant lower bleeding times for microfibrillar collagen with quicker resorption rate than for traditional oxidized regenerated cellulose. Histopathologically, collagen fleece did not induce more tissue reaction than oxidized regenerated cellulose. In contrast, to oxidized regenerated cellulose, collagen fleece did not induce the formation of polynucleated giant cells.
They concluded that collagen fleece established faster hemostasis and that it was resorbed faster than oxidized regenerated cellulose. Collagen fleece is therefore, a suitable hemostatic agent for the use in neurosurgical procedures.

Rybock and Long (29) compared the hemostatic properties of microfibrillar collagen versus a gelatinefoam in suction evacuation lesions of the canine cortex. Microfibrillar collagen was found to be faster and more effective in achieving hemostasis than gelatine foam. Histological analysis of the lesions at 2, 4 and 6 months postoperatively showed no significant difference in the amount or type of tissue reaction to the two agents.

Product	Hemostasis	Blood Loss	Handling	Resorption	Biocompatibility
Sangustop® Tachosil® Surgicel®	Sangustop® > Tachosil® > Surgicel®	NT	NT	NT	Sangustop® > Surgicel® > Tachosil®
Collagen Tabotamp® Topostatin®	Collagen > Tabotamp® and Topostatin®	Collagen > Tabotamp® and Topostatin®	NT	NT	NT
Tisseel® Cardial® Colgen®	Tisseel® > Colgen® and Cardial® signif.	Tisseel® > Colgen® > Cardial® signif.	NT	NT	NT
Avitene® Surgicel® Floseal®	Avitene® and Surgicel® and Floseal® < 1 min	NT	NT	Avitene® = Surgicel®	NT
Avitene® Gelfoam® Surgicel®	Avitene® > Gelfoam® > Surgicel®	NT	NT	NT	NT
Novacol® Surgicel®	Novacol® > Surgicel®	NT	NT	Novacol® > Surgicel®	Novacol® > Surgicel®
Avitene® Gelfoam®	Avitene® > Gelfoam®	NT	NT	NT	Avitene® = Gelfoam®

Legend: NT: Not tested, ND: No details, > better or faster, = equal, < smaller

Clinical Evidence

Clinical trials comparing the hemostatic effect of collagen based hemostat with various products used for hemostasis.

Sirlak et al. (30) compared in their study the efficacy of a microfibrillar collagen hemostat and oxidized cellulose on bleeding in cardiac operations with a predicted high risk of bleeding.

In total, 71 patients undergoing an elective high risk bleeding surgery were randomized to receive either a microfibrillar collagen hemostat or oxidized cellulose at the anastomosis or atriotomies. The drainage of the mediastinal blood was measured hourly.

There was no significant difference with respect to the surgical procedures and pre- and postoperative hematologic profile between the two groups. The volume of chest tube drainage in the first 24 hours was 373 ±143 ml in the collagen group and 571 ±144 ml in the cellulose group (p= 0.01). Total postoperative chest tube drainage was 423 ±154 ml in the collagen group and 677 ±128 ml in the cellulose group (p= 0.01). Blood loss in the first 3 postoperative hours was significantly less in the collagen group (132 ±41 ml vs 228 ±57 ml, p= 0,001). In the following 3 hour intervals this significant difference persisted (67 ±24 vs 121 ±49 ml, p= 0.001). In the remaining 3 hour intervals the blood loss in the collagen group was lower compared with the cellulose group. Six patients who were allocated to microfibrillar collagen hemostat treatment received 28 units of packed red blood cells, whereas in the cellulose group 20 patients received 120 units. Blood coagulation was further improved by the administration of a total of 46 units of fresh frozen plasma in 8 patients of the cellulose group and

Table 2: Trials comparing Collagen based hemostats versus other agents used for hemostasis.

Study	Year	Patient
Sirlak et al.	2003	71
Schonauer et al.	2004	NA

only 8 units of fresh frozen plasma in 2 patients of the collagen group. The cost of topical hemostatic agent treatment and the transfusion requirement were significantly lower in patients treated with microfibrillar collagen hemostat compared with the patients receiving oxidized cellulose ($152 ±$22 vs $202 ±$29, p< 0.001).

The easy application, low cost and significant blood loss reduction effect of microfibrillar collagen powder renders this agent attractive for cardiac operations associated with high risk of bleeding.

Schonauer et al. (15) reviewed several clinical and animal studies using different common topical hemostats with regard to their properties, mechanisms of action and complication rate.

In one of the reviewed studies rabbits received cerebral lesions which were filled with oxidized regenerated cellulose or collagen fleece. Results showed lower bleeding times for microfibrillar collagen, with quicker resorption rate than for traditional oxidized regenerated cellulose. They conclude that a collagen fleece established faster hemostasis than oxidized cellulose and that it was resorbed faster than oxidized cellulose.

Another reported study compared the hemostatic properties of microfibrillar collagen versus Gelfoam® in suction evacuation lesions of canine cortex. Microfibrillar collagen was found to be faster and more effective than Gelfoam® in achieving hemostasis. They concluded that microfibrillar collagen appeared to be as good as, or better than Gelfoam® because it is absorbable, doesn´t lead to major tissue reaction, doesn´t swell significantly, and is quickly effective even in the presence of coagulation disorders.

In another study six commonly used topical hemostatic agents were compared in terms of their ability to mediate platelet aggregation, deposition and activation in a series of in vitro tests. The overall activity ranking of the materials used were: collagen > Gelfoam® > oxidized cellulose.

Furthermore, microfibrillar collagen was shown to be the best overall hemostatic agent in microvascular surgery in another study.

Product	Hemostasis	Blood Loss	Handling	Resorption	Complication
Colgel® Surgicel®	Colgel® > Surgicel®	132 ml 228 ml p= 0.001	Colgel® > Surgicel®	NT	NT
Avitene® Gelfoam® Surgicel®	Avitene® > Gelfoam® > Surgicel®	NT	NT	Avitene® > Surgicel®	No tissue reaction

Legend: NT: Not tested, NA: Not available, > better or faster

Clinical Evidence

Evaluation of the hemostatic effect of Lyostypt® versus other hemostatic agents.

COBBANA Study [NCT00837954]
The COBBANA study, a randomized controlled, prospective, patient-blinded trial, evaluated the hemostatic effect of Lyostypt® (microfibrillar collagen) versus Surgicel® (oxidized regenerated cellulose) in arterial bypass anastomoses. It was designed to demonstrate superiority of Lyostypt® to Surgicel® for hemostasis (22).

Thirty-two patients undergoing an elective peripheral vascular reconstruction due to peripheral vascular disease were included. Suture hole bleeding occurring at the arterial bypass anastomoses using a PTFE prosthesis were stopped by the application of Lyostypt® and / or Surgicel®. The proximal anastomosis was randomized intraoperatively. The patients were allocated into 4 different groups. Group 1: Lyostypt® distal / Surgicel® proximal, group 2: Lyostypt® proximal / Surgicel® distal, group 3: Surgicel® distal and proximal and group 4: Lyostypt® distal and proximal. Primary endpoint of the study was time to hemostasis. Secondary endpoints were the number of intraoperatively used hemostatic devices, postoperative mortality within 30 days as well as the intraoperative efficacy rating of the two devices evaluated by the surgeon. As a safety secondary parameter the local and general complication rate occurring till 30 days after surgery were also analysed.

The data showed that Lyostypt® (L) significantly reduce the time to hemostasis in comparison to Surgicel® (S), ($p< 0.0001$). There was a reduction in the bleeding time by factor three when Lyostypt® was used in comparison to Surgicel® (124.7 sec versus 416.3 sec). In the S-L and L-S groups 11 patients had bleeding times > 5 minutes on the Surgicel® anastomosis only, whereas no patient experienced a bleeding time between 5 and 10 minutes on the Lyostypt® anastomosis ($p= 0.0004$). In the S-L and L-S groups 5 patients had bleeding times > 10 minutes on the Surgicel® anastomosis only, whereas no patient experienced such a long bleeding time on the Lyostypt® anastomosis. In the S-S group there were two patients with three bleeding times longer than 10 minutes and none in the L-L group. In the S-S group there were seven out of eight patients with bleeding times longer than 5 minutes, but none in the L-L group ($p= 0.0004$). In total there were 7 failure (bleeding times longer than 10 min) observed than Surgicel® was used to stop suture hole bleedings. In contrast, no failure was seen with Lyostypt®. All 32 anastomotic bleedings treated with Lyostypt® could be stopped by the application of only one device. In contrast, only 11 anastomoses treated with Surgicel®

could be stopped after the application of one device, there were in addition 21 cases which need the application of a second Surgicel® device. Adhesion to the anastomosis and surgical handling was significantly better rated for Lyostypt® than for Surgicel®. Thirty-one of 32 Lyostypt® device immediately adhere to the anastomosis and only one after a short while. Twelve of 32 Surgicel® devices adhere immediately to the anastomosis, 3 devices after a short while and 3 Surgicel® devices needed a repositioning. Twenty-nine of 32 Lyostypt® devices were easy to place and needed no repositioning, this was only seen with 21 of 32 Surgicel® devices. Three of 32 Lyostypt® devices were easy to place and needed a repositioning and this was also possible; in contrast this happened with 8 of 32 Surgicel® devices. The rating: easy placement, repositioning needed but not possible, was recorded 3 times but only for Surgicel® devices. Complication such as wound healing disorders and wound infections were not recorded.

The study showed that the hemostat Lyostypt® stopped suture hole bleedings significantly faster in comparison to Surgicel® after arterial bypass anastomosis. Handling parameters and adhesion was also significantly better rated for Lyostypt® than for the Surgicel® (23).

Engelhardt et al. (17) evaluated the efficacy and the biocompatibility of two collagen-based hemostats in a prospective randomized study. An usual agent Collastypt® and a fluid-stabilized agent Lyostypt® were compared.

The difference between the two products were that Lyostypt® had a better mechanical stability in a wet environment, that it showed a reduced adhesion to instruments and that it has a lower mass per unit area in comparison to Collastypt®. The hemostatic effect (bleeding time and blood loss) of the two products were analysed after liver trauma in 45 rats. Untreated liver wounds were used as a control. The biocompatibility was investigated in 48 rats, in which both hemostatic agents were implanted subcutaneously for different time points.

The results showed that in the untreated control the time to hemostasis was 388 sec, whereas the use of Collastypt® significantly reduced it to 78 sec. The application of Lyostypt® was efficient with 47 sec ($p < 0.002$). The blood loss was 1091 mg in the untreated control and only 712 mg in the Collastypt® group (the devices were weighted after the experiment). Liver wounds treated with Lyostypt® showed a significantly reduced blood loss of 344 mg. Histological analysis indicated a very good biocompatibility of both agents. No foreign body reaction or cellular activity was seen after the implantation of the two products. In comparison to Collastypt® a delayed absorption was seen with Lyostypt® due to its higher mechanical stability. Residues of Lyostypt® were absorbed after 14 days.

The authors concluded that Lyostypt® has a very good biocompatibility and that it is superior to Collastypt® in respect to achieving hemostasis. Collagen based hemostats with a low mass and a delayed absorption should be preferred. Lyostypt® led to a significantly reduced bleeding time and blood loss.

Krüger et al. (31) performed a prospective, randomized, controlled trial to compare the hemostatic effect of Lyostypt® versus a gelatine foam in neurosurgical operations.

One hundred patients were allocated to each group. The following parameters were investigated: application, adhesion to instruments and gloves, adhesion to the bloody surface, the hemostatic effect and the stability of the products in a wet environment. Furthermore, postoperative wound infection, fever, wound secretion, allergic reaction, and epidural adhesion were analysed.

In 167 cases the hemostats were used epidural and peridural, in 27 cases the application of the products took place on the brain parenchyma and in 6 cases the hemostatic agents were applied in the paranasal sinuses. The analysis demonstrated that the hemostatic effect of Lyostypt® was significantly better as that of the Gelfoam®. No difference was seen between the two products with respect to adhesion to bloody surface, wet stability, modelling and application. Attachment to the instruments appeared more often in the Lyostypt® group but this was due to adaptation of the use of a new product. In the course of time the rating of the surgeon with regard to the adhesion to instruments became much better. Postoperatively one infection, two wound seroma and two liquor circulation defects were present in the Gelfoam® group but no significant difference was noted. In patients treated with Lyostypt® one liquor circulation defect was observed. None of these events were in causal connection with the applied product. No allergenic reaction, tissue adhesion, postoperative bleedings or epileptic reactions were noticed.

Clinical Evidence

These study showed that Lyostypt® is very efficient in hemostasis. Lyostypt® stopped bleedings significantly faster than Gelfoam®.

The randomized controlled clinical multi-centre trial performed by **Pingsmann et al. (32)** was conducted to demonstrate the safety and equivalence in the clinical efficacy of an absorbable and degradable sealant of bone surface (Bone Seal®) to that of Lyostypt®. The equivalence in efficacy and safety was shown for topical hemostasis after iliac crest bone graft harvesting.

In total 112 eligible patients were randomized at seven orthopaedic and trauma surgery centres to receive one of the two products. Safety was determined by a wound healing score and the incidence of adverse clinical effects. Furthermore, efficacy was studied using a compound bleeding score, handling properties and the adhesion to the bone surface were also evaluated. The mean follow-up period was 15 - 16 days.

Table 3: Trials comparing Lyostypt® versus other hemostatic agents.

Study	Year	Patients
COBBANA	2012	peripheral, arterial anastomosis N = 64
Engelhardt et al.	1989	45 liver trauma
Krüger et al.	1992	Neurosurgical operations N = 200
Pingsmann et al.	2005	orthopaedic, trauma surgery N = 112
Heidemann	1989	

The results showed equivalence of the primary efficacy parameter bleeding score for both groups. Bone Seal® had significantly less favourable manageability score, meaning that it was significantly more inconvenient in handling than the collagen fleece Lyostypt®. Usage of the collagen fleece resulted in significantly higher application scores. Wound healing and the incidence of adverse events were comparable in both groups. There was no difference in the hemostatic effect of the two applied products.

In summary Bone Seal® was as effective in topical hemostasis as the collagen fleece Lyostypt® and also clinically safe. Furthermore, Bone Seal® showed better adhesion to the donor site, but Lyostypt® was easier to handle.

Product	Hemostasis	Blood Loss	Handling	Complication	Biocompatibility
Lyostypt® Surgicel®	124.7 sec 416.3 sec p< 0.0001	NT	Lyostypt® > Surgicel®	None	NT
Lyostypt® Collastypt® Control	47 sec. 78 sec. 388 sec. p< 0.002	344 mg 712 mg 1091 mg	NT	No foreign body reaction	Very good Lyostypt® = Collastypt®
Lyostypt® (100) Gelfoam® (100)	Lyostypt® > Gelfoam® signif.	NT	Lyostypt® = Gelfoam®	Lyostypt®: 1x Gelfoam®: 5x	No allergenic reaction
Lyostypt® Bone Seal®	Lyostypt® = Bone Seal®	NT	Lyostypt® > Bone Seal®	Lyostypt® = Bone Seal®	NT
Lyostypt® Gelita® Tabotamp®	NT	NT	NT	NT	Lyostypt® > Gelita® > Tabotamp®

Legend: NT: Not tested, = equal, > better

Key Messages

Lyostypt® is a wet stable collagen hemostat composed of native collagen fibrils of bovine origin and offers the following advantages:

- Lyostypt® stops suture hole bleedings significantly faster than Surgicel® at the anastomoses of peripheral vascular femoro-popliteal prosthesis. Adhesion and surgical handling rating was significantly better than that of Surgicel® (23)
- Effective and fast hemostasis (17, 18, 20, 26, 29-32)
- Faster hemostasis and faster absorption in comparison to oxidized cellulose (17, 18, 19, 22, 26, 30)
- Superiority to Gelfoam® with respect to hemostasis (17, 18, 26, 29)
- Excellent biocompatibility (19, 24, 29, 30)
- Low tissue reaction (19, 26)
- Fast absorption (19, 26)
- Easy handling (22, 32)
- Low adhesion to instruments
- No detectable device-related postoperative complication (22, 31, 32)
- Proven clinical safety and effectiveness (17, 31, 32)
- No reduction of the proliferation of fibroblasts (24)
- Activation of coagulation factor XII (17)
- Induction of thrombocytes adhesion (17)

Abstracts

Biomaterials. 1996;17:1733-8.

Comparative investigation of drug delivery of collagen implants saturated in antibiotic solutions and a sponge containing gentamicin.

Wachol-Drewek Z, Pfeiffer M, Scholl E.

Collagen implants of various structures and a gelatine sponge were placed in five different antibiotic solutions until complete saturation occurred. The antibiotics were chosen to represent different drug classes (gentamicin sulphate, cefotaxim, fusidic acid, clindamycin, vancomycin). The collagen implants saturated with antibiotic solution and a lyophilized collagen sponge containing gentamicin sulphate were eluated in 0.066 M phosphate buffer (pH= 7.4) at 37 degrees C. The total eluation period is 7 d with buffer changes every 24 h. The antibiotic delivery by the collagen implants and the lyophilized sponge containing gentamicin sulphate is complete after a maximum of 4 d. If an implant that has a protective effect against wound infections over a period of 24 - 48 h is required, the materials described here are suitable. However, where treatment in infected areas should ensure antibiotic cover for 5 - 10 d, neither collagen materials immersed in antibiotic solutions nor collagen sponges containing gentamicin are suitable.

Surg Innov. 2010;17:346-52.

Efficacy of Different Hemostatic Devices for Severe Liver Bleeding: A Randomized Controlled Animal Study.

Takács I, Wegmann J, Horváth S, Ferencz A, Ferencz S, Jávor S, Odermatt E, Rõth E, Weber G.

BACKGROUND: Correct hemostasis in liver surgery is hard to achieve because of the oozing bleeding. The aim of this study was to compare the potential benefits of a new compress to the 2 commercial hemostatic compresses.

METHODS: Collagen- and cellulose-based hemostatics were investigated. A standardized resection was treated by applying different hemostatics in a randomized order, and bleeding times were measured. Macroscopic evaluation of the liver and tissue sampling for histological investigations were carried out after 21 days. Results. The bleeding times of bovine collagen (BoCo), protein-coated equine collagen (PECo), and oxidized cellulose (OxCe) were 140 ±88, 243 ± 140 (p= .005 vs BoCo), and 352 ±70 s (p< .001 vs BoCo), respectively. Microscopic evaluation of the PECo presented fibrosis and significant inflammation in the implantation zone, whereas BoCo and OxCe caused only fibrosis in the wound area.

CONCLUSION: BoCo showed significantly better hemostatic effect than PECo and OxCe.

J Thorac Cardiovasc Surg. 2003;126:666-70.

Comparative study of microfibrillar collagen hemostat (Colgel) and oxidized cellulose (Surgicel®) in high transfusion-risk cardiac surgery.

Sirlak M, Eryilmaz S, Yazicioglu L, Kiziltepe U, Eyileten Z, Durdu MS, Tasoz R, Eren NT, Aral A, Kaya B, Akalin H.

OBJECTIVE: The effects of microfibrillar collagen hemostat (Colgel) and oxidized cellulose (Surgicel®) on bleeding and allogeneic transfusions were compared incardiac operations with a predicted high risk of bleeding.

METHODS: Between August 1999 and November 2001, 71 patients undergoing elective, high risk of bleeding operations were studied after giving informed consent. The procedures included repeat cardiac operations (aorta-coronary bypass operations or valvular operations), ascending aortic aneurysm repair necessitating deep hypothermic circulatory arrest, and ascending aortic grafting without deep hypothermic circulatory arrest. Subjects were excluded if they had recent (< 5 days) acetylsalicylic acid ingestion, thrombolytic therapy, or anticoagulant therapy (heparin < 4 hours preoperatively or warfarin < 3 days preoperatively). Consenting subjects were randomized to receive either Colgel or Surgicel®.

RESULTS: Chest tube drainage in the first 24 hours was 373 +/-143 mL in the Colgel group and 571 +/-144 mL in the Surgicel® group (p= .01). Total postoperative chest tube drainage was 423 +/-154 mL (range, 280-1100 mL) in the Colgel group and 677 +/-128 mL (range, 285-1350 mL) in the Surgicel® group (p= .01). In addition, chest tube drainage was compared between the 2 groups every 3 hours after operation. Blood loss in the first 3 postoperative hours was significantly less in the Colgel group (132 +/-41 vs 228 +/-57 mL, p< .001). In the following 3-hour interval, this significant difference persisted (67 +/-24 vs 121 +/-49 mL, p< .001).

CONCLUSIONS: In conclusion, the easy application, low cost, and significant blood-loss reduction effect of microfibrillar collagen powder renders this agent attractive for cardiac operations associated with high risk of bleeding.

Abstracts

Eur Spine J. 2004;13:89-96.

The use of local agents: bone wax, gelatin, collagen, oxidized cellulose.

Schonauer C, Tessitore E, Barbagallo G, Albanese V, Moraci A.

The use of local agents to achieve hemostasis is an old and complex subject in surgery. Their use is almost mandatory in spinal surgery. The development of new materials in chemical hemostasis is a continuous process that may potentially lead the surgeon to confusion. Moreover, the more commonly used materials have not changed in about 50 years. Using chemical agents to tamponade a hemorrhage is not free of risks. Complications are around the corner and can be due either to mechanical compression or to phlogistic effects secondary to the material used. This paper reviews about 20 animal and clinical published studies with regard to the chemical properties, mechanisms of action, use and complications of local agents.

Trials. 2009;10:91.

A randomized, controlled, prospective trial to evaluate the haemostatic effect of Lyostypt® versus Surgicel® in arterial bypass anastomosis: 'COBBANA' trial.

Baumann P, Schumacher H, Hüsing J, Luntz S, Knaebel HP.

BACKGROUND: The development of suture hole bleeding at peripheral arterial bypass anastomoses using PTFE graft prostheses is a common problem in peripheral vascular surgery. Traditionally the problem is managed by compression with surgical swabs and reversal heparin or by using several haemostatic device (e.g. different forms of collagen, oxidized cellulose, gelatine sponge, ethylcyanoacrylate glue or fibrin) with various success. Preclinical data suggest that the haemostatic effect of collagen is stronger than that of oxidized cellulose, but no direct clinical comparison of their hemostatic performance has been published so far.

DESIGN: This randomized, controlled, prospective trial evaluates the haemostatic effect of Lyostypt® versus Surgicel® in arterial bypass anastomosis. 28 patients undergoing an elective peripheral vascular reconstruction due to peripheral vascular disease will be included. Suture hole bleeding occurring at the arterial bypass anastomosis using a PTFE prostheses will be stopped by the application of Lyostypt® and / or Surgicel®. The proximal anastomoses will be randomized intraoperatively. The patients will be allocated into 4 different treatment groups. Group 1: Lyostypt® distal / Surgicel® proximal; Group 2: Lyostypt® proximal / Surgicel® distal; Group 3: Surgicel® distal and proximal; Group 4: Lyostypt® distal and proximal. Primary endpoint of the study is time to haemostasis. Secondary endpoints are the number of intraoperatively used haemostatic devices, postoperative mortality within 30 days as well as the intraoperative efficacy rating of the two devices evaluated by the surgeon. As a safety secondary parameter, the local and general complication occurring till 30 +/-10 days postoperatively will also be analysed. After hospital discharge the investigator will examine the enrolled patients again at 30 days after surgery.

DISCUSSION: The COBBANA trial aims to assess, whether the haemostatic effect of Lyostypt® is superior to Surgicel® in suture hole bleedings of arterial bypass anastomoses. COBBANA Trials

Abstracts

Spine. 2005;30:1911-7.

Efficacy and safety of a novel moldable, resorbable, and degradable sealant of bone surfaces for hemostasis after bone graft harvesting from the iliac crest.

Pingsmann A, Blatt R, Breusch S, Jürgens C, Thietje R, Krödel A, Zinser W, Michiels I, Niethard FU, Niedhart C, Renzing-Köhler K, Pfefferle HJ.

STUDY DESIGN: A prospective, controlled, open, randomized multicenter study.

OBJECTIVE: The study's objective was to demonstrate equivalence of a novel, moldable, resorbable, and degradable synthetic polymer (Bone Seal®) compared with a collagen fleece (Lyostypt®) in efficacy and safety for topical hemostasis after iliac crest bone graft harvesting.

SUMMARY OF BACKGROUND DATA: Harvesting cortico-cancellous bone from the iliac crest is a well established procedure in orthopedic and particularly in spine surgery. It is associated with significant morbidity at the donor site where hematoma formation may cause impaired wound healing and infections in up to 10 % of cases.

METHODS: A total of 112 patients were included in the safety analysis. Safety was determined by a compound wound healing score and the incidence of adverse clinical effects. One hundred and eight patients were studied for equivalence in efficacy using a compound bleeding score. The handling properties and the application to the bone surface of either device were measured with two additional compound scores.

RESULTS: The mean bleeding scores in the final analysis was 4.5 +/-1.3 for the Bone Seal® group and 4.2 +/-1.3 for the collagen fleece group. Bone Seal® was better applicable to the bleeding bone surfaces than the collagen fleece, even though its handling was more complicated. Wound healing and the incidences of adverse clinical events were comparable in either study group.

CONCLUSIONS: Bone Seal® is an effective and safe hemostatic material for sealing bleeding bone surfaces after iliac crest bone graft harvesting. By virtue of its hemostatic efficacy, Bone Seal® is preventive for wound healing disorders.

Abstracts

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