New Method

Hemostatic Effectiveness of a New Application Method for Fibrin Glue, the "Rub-and-Spray Method", in Emergency Aortic Surgery for Acute Aortic Dissection

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Purpose: This study was performed to evaluate the clinical hemostatic effectiveness of a new application method for fibrin glue, the rub-and-spray method, in aortic surgery.
Methods: Twenty consecutive patients undergoing emergency ascending aorta or ascending-hemiarch replacement for Stanford type A acute aortic dissection were prospectively randomized into 2 groups, one with the rub-and-spray method (group G, 10 patients) and one without fibrin glue (group C, 10 patients). The rub-and-spray method consists of using a finger to rub the fibrinogen solution over needle holes, then spraying the fibrinogen solution and the thrombin solution simultaneously over the anastomosis, using an application nozzle. The number of bleeding needle holes at the proximal and distal anastomoses just after reperfusion, the hemostatic period (time from administration of protamine sulfate until closure of the pericardium), and the amounts of blood losses during this hemostatic period were measured.
Results: The values in group G and group C were as follows: proximal needle holes (26.8 ± 1.5, 26.4 ± 2.4, p = 0.466); proximal bleeding needle holes (0.2 ± 0.4, 19.3 ± 3.5, p <0.001); distal needle holes (28.7 ± 2.5, 27.8 ± 4.4, p = 0.675); distal bleeding needle holes (1.3 ± 1.2, 19.9 ± 5.0, p <0.001); estimated bleeding proportion of the proximal needle holes (0.7 ± 1.6%, 73.8 ± 16.0%, p <0.001); estimated bleeding proportion of the distal needle holes (4.4 ± 3.7%, 71.9 ± 15.7%, p <0.001); estimated median hemostatic period (41.5 min [32–49], 51 min [44–89], p = 0.036); amounts of blood losses during this hemostatic period (99 ± 76 ml, 257 ± 163 ml, p = 0.016). The number of bleeding needle holes, the bleeding proportion of the proximal and distal needle holes, the hemostatic period, and the amounts of bleeding during this hemostatic period were significantly less in group G.
Conclusion: This new application method for fibrin glue, the rub-and-spray method, revealed significant hemostatic effectiveness, even in hemostatically difficult surgery of acute aortic dissection that requires systemic heparinization and prolonged cardiopulmonary bypass with deep hypothermia. (Ann Thorac Cardiovasc Surg 2009; 15: 265–271)

Key words: fibrin glue, hemostasis, cardiovascular surgery, aortic surgery, acute aortic dissection

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Introduction

Fibrin glue is polymerized from two components (fibrinogen and thrombin), first introduced by Spängler et al.[1] in 1976, and has been used as a hemostatic agent in cardiovascular surgery for more than 30 years. The two components are applied by different methods to the anastomoses or the bleeding sites: the separate dripping

method using two separate syringes, the simultaneous dripping method with a syringe applicator, and the spray method using a spray applicator. Further developments would be required concerning these methods or the delivery system to obtain a more effective hemostasis and suture support after surgery.[2] Recently, a new application method of applying fibrin glue, the rub-and-spray method, was reported by Minato et al. for a more effective hemostasis in cardiovascular surgery.[3] This method requires rubbing the fibrinogen solution followed by spraying the fibrinogen and thrombin solutions simultaneously with the spray applicator. They reported that the rub-and-spray method experimentally and pathologically proved to have the strongest sealing and hemostatic effects of the methods described.[3] Several reports insisted on the clinical effectiveness of the fibrin glue as a hemostatic agent according to the reduction of intraoperative or postoperative blood loss, blood transfusion, operation time, and duration of postoperative hospital stay. However, they were not direct indicators of the hemostatic effectiveness of the fibrin glue because they would be greatly changed according to the different surgical procedures, duration of extracorporeal circulation, and whether with or without hypothermia. The total amount of bleeding from the drainage tube after surgery does not always come from the anastomoses with fibrin glue application, but from other dissected surfaces or sternal bone marrow, especially in cardiovascular surgery. In this report, we clinically evaluated the hemostatic effectiveness of a new application method for fibrin glue, the rub-and-spray method, in randomized controlled trials by counting the number of bleeding needle holes at the anastomosis as a direct indicator of hemostatic effectiveness in patients with the ascending or ascending-hemiarch aortic replacement for acute aortic dissection.

Patients and Methods

From April 2004 to August 2006, 45 consecutive patients were operated on at Fukuoka Tokushukai Hospital for Stanford type A acute aortic dissection. To uniform the surgical procedures, we selected 20 patients with emergency replacement of the ascending aorta or the ascending-hemiarch for this study. Exclusion criteria were as follows: patients with cardiac collapse requiring preoperative cardiac massage (3); those with cardiac tamponade and shock requiring open pericardial drainage at the emergency room (3); those with acute myocardial infarction (2); those with the Bentall procedure (2); those with the total arch replacement (10); those with Bentall + total arch replacement (5). The patients were prospectively randomized into 2 groups, one with the rub-and-spray method of fibrin glue (group G, 10 patients, 3 men and 7 women), and one without fibrin glue (control: group C, 10 patients, 4 men and 6 women) (Fig. 1). The mean age was 70.1 ± 7.2 (62–81) in group G and 65.8 ± 10.1 (50–77) in group C (Table 1).

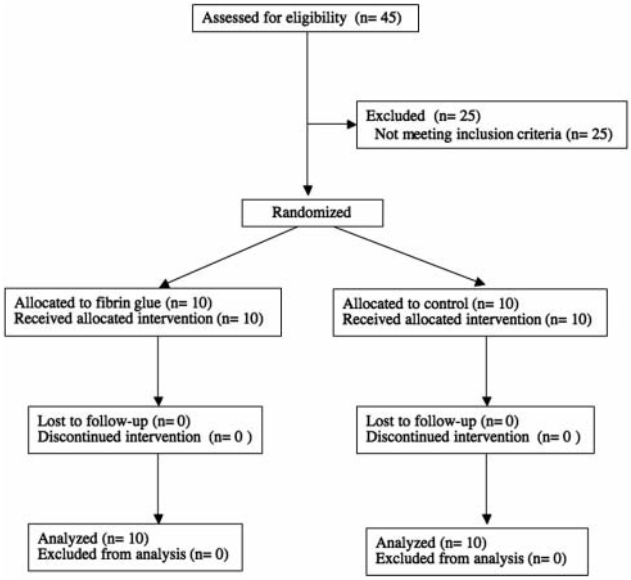

Fig. 1. Flow diagram of subject progress through phases of the clinical trial according to the CONSORT statement.

Surgical procedure

The patients were placed in the supine position with neuroleptanesthesia of fentanyl, diazepam, vecuronium bromide, and enflurane. Aprotinin (1 IU/kg) was administered every 60 min before the sternotomy until the end of the extracorporeal circulation. After administration of heparin sodium (3,000 U/kg) to maintain the activated coagulation time more than 400 seconds, a hypothermic cardiopulmonary bypass (CPB) was established with right atrial drainage and right axillary artery or femoral artery return. Surgical strategy was to replace the dissecting aorta where the primary intimal tear existed. In cases with a patent false lumen without much thrombus in the ascending aorta, the ascending aorta was cross clamped, and the proximal aorta was transected at 1 cm above the sinotubular junction (STJ) and reinforced by placing felt strips inside and outside of the lumen. No gelatin-resorcin-formalin (GRF) glue or fibrin glue was used in the false lumen. At 25°C rectal temperature, temporal hypothermic circulatory arrest (HCA) was obtained,

Table 1. Baseline data

	Group G (glue+)	Group C (control)	P value	Statistics
Patient number	10	10		
Gender (men/women)	3/7	4/6	1.000	Fisher's exact test
Age	70.1 ± 7.2	65.8 ± 10.1	0.286	Unpaired t test
Diabetes mellitus	1	2	1.000	Fisher's exact test
Hyperlipidemia	3	4	1.000	Fisher's exact test
Smoking	3	0	0.211	Fisher's exact test
Hypertension	10	9	1.000	Fisher's exact test
Previous cardiovascular surgery	1*	0	1.000	Fisher's exact test
Cardiopulmonary bypass time (min)	159 ± 31	170 ± 20	0.769	Log-rank test
Brain circulatory arrest time (min)	30 ± 5	28 ± 4	0.371	Log-rank test
Minimal rectal temperature (°C)	20	20	ns	

ns, not significant; *, graft replacement for abdminal aortic aneurysm.

and the aortic clamp was removed to inspect the intimal tear in the arch. Ascending or ascending-hemiarch replacement was indicated when the intimal tear could be resected by these methods. The aorta was then reclamped and CPB restarted for further cooling to 20°C. The proximal anastomosis was first performed with a collagen-coated woven polyester graft (InterGard woven, Intervascular Inc., La Ciotat Cedex, France), and the open distal anastomosis was followed during HCA at 20°C rectal temperature. On the other hand, in cases with much thrombus in the false lumen of the ascending aorta, the patient was cooled to 20°C without clamping the ascending aorta. The distal portion of the ascending aorta was transected, and the arch was inspected during HCA. If the ascending aorta or ascending-hemiarch replacement was indicated, the open distal anastomosis was first performed, followed by the proximal anastomosis. All the aortic stumps were reinforced with felt strips as described without the use of GRF glue or of fibrin glue in the false lumen. All anastomoses between the reinforced aorta and the graft were performed by running suture of monofilament polypropylene (Prolene 4-0 SH-1, needle length 22 mm, Ethicon Inc., Piscataway, USA).

Randomization

The use of fibrin glue, the rub-and-spray method, at the anastomosis was assigned according to the permuted block randomized method when the ascending or ascending-hemiarch replacement was indicated.

A commercially available fibrin sealant, Bolheal (Chemo-Sero Therapeutic Institute, Kumamoto, Japan), is composed of solutions A and B. Solution A contains 80 mg/ml of human fibrinogen, 75 U/ml of human plasma-derived coagulation factor XIII, and 1,000 KIE of bovine aprotinin. Solution B contains 250 IU/ml of human thrombin and 5.9 mg/ml of calcium chloride. Blood components were extracted from blood samples of volunteer blood donors in Japan after screening for human parvovirus (HPV) B19 antigen, HBs antigen, anti-HBc/HCV/HIV antibody, HBV-DNA/HCV-RNA/HIV-RNA, HPV B19-DNA (NAT), and antihuman T cell lymphoma virus 1 antibody. To prevent viral contamination, fibrinogen and coagulation factor XIII were treated in dry heating at 65°C for 144 hours, and thrombin was treated in dry heating at 65°C for 96 hours. Fibrinogen was nanofiltrated with Planova 19N (pore size 19 nm, Asahi Chemical Industry, Tokyo, Japan) and coagulation factor XIII, thrombin, and bovine aprotinin were filtrated with Planova 15N (pore size 15 nm).

The fibrin glue rub-and-spray method was applied to the proximal and distal anastomoses in group G as follows: dripping A solution over the needle holes and rubbing it on with the fingers, then spraying A and B solutions on the anastomosis simultaneously, using an application nozzle at a pressure of 0.75 mmHg atmospheres. Three minutes after the application of the rub-and-spray method, perfusion was restarted. No glue was used in group C.

The number of total needle holes and the bleeding needle holes at the proximal and distal anastomoses just after reperfusion, the hemostatic period (time from administration of protamine sulfate until closure of the pericardium), the amounts of blood losses during this hemostatic period, and the amounts of postoperative mediastinal blood losses during the first 12 hours after surgery were measured. The bleeding needle holes were counted by using a Jamieson's suction instrument with a small suctioning head during the pouring of saline solution over the anastomosis from an injector. The bleeding needle holes were left as they were until the administra-

Table 2. Outcome and estimation

	Group G (n = 10)	Group C (n = 10)	P value	Statistics
Needle holes				
Proximal	26.8 ± 1.5 (23–28)	26.4 ± 2.4 (23–31)	0.466	Wilcoxon rank sum test
Distal	28.7 ± 2.5 (25–34)	27.8 ± 4.4 (22–35)	0.675	Wilcoxon rank sum test
Bleeding needle holes				
Proximal	0.2 ± 0.4	19.3 ± 3.5	<0.001	Wilcoxon rank sum test
Distal	1.3 ± 1.2	19.9 ± 5.0	<0.001	Wilcoxon rank sum test
Needle hole bleeding proportion (%)				
Proximal	0.7 ± 1.6	73.8 ± 16.0	<0.001	Wilcoxon rank sum test
Distal	4.4 ± 3.7	71.9 ± 15.7	<0.001	Wilcoxon rank sum test
Needle hole bleeding rate				
Proximal	0.008	0.731	RR = 0.010 (95%CI, 0.003–0.041)	
Distal	0.045	0.716	RR = 0.063 (95%CI, 0.036–0.111)	
50% hemostatic period (min)	41.5 (32–49)	51 (44–89)	0.036	Log-rank test
Blood loss during hemostatic period (ml)	99 ± 76	257 ± 163	0.016	Unpaired t test*
Blood loss during postoperative 12 hours (ml)	268 ± 93	526 ± 363	0.054	Unpaired t test*

Bleeding proportion, the mean of (bleeding needle holes/needle holes) per a patient; bleeding rate, bleeding risk per a needle hole (total bleeding needle holes/total needle holes); RR, bleeding risk ratio (bleeding rate of group G/bleeding rate of group C); 95%CI, 95 percent confidence interval; hemostatic period, time from the administration of protamine sulphate until pericardial closure; *, Welch's t test.

tion of protamine sulfate (10 mg for 1,000 U of heparin sodium). When bleeding continued from the needle holes after the use of protamine sulfate, hemostatic stitches of 4-0 polypropylene mattress suture with a felt pledget were added for hemostasis.

The patient received a blood transfusion anytime the hematocrit values decreased less than 20% during CPB in this series. In this strategy, the amount of transfusion would not reflect the hemostatic effectiveness of fibrin glue because the preoperative patient's conditions notably varied in regard to anemia, tamponade, and patient's body size.

Statistical methods

The bleeding proportion, a bleeding risk per patient, was calculated with the number of bleeding needle holes divided by the number of needle holes in each patient. The bleeding rate, a bleeding risk per needle hole, was calculated with the total number of all bleeding needle holes divided by the total number of all needle holes in all patients. The bleeding risk ratio (RR) was calculated to evaluate a difference between the two groups. The value of RR refers to the needle hole bleeding rate of group G divided by the same of group C. Whether such a risk differs or not between the two groups was then evaluated.

Referring to continuous variables, we made a series of comparisons using Student's t-test for parametric variables and Wilcoxon's rank sum test for nonparametric variables. A Welch test was employed whenever necessary, with any case of heteroscedasticity taken into account. The 50% hemostatic period data were obtained according to Kaplan-Meier's method using the log-rank test for comparison. The level of significance for tests was set to be not more than 5% at both sides, with the confidence coefficient of 95% at both sides. The SAS Institute (Cary, NC, USA) was used for all statistical analyses.

The Institutional Ethical Committee was informed of the study and did not require approval. Informed consent was obtained from conscious patients or from the family when a patient was unconscious or hemodynamically unstable in the emergency room.

Results

Twenty enrolled patients with ascending aorta or ascending-hemiarch replacement survived the operations. There were no resternotomies for postoperative bleeding.

Baseline data

No difference was observed between the two groups referring to the baseline data (Table 1) and the number of proximal and distal needle holes at anastomoses (Table 2).

Outcome and estimation

1. Bleeding from needle holes at anastomoses

Hemostatic effectiveness of the fibrin glue rub-and-spray method was evaluated with the bleeding proportion of needle holes per patient and the total bleeding rate indicating a bleeding risk per needle hole (Table 2).

First, the bleeding proportion of the proximal anastomosis was 0.7 ± 1.6% (mean ± standard deviation [SD]) with group G and 73.8 ± 16.0% with group C; the same of the distal anastomosis was 4.4 ± 3.7% with group G and 71.9 ± 15.7% with group C, respectively. The fibrin glue rub-and-spray method significantly reduced the needle-hole bleeding proportions at the proximal and distal anastomoses (Wilcoxon's test, p <0.001).

Next, the total bleeding rate at the proximal anastomosis was 0.008 (2/268) with group G and 0.731 (193/264) with group C; the same at the distal anastomosis was 0.045 (13/287) with group G and 0.716 (199/278) with group C, respectively. The fibrin glue rub-and-spray method significantly reduced total RR at the proximal and distal anastomoses (RR: proximal side – 0.010 [95%CI, 0.003–0.041]; distal side – 0.063 [95%CI, 0.036–0.111]).

2. Hemostatic period and blood loss

Hemostatic effectiveness of the fibrin glue rub-and-spray method was evaluated based on the hemostatic period and blood loss (Table 2, Fig. 2).

The 50% hemostatic period estimated by Kaplan-Meier's survival function (Fig. 2) was 41.5 min (interquartile range, 32–49) with group G and 51 min (44–89) with group C, significantly shortened by the fibrin glue rub-and-spray method (log-rank test, p = 0.036).

The blood loss in the hemostatic period was 99 ± 76 ml (mean ± SD) with group G and 257 ± 163 ml with group C, respectively, reduced significantly by the fibrin glue rub-and-spray method (Welch's t test, p = 0.016).

The blood loss 12 hours after the operation was 268 ± 93 ml (mean ± SD) with group G and 526 ± 363 ml with group C, respectively, being reduced by the fibrin glue rub-and-spray method, though insignificantly (Welch's t test, p = 0.054).

3. Blood transfusion amount, operation time, and duration of hospital stay

The amount of blood transfusion was 7.2 ± 4.6 units (mean ± SD) for group G and 5.2 ± 3.8 units for group C. The operation time was 292 ± 51 min for group G and 320 ± 44 min for group C. The duration of hospital stay for Group G was 21 ± 6 days (mean ± SD, for 6 patients after an exclusion of 4 who were obliged to stay longer because of muscle weakness, respiratory failure, and other reasons). The duration was 20 ± 8 days for Group C (for 8 patients after an exclusion of 2 obliged to stay longer because of ultraobesity and respiratory failure). There were no statistical differences in these data between the two groups.

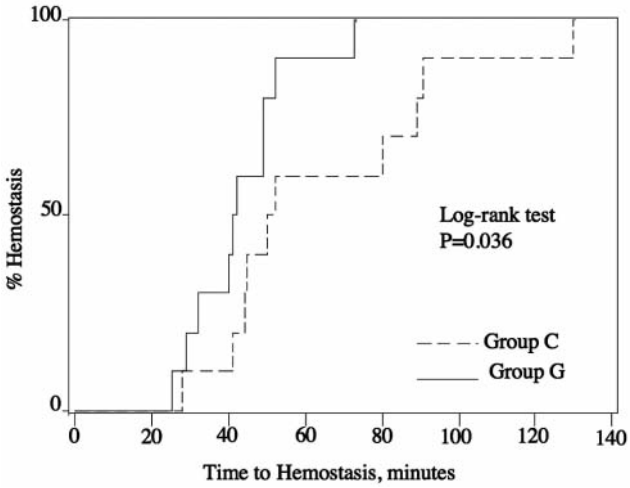

Fig. 2. Cumulative hemostasis rate curve of the hemostasis time. The 50% hemostatic period estimated by Kaplan-Meier's survival curve in group G (fibrin glue rub-and-spray method) and group C (control).
The estimated 50% hemostatic period was significantly shortened by the fibrin glue rub-and-spray method (p = 0.036).

Comment

In cardiovascular surgery with a large dose of heparin sodium and prolonged extracorporeal circulation, the prevention of troublesome bleeding from the suture lines, friable vessels, and needle holes that necessitates resternotomy for hemostasis is very important for the patient's early recovery. The hemostatic effectiveness of fibrin glue in the field of peripheral vascular surgery, cardiac surgery, and aortic surgery had been presented in experimental studies,[4–6] retrospective clinical studies,[7–9] and prospective randomized trials.[10–13] However, well-designed randomized clinical trials of the fibrin glue in aortic surgery were not found in the English language literature. In the clinical reports, the hemostatic effectiveness of the fibrin glue was evaluated usually from the viewpoints of reduction of blood loss, blood transfusion, operating time, reoperation rate, and postoperative hospital stay. However, these factors were not always direct indicators of the hemostatic effectiveness of the fibrin

glue because they would greatly change according to the patients' diseases and preoperative conditions, surgical methods, and duration of extracorporeal circulation with or without deep hypothermia. Also, the mediastinal blood loss expresses not blood loss from the anastomosis with fibrin glue application, but from a total amount of blood losses from elsewhere in the surgical field. Concerning these problems, we uniformed the patient's disease and the surgical procedure to Stanford type A acute aortic dissection and the emergency ascending aorta or ascending-hemiarch replacement via deep HCA. We focused on the number of bleeding needle holes as a direct indicator of the hemostatic effectiveness of the fibrin glue rub-and-spray method, besides the other indicators described in this report.

In this clinical study, the rub-and-spray method significantly reduced the needle hole bleeding proportion per patient in the proximal anastomosis (0.7% in group G vs. 73.8% in group C, $p < 0.001$), and in the distal anastomosis (4.4% in group G vs. 71.9% in group C, $p < 0.001$). It also significantly reduced the total bleeding risk per needle hole (RR) in the proximal anastomosis (bleeding rate 0.008 in group G vs. 0.731 in group C; RR 0.010) and in the distal anastomosis (bleeding rate 0.045 in group G vs. 0.716 in group C; RR 0.063). The rub-and-spray method significantly shortened the 50% hemostatic period on Kaplan-Meier's curve (41.5 min in group G vs. 51 min in group C, $p = 0.036$), and it significantly reduced the amounts of bleeding during this hemostatic period (99 ml in group G vs. 257 ml in group C, $p = 0.016$). It also had a tendency to reduce the amounts of postoperative mediastinal blood loss during the first 12 hours after surgery (268 ml in group G vs. 526 ml in group C, $p = 0.054$). These data suggested the significant hemostatic effectiveness of the fibrin glue rub-and-spray method in clinical settings. On the other hand, this method did not affect the amount of blood transfusion, operating time, or duration of postoperative hospital stay in patients with Stanford type A acute aortic dissection with the ascending aorta or ascending-hemiarch replacement, probably because of the preoperative differences of the patients' conditions, such as anemia, intrapericardial bleeding, thrombosis of the false lumen, and hemodynamic instability.

The hemostatic mechanisms of fibrin glue are the compressive covering of the surface of the bleeding area and the sealing of a needle hole or an anastomotic gap.[3] Oozing and venous hemorrhage would be easily treated; however, pulsatile hemorrhaging could not be arrested with fibrin glue's application alone. If it is to be prevented, the sealing of the needle hole or the anastomotic gap with fibrin glue before reperfusion is essential. Moreover, the adhesive strength of the fibrin glue against blood pressure is also important to maintain hemostasis. This strength against pressure and adhesive characteristics is variable by application methods and by the concentrations of the contents.[3,6,14] The spray method had been proved to have a strong sealing effect because of its homogenous application and complete mixing of the two components of the fibrin glue.[8,15] In the pathological study of fibrin glue application over the needle holes on polytetrafluoroethylene graft by Minato et al.[3] there were differences in the reaching depth of fibrin glue into the needle hole between 4 application methods: dripping, spray, spray-and-rub, rub-and-spray. The rub-and-spray method invaded and plugged deeper into the needle hole than the other methods. And this plugging mechanism produced the strongest resistance against pressure. In the rub-and-spray method, the first stage of the rubbing A solution (containing fibrinogen) on the needle holes allowed an easy invasion of fibrinogen into the holes; the second stage of spraying A and B solutions (containing thrombin and calcium chloride) made a certain polymerization of the fibrin glue in the needle holes. However, concern was pointed out about a possibility of penetration by the fibrin glue into the vascular lumen through the needle hole, which would provoke intravascular thrombosis or coagulopathy.[3,16] The larger the needle hole, the greater the possibility of glue-penetration into the vascular lumen. However, there were no reports of intravascular thrombosis or coagulopathy caused by the fibrin glue application over the vessels in the 30-year history of clinical use. Kheirabadi et al.[5] reported that pathological examination showed no intravascular thrombosis, and they had no animal deaths caused by thrombotic events. They explained that a complete mixing of fibrinogen and thrombin in the preparation leaves no residually active thrombin that would possibly cause intravascular thrombosis. Minato et al.[3] microscopically showed no abnormal thrombus formation around the fully polymerized fibrin glue being exposed to the blood stream in the rub-and-spray method. On the other hand, the surface of autologous thrombus, which naturally plugged the needle hole from the inside, was rather irregular on the needle hole without fibrin glue application. These facts suggested less thrombogenicity of the fully polymerized fibrin glue; however, further investigation for long-term effects is necessary.

The limitations of this study were due to the additional hemostatic maneuvers on the anastomosis, such as additional sutures or compression with oxidized cotton when bleeding continued in the clinical situations. Also, we could not compare the hemostatic effectiveness with other application methods of fibrin glue, such as the spray or the spray-and-rub methods, because we found few patients with Stanford type A acute aortic dissection in one hospital in such a short period.

Conclusions

The rub-and-spray method of fibrin glue was clinically proved to be extremely effective for the hemostasis of needle holes in emergency aortic surgery for acute aortic dissection. This method can be used safely and effectively as a sealant for hemostasis in cardiovascular surgery with systemic heparinization, prolonged CPB, and deep hypothermia.

References

1. Spängler HP, Braun F, Holle J, Moritz E, Wolner E. The local application of fibrinogen and collagen for hemostasis in heart surgery. *Wien Med Wochenschr* 1976; **126**: 86–9.
2. Jackson MR. New and potential uses of fibrin sealants as an adjunct to surgical hemostasis. *Am J Surg* 2001; **182** (2 Suppl): 36–9S.
3. Minato N, Shimokawa T, Katayama Y, Yamada N, Sakaguchi M, et al. New application method of fibrin glue for more effective hemostasis in cardiovascular surgery: rub-and-spray method. *Jpn J Thorac Cardiovasc Surg* 2004; **52**: 361–6.
4. Kram HB, Nugent P, Reuben BI, Shoemaker WC. Fibrin glue sealing of polytetrafluoroethylene vascular graft anastomoses: comparison with oxidized cellulose. *J Vasc Surg* 1988; **8**: 563–8.
5. Kheirabadi BS, Pearson R, Rudnicka K, Somwaru L, MacPhee M, et al. Development of an animal model for assessment of the hemostatic efficacy of fibrin sealant in vascular surgery. *J Surg Res* 2001; **100**: 84–92.
6. Dickneite G, Metzner H, Pfeifer T, Kroez M, Witzke G. A comparison of fibrin sealants in relation to their in vitro and in vivo properties. *Thomb Res* 2003; **112**: 73–82.
7. Walterbusch G, Haverich A, Borst HG. Clinical experience with fibrin glue for local bleeding control and sealing of vascular prostheses. *Thorac Cardiovasc Surgeon* 1982; **30**: 234–5.
8. Spotnitz WD, Dalton MS, Baker JW, Nolan SP. Reduction of perioperative hemorrhage by anterior mediastinal spray application of fibrin glue during cardiac operations. *Ann Thorac Surg* 1987; **44**: 529–31.
9. Séguin JR, Frapier JM, Colson P, Chaptal PA. Fibrin sealant improves surgical results of type A acute aortic dissections. *Ann Thorac Surg* 1991; **52**: 745–9.
10. Rousou J, Levitsky S, Gonzalez-Lavin L, Cosgrove D, Magilligan D, et al. Randomized clinical trial of fibrin sealant in patients undergoing resternotomy or reoperation after cardiac operations. A multicenter study. *J Thorac Cardiovasc Surg* 1989; **97**: 194–203.
11. Jackson MR, Gillespie DL, Longenecker EG, Goff JM, Fiala LA, et al. Hemostatic efficacy of fibrin sealant (human) on expanded polytetrafluoroethylene carotid patch angioplasty: a randomized clinical trial. *J Vasc Surg* 1999; **30**: 461–6.
12. Codispoti M, Mankad PS. Significant merits of a fibrin sealant in the presence of coagulopathy following paediatric cardiac surgery: randomised controlled trial. *Eur J Cardiothorac Surg* 2002; **22**: 200–5.
13. Taylor LM Jr, Mueller-Velten G, Koslow A, Hunter G, Naslund T, 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.
14. Sawamura Y, Asaoka K, Terasaka S, Tada M, Uchida T. Evaluation of application techniques of fibrin sealant to prevent cerebrospinal fluid leakage: a new device for the application of aerosolized fibrin glue. *Neurosurgery* 1999; **44**: 332–7.
15. Redl H, Schlag G, Dinges HP. Methods of fibrin seal application. *Thorac Cardiovasc Surgeon* 1982; **30**: 223–7.
16. Kheirabadi BS, Field-Ridley A, Pearson R, MacPhee M, Drohan W, et al. Comparative study of the efficacy of the common topical hemostatic agents with fibrin sealant in a rabbit aortic anastomosis model. *J Surg Res* 2002; **106**: 99–107.