

Clinical Surgery

Collagen hemostat significantly reduces time to hemostasis compared with cellulose: COBBANA, a single-center, randomized trial

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Hemostasis;
Topical hemostatic agent;
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Abstract

BACKGROUND: This single-center, randomized trial compares the hemostatic effectiveness of microfibrillar collagen and oxidized cellulose in arterial bypass surgery.

METHODS: In patients undergoing arterial bypass surgery, 2 hemostats, microfibrillar collagen and oxidized cellulose, were randomly used to achieve hemostasis. The primary endpoint was the time to hemostasis. The secondary endpoints were the complication rate, mortality, number of hemostats required, handling, and adhesion.

RESULTS: Collagen achieved hemostasis significantly faster than cellulose, with considerably less hemostats. In addition, its ease of use was rated substantially better.

CONCLUSION: In arterial bypass surgery, microfibrillar collagen is more effective than oxidized cellulose in achieving hemostasis.

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In arterial bypass surgery, hemostasis is more difficult to achieve because arterial and graft sutures and anastomoses must be carefully performed; this is often under a high dose of antiplatelet medication for cardiovascular comorbidities. The lack of elasticity of polytetrafluorethylene (PTFE), a bypass graft material widely used when no autologous saphenous vein is available, may cause suture hole bleeding,

which can be controlled with various success by different hemostats.¹⁻⁵

Preclinical studies strongly suggest that collagen hemostats are more effective than those made out of oxidized regenerated cellulose.⁶ Although they both have been in clinical use for many years, no direct clinical comparison has been performed yet. Therefore, the COBBANA (Control of Bleeding after Bypass ANastomoses) trial was designed to show the superiority of microfibrillar collagen in this surgical setting.

Methods

To ensure transparency, the study protocol of the COBBANA trial has already been registered (www.clinicaltrials.gov), published,⁷ and approved in its final version by the

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Ethics Committee of the Landesärztekammer Hessen, Frankfurt, Germany. It was sponsored and conducted by Aesculap AG, Tuttlingen, Germany. The Coordination Center for Clinical Trials (Koordinierungszentrum für Klinische Studien), Heidelberg, Germany, was responsible for database maintenance and biometrics. Patients were enrolled at 1 center in Germany (Klinikum Hanau GmbH).

Study objectives

The primary objective of this trial was to show that Lyostypt (Aesculap AG, Tuttlingen, Germany), a microfibrillar collagen hemostat, is more effective than Surgicel (Johnson & Johnson Medical Ltd, North Yorkshire, UK), an oxidized cellulose hemostat, in stopping suture hole bleeding after arterial bypass surgery. The primary endpoint was the time to hemostasis, which was determined from the release of the cross-clamp, to the moment the wound was completely or sufficiently dry as judged by a single investigator.

To assess the safety of the hemostat, complications (eg, recurrence of bleeding, infection and occlusion of the PTFE prosthesis, stenosis, thrombosis of the leg artery, reoperation, wound infections, and healing disorders) within 30 ± 10 days after surgery were used as secondary endpoints. The form and shape of the hemostat and its tissue adhesion are important to enable proper handling, which is essential to control bleeding.⁵ Therefore, the number of hemostats required, surgical handling, and adhesion (rated in terms of ease of use) were evaluated as secondary endpoints. The base for scales was a modified Likert scale. For adhesion, the following categories were possible: “immediately adhering,” “after a short while adhering,” “repositioning,” or “no adhesion” and for surgical handling “easy placement/no repositioning needed,” “easy placement/repositioning needed and possible,” “difficult placement/repositioning/no additional product needed,” or “difficult placement (ie,

sticks to the instruments or glove)/additional product needed.” In addition, the postoperative mortality within 30 days was also recorded.

Eligibility and intervention

The inclusion and exclusion criteria (Table 1) and the surgical procedures are described in detail in the published study protocol.⁷ Written informed consent was obtained from all participating patients.

The same standard procedure was used in each case. A saphenous vein could not be used in the participating patients. In all randomized patients, the use of a PTFE graft was indicated. A PTFE prosthesis with a diameter of 6 or 8 mm was implanted using nonabsorbable polypropylene suture material (*United States Pharmacopeia* 5-0). The surgeon first performed the distal anastomosis. Then, he released the clamp and checked for bleeding at the suture line. If it was still bleeding, he closed the clamp and opened a randomization envelope containing the study material. Then, he removed the clamp at the distal anastomosis and applied the randomized hemostat, cut in half, around the anastomosis for 3 minutes timed by a stopwatch. Observing the suture line, he recorded the time required to achieve hemostasis. If it was not achieved after 3 minutes, he placed another hemostat of the same kind on the wound and checked for hemostasis at 5 and 10 minutes. If it was not achieved within 10 minutes or if additional interventions were required, it was considered a treatment failure. At the proximal anastomosis, the same procedure was repeated. The number and type of hemostats and the time after clamp removal were recorded. Both devices were removed after hemostasis.

The artery wall was described as normal in 5 patients; in 23 patients, a soft plaque was recorded and in 1 a calcified plaque (data not shown). All patients received heparin (3,000 U) as a standard in the clinic independent from the

Table 1 Eligibility

Inclusion criteria	Exclusion criteria
Patients >18 years	Emergency surgery
Informed consent	Patients with coagulopathy or uremia
Indication for a peripheral vascular reconstruction caused by peripheral vascular disease including femorofemoral, femoropopliteal, and femorocrural reconstructions or the need of a crossover including femorofemoral or ilacofemoro reconstruction	Reoperation within 1 month at the same location
Suture hole bleeding of peripheral arterial bypass anastomosis using PTFE graft	Known or suspected allergies or hypersensitivity to any of the used devices
	Pregnant and breast-feeding women
	Patients requiring continuous postoperative anticoagulation
	Severe comorbidity (ASA ≥ 4)
	Life expectancy less than 12 months
	Current immunosuppressive therapy
	Chemotherapy within last 4 weeks
	Radiotherapy on the treated region within the last 2 weeks
	Severe psychiatric or neurologic diseases
	Lack of compliance

ASA = American Society of Anesthesiologists.

body mass index of patients but without protamine. The hemostats, Lyostypt (5×8 cm) and Surgicel (oxidized regenerated cellulose, 5×7.5 cm) were used.

Lyostypt is a γ -sterilized, absorbable, wet-stable hemostat made of collagen from cattle skin of a controlled herd in Germany, slaughtered in controlled abattoirs, and treated with sodium hydroxide and acetone to inactivate the scrapie agent (reduction factor $>6 \log_{10}$). Its biocompatibility was shown in tests according to ISO 10993.

Randomization

Sequentially numbered (1–32), opaque, sealed envelopes were used to allocate the patients according to a randomization list prepared by a statistician to receive either microfibrillar collagen (COLL) or oxidized cellulose (ORC). The patients were divided into 4 equally large groups: group 1: distal COLL/proximal ORC, group 2: distal ORC/proximal COLL, group 3: distal and proximal ORC, and group 4: distal and proximal COLL.

An untreated control group was not included because of the nature of the study and because animal studies have clearly shown that the time to hemostasis increases if no hemostat is used.^{8–12} The products make blinding impossible.

Sample size estimation

This study used a 2-step design. Bleeding times obtained from preclinical evaluations served as a basis for sample size calculation (internal, unpublished data). It was estimated that 28 patients would need to be enrolled. The test was performed with a significance level of $\alpha_1 = .0102$. The exact number was dependent on the number of patients with bleeding anastomoses, as they were accrued until 56 instances of randomized hemostat application had been recorded. The main test was carried out as the parameter test outlined in the statistical analysis section.

The trial was to be stopped for success if the null hypothesis was rejected with a one-sided p-value lower than α_1 , and for futility if it was higher than .50. For the final analysis, applying the approach of Bauer and Köhne,¹³ the level of significance was set at $\alpha_2 = .00380/p_1$, p_1 being the p-value from the one-sided test of the primary endpoint in the interim analysis. The significance level was maintained at .025 and with a power of 80%, values obtained by simulation based on 300 replicates.

Statistical analysis

To evaluate the primary endpoint, the anastomosis was used as the observational unit. Time to hemostasis, the primary endpoint censored at 10 minutes, was included as the response parameter in an accelerated failure time regression model assuming a Weibull distribution^{14,15} for bleeding time with the following explanatory parameters: treatment of anastomosis (COLL/ORC), treatment of

opposite anastomosis (COLL/ORC), and site of anastomosis (proximal/distal). Subjects were included as shared frailty terms with log-normal distribution. The formal null hypothesis to be tested at a level of $\alpha = .025$ was as follows: “Anastomosis bleeding time under COLL is at least as long as under ORC.”

The primary endpoint was analyzed using PROC NLMIXED (SAS Institute Inc., Cary, NC, USA) with a Weibull distribution and subjects used as log-normal random effects. Exact and sign tests were used. Convergence problems made it impossible to capture hemostasis at 5 and 10 minutes, the complication rate within 30 ± 10 days after surgery, and the number of additional hemostats required as intended in a logistic mixed model. Subjects were treated as random effects.

Ease of use was rated on a 4-point scale for adhesion and on a 5-point scale for handling and separately modeled using a linear mixed model with equidistant responses. This model used the same covariates as the main model as fixed effects and the surgeon and subject as random effects. Every adverse event was recorded. Patients were analyzed using the intention-to-treat principle.

Results

Recruitment

Between February and July 2009, 32 patients, 4 more than originally planned, were recruited at 1 center (Klinikum Hanau GmbH, Department of Vascular Surgery) to allow randomization into 4 blocks of 8 (ie, ORC-COLL, COLL-ORC, COLL-COLL, and ORC-ORC). One patient died 25 days after surgery from heart failure (Fig. 1).

Demography

In the 4 groups, there was no significant difference in age and sex (Table 2) and American Society of Anesthesiologists status. More obese patients (ie, body mass index ≥ 30 kg/m²) were randomized into the “ORC distal/COLL proximal” group. Six women and 3 men were smokers. More than half of them were randomized into the “COLL distal/ORC proximal” group. Nine patients had diabetes mellitus (COLL-COLL: n = 3; COLL-ORC: n = 3; ORC-COLL: n = 2; ORC-ORC: n = 1).

Surgical intervention

Most reconstructions were suprageneal femoropopliteal reconstructions with distal anastomosis (n = 23) in addition to a few infrageneal femoropopliteal (n = 4), femorofemoro crossover (n = 4), and femorocrural reconstructions (n = 1). Suture hole bleeding occurred in all patients at both anastomosis sites who were all treated according to the study protocol.

A PTFE prosthesis from Gore (Putzbrunn, Germany) was mainly used for the intervention. There were only 2 cases in

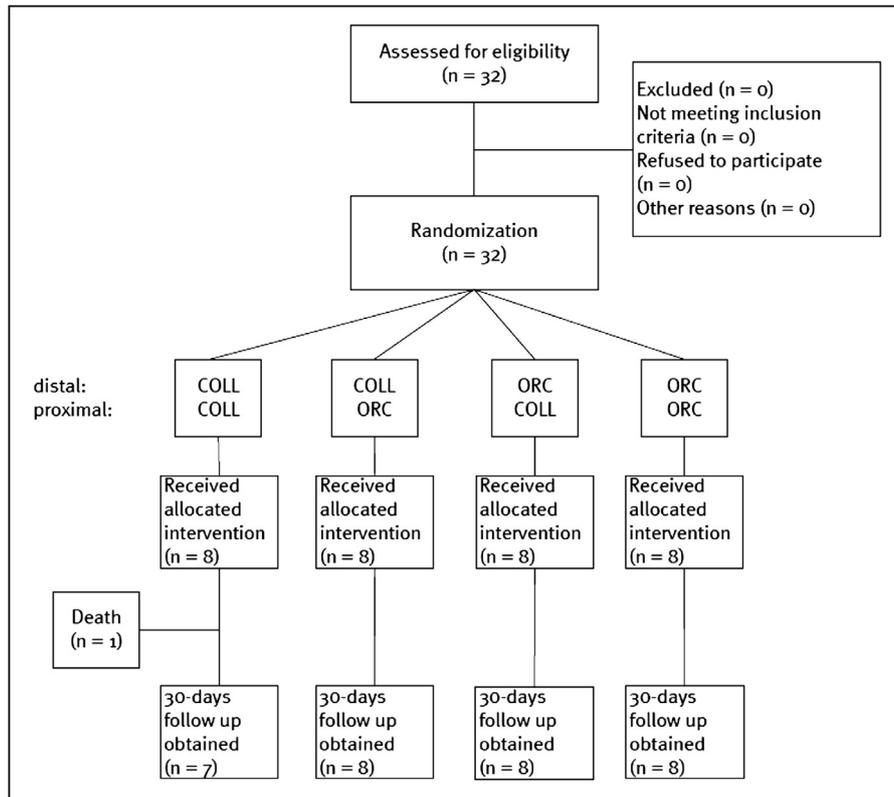


Figure 1 A flowchart of COBBANA patients according to consolidated standards of reporting trials (CONSORT).²⁷

which a PTFE prosthesis from Bard (Crawley, UK) was applied. The average length of the PTFE prosthesis used was 40 cm, and a diameter of 8 mm was commonly used. There were only 2 cases in which a prosthesis with a diameter of 6 mm was used (data not shown). No other grafts were implanted.

Primary endpoint

The primary endpoint was time to hemostasis (ie, the mean bleeding time). For COLL, it was 124.7 ± 66.8

seconds (minimum = 29 seconds, maximum = 296 seconds; ie, 117.4 ± 62.2 seconds at the distal and 131.9 ± 72.5 seconds at the proximal anastomosis). In contrast, for ORC, the mean bleeding time was 416.3 ± 226.2 seconds (minimum = 82 seconds, maximum = 843 seconds; ie, 443.7 ± 200.3 seconds at the distal and 389.3 ± 253.0 seconds at the proximal anastomosis (Fig. 2). The difference is statistically significant ($P < .001$). The side of the anastomosis (distal or proximal) had no influence on bleeding time ($P = .7578$).

Table 2 Demography and baseline characteristics

Treatment group:	COLL-COLL (n = 8)	COLL-ORB (n = 8)	ORB-COLL (n = 8)	ORB-ORB (n = 8)
Sex				
Men	7	5	5	4
Women	1	3	3	4
Age (y)				
Men	69.7 ± 7.0	71.6 ± 8.4	66.6 ± 9.8	71.0 ± 2.9
Women	80.0	62.7 ± 4.0	70.7 ± 3.1	70.5 ± 8.2
BMI (kg/m ²) mean \pm SD	26.8 ± 4.2	24.9 ± 4.0	30.0 ± 4.1	25.2 ± 3.5
ASA				
P1		2		
P2	1	1	2	3
P3	7	5	6	5
Smoking yes				
Men		3		
Women	1	2		3

ASA = American Society of Anesthesiologists; BMI = body mass index; SD = standard deviation.

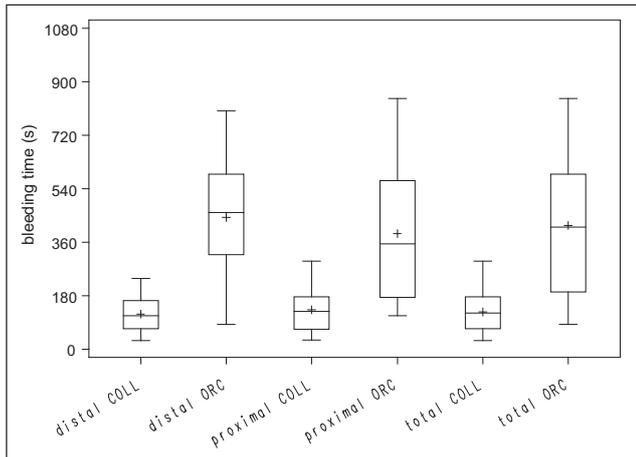


Figure 2 Bleeding times measured at the anastomoses.

In 27 of 32 cases, hemostasis was achieved within 3 minutes using COLL but only in 8 using ORC. It was achieved within 3 to 5 minutes in 5 cases using COLL and in 3 using ORC. In 13 cases, 5 to 10 minutes were needed using ORC. ORC treatment failed (longer than 10 minutes) 8 times versus none for COLL (Table 3).

In the ORC-COLL and COLL-ORC groups, 5 patients treated with ORC had a bleeding time >10 minutes and none treated with COLL ($P = .03125$, one sided). In the ORC-ORC group, 2 patients had a bleeding time >10 minutes in 3 cases and none in the COLL-COLL group ($P = .25$, one sided). The overall result was significant at the one-sided 0.025 level. In the ORC-COLL and COLL-ORC groups, 11 patients treated with ORC had a bleeding time >5 minutes and none of those treated with COLL ($P = .0005$, one sided). Seven of 8 patients in the ORC-ORC group had a bleeding time >5 minutes but none in the COLL-COLL group ($P = .0004$, one sided). The result was significant at a one-sided .025 level (data not shown). No additional suturing was required.

Secondary endpoints

Number of hemostats. In all cases using COLL, one hemostat sufficed to achieve hemostasis but in only 11 of 32 (34%) using ORC. In all other cases ($n = 21$, 66%), a second ORC hemostat was required. Thus, in total, 32 COLL and 53 ORC hemostats were required.

Ease of use rating. Five surgeons rated the ease of use of the hemostat on a 4-point scale for “adhesion” and on a 5-point scale for “surgical handling” (data not shown). The

surgeons rated the COLL hemostat significantly better regarding both factors and expressed their preference for this hemostat.

Complication rate at 30 days postoperatively. Only one adverse event unrelated to treatment was reported. One patient suffered a myocardial infarct on the day of surgery and died 25 days later. This corresponds to a postoperative mortality rate of 3% (1/32).

Interim analysis. The interim analysis yielded a P value lower than its prespecified level, thus rejecting the null hypothesis. The trial was stopped for efficacy.

Comments

Several preclinical studies in different animal models have shown the efficacy of the ORC and COLL hemostats,^{16–20} but they have never been directly compared as in this COBBANA trial. ORC decreases pH and generates an artificial clot.²¹ It does not stimulate platelet aggregation. On the other hand, the efficacy of collagen hemostats has also been shown in man.^{22–26} Hemostasis is induced by collagen in 2 ways: first it activates the aggregation of thrombocytes, and second it invokes factor XIII, which promotes the formation of a fibrin clot. The advantages of COLL lie in rapid hemostasis, low tissue reaction, and fast absorption. In addition, any excess can be teased away without reinitiating bleeding.

In comparison to the ORC hemostat, the COLL hemostat significantly reduces bleeding time and is more economic by 40%. It would reduce surgery time by about 9 minutes. With a calculation of \$65 to 130 per operation minute, the application of COLL can potentially save \$585 to 1,170. The cost advantage associated with the use of microfibrillar collagen is in most cases at least \$2 per anastomoses.

In conclusion, COLL stops suture hole bleedings significantly faster than ORC, much less COLL hemostats are needed to achieve hemostasis, it decreases costs, and it was considerably better rated than ORC for ease of use (adhesion and surgical handling). The single-center design and the lack of blinding because of the nature of the products constitute limitations of our study. Furthermore, time to hemostasis was assessed subjectively, which is a possible source of bias. However, this is acceptable when no better method is available as comparable studies show.^{28–31} In summary, our findings indicate that collagen hemostats should be preferred in this setting.

References

1. Czerny M, Verrel F, Weber H, et al. Collagen patch coated with fibrin glue components. Treatment of suture hole bleedings in vascular reconstruction. *J Cardiovasc Surg* 2000;41:553–7.

Table 3 Bleeding time of the anastomoses against treatment

	<3 min	3 ≤ 5 min	5 ≤ 10 min	>10 min	Total
COLL	27 (84)	5 (16)			N = 32
ORC	8 (25)	3 (9)	13 (41)	8 (25)	N = 32

2. Joseph T, Adeosun A, Paes T, et al. Randomised controlled trial to evaluate the efficacy of TachoComb H patches in controlling PTFE suture-hole bleeding. *Eur J Vasc Endovasc Surg* 2004;27:549–52.
3. Jackson MR, Gillespie DL, Longenecker EG, et al. Hemostatic efficacy of fibrin sealant (human) on expanded poly-tetrafluoroethylene carotid patch angioplasty: a randomized clinical trial. *J Vasc Surg* 1999;30:461–6.
4. Taylor Jr LM, Mueller-Velten G, Koslow A, et al. Prospective randomized multicenter trial of fibrin sealant versus thrombin-soaked gelatin sponge for suture- or needle-hole bleeding from polytetrafluoroethylene femoral artery grafts. *J Vasc Surg* 2003;38:766–71.
5. Tomizawa Y. Clinical benefits and risks analysis of topical haemostats: a review. *J Artif Organs* 2005;8:137–42.
6. Schonauer C, Tessitore E, Barbagallo G, et al. The use of local agents: bone wax, gelatin, collagen, oxidized cellulose. *Eur Spine J* 2004;13: 89–96.
7. Baumann P, Schumacher H, Hüsing J, et al. A randomized, controlled, prospective trial to evaluate the haemostatic effect of Lyostypt versus Surgicel in arterial bypass anastomosis: “COBBANA” trial. *Trials* 2009;10:91.
8. Ereth MH, Schaff M, Ericson EF, et al. Comparative safety and efficacy of topical hemostatic agents in rat neurosurgical model. *Neurosurgery* 2008;63:369–72.
9. Engelhardt GH, Gerhardt HJ, Nagelschmidt M. Action and biocompatibility of two collagen-based hemostatics in animal experiments. *Arzneimittelforschung* 1989;39:259–62.
10. Ünlü Y, Vural Ü, Kocak H, et al. Comparison of the topical haemostatic agents for the prevention of suture hole bleeding. An experimental study. *Eur J Vasc Endovasc Surg* 2002;23:441–4.
11. Glickman M, Gheissari A, Money S, et al. A polymeric sealant inhibits anastomotic suture hole bleeding more rapidly than gelfoam/thrombin. *Arch Surg* 2002;137:326–31.
12. Haußmann P, Mergand UE, Köhnlein HE. Zur Wirkung verschiedener hämostypitka. *Fortschr Med* 1974;13:579–80.
13. Bauer P, Köhne K. Evaluation of experiments with adaptive interim analysis. *Biometrics* 1994;50:1029–41.
14. Hougaard P. Fundamentals of survival data. *Biometrics* 1999;55: 13–22.
15. Keiding N, Andersen PK, Klein JP. The role of frailty models and accelerated failure time models in describing heterogeneity due to omitted covariates. *Stat Med* 1997;16:215–24.
16. Rybock JD, Long DM. Use of microfibrillar collagen as a topical hemostatic agent in brain tissue. *J Neurosurg* 1977;46:501–5.
17. Wagner WR, Pachence JM, Ristich J, et al. Comparative in vitro analysis of topical hemostatic agents. *J Surg Res* 1996;66:100–8.
18. Finn MD, Schow SR, Schneideman ED. Osseous regeneration in the presence of four common hemostatic agents. *J Oral Maxillofac Surg* 1992;50:608–12.
19. Raccuia JS, Simonian G, Dardik M, et al. Comparative efficacy of topical hemostatic agents in a rat kidney model. *Am J Surg* 1992;163:234–8.
20. Takács I, Wegmann J, Horváth S, et al. Efficacy of different haemostatic devices for severe liver bleeding: a randomised controlled animal study. *Surg Innov* 2010;17:346–52.
21. Johnson and Johnson: Tabotamp, Hämostyptikum zur sicheren lokalen Blutstillung. Gebrauchsanweisung, Hamburg June, 2005.
22. Haris WH, Crothers OD, Moyon BJL. Topical hemostatic agents for bone bleeding in humans. *J Bone Joint Surg Am* 1978;60:454–6.
23. Rengachary SS, Manguoglu AB. Control of bone bleeding during Cloward procedure. *J Neurosurg* 1980;52:138–9.
24. Craig CC, Asher MA. Hemostasis in human iliac crest donor sites with microfibrillar collagen. *Spine* 1977;2:313–7.
25. Silverstein ME, Chvapil M. Experimental and clinical experience with collagen fleece as a hemostatic agent. *J Trauma* 1981;21:388–93.
26. Bland JM, Bland DG. Statistics notes: one and two sided tests of significance. *BMJ* 1994;309:248.
27. Moher D, Schultz KF, Altman DG, et al. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 2001;14:1191–4.
28. Schwartz M, Madariaga J, Hirose R, et al. Comparison of a new fibrin sealant with standard topical hemostatic agents. *Arch Surg* 2004;139: 1148–54.
29. Chapman WC, Clavien PA, Fung J, et al. Effective control of hepatic bleeding with a novel collagen-based composite combined with autologous plasma: results of a randomized controlled trial. *Arch Surg* 2000;135:1200–4.
30. Frilling A, Stavrou GA, Mischinger HJ, et al. Effectiveness of a new carrier-bound fibrin sealant versus argon beamer as haemostatic agent during liver resection: a randomised prospective trial. *Langenbecks Arch Surg* 2005;390:114–20.
31. Siemer S, Lahme S, Altziebler S, et al. Efficacy and safety of TachoSil as haemostatic treatment versus standard suturing in kidney tumour resection: a randomised prospective study. *Eur Urol* 2007;52:1156–63.