

Multicenter, Open Trial in Japan of the Novel Completely Autologous Fibrin Sealant CryoSeal® FS System: Excellent Performance, Efficacy and Safety Demonstrated for Use during Surgical Procedures

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INTRODUCTION

Commercial fibrin sealants used in surgery are derived from pooled human plasma or bovine materials¹⁻³. Specifically, the thrombin in autologous fibrin sealant is derived from pooled human plasma⁴⁻⁶. In either case, the possibility of infection from products derived from sources other than the patient can not be ruled out⁷⁻⁹.

CryoSeal® (trial code name AMF-1408), a completely autologous fibrin sealant production system used in the trial reported here, uses autologous plasma collected from the patient before surgery to simultaneously separate autologous cryoprecipitate and generate autologous thrombin in a closed circuit[®]. By spreading or dripping the cryoprecipitate and thrombin produced by this system onto the surgical area with a specialized spray device, it has become possible to realize the use of a completely autologous fibrin sealant.

CryoSeal® was developed by ThermoGenesis Corporation (US) and is a novel medical device tested in clinical trial in Japan by Asahi Kasei Medical Company, Ltd. The purpose of this trial was to study the efficacy, safety and usefulness of CryoSeal®, in patients undergoing orthopedic, gastrointestinal, neuro- or cardiovascular surgery.

METHODS

Study device

Table 1: Components of CryoSeal®

Study device	Name
Machine	Cryo-processor Plasma processing unit Cryoprecipitate chamber Thrombin activation device (TAD)
Disposable parts	Syringe
Aerosol:	Spray tips, Line dot tips
Reagents:	CaCl ₂ , Ethanol

Study design

Multicenter, open trial conducted in 6 hospitals, with surgery performed in 2 clinical departments each among orthopedic, gastrointestinal, neuro- or cardiovascular surgery.

Subjects

Patients who were planning to use autologous blood and fibrin sealant for surgery.

Inclusion criteria

Patients for whom the procedure was indicated and agreed to the use of autologous transfusion with written informed consent.

Patients from whom 400 mL or more of their own blood could be collected for autologous transfusion before surgery.

Exclusion criteria

Under age 17 or over age 81
Pregnant women, possibly pregnant women and nursing mothers
Genetic coagulation disorders

Plasma fibrinogen concentration at or below 100 mg/dL
Platelet count less than 100,000/ μ L

Patients given warfarin potassium
Patients in clinical trials in the past 6 months

Patients considered inappropriate for participation in the trial by the physician

METHODS -Continued-

Evaluation of coagulation activity *in vitro*

Coagulation activity was tested by mixing the same volume of cryoprecipitate and thrombin using KC1A Micro (Sigma Diagnostics) and was evaluated at 4 levels: excellent, good, fair or poor.

Evaluation of clinical efficacy

Evaluation was made of the appropriate items for each disease from the following:

1. coagulation
2. hemostasis of the anastomosis
3. hemostasis of the other areas
4. cerebrospinal fluid leakage
5. lymph fluid leakage
6. coverage of the cut surface
7. adhesion of the cut surface
8. filling of bone deficient space

Integrated evaluations of clinical efficacy were made and divided into 3 categories: "very effective" when satisfactory results were obtained in more than 80% of the cases, "effective" for satisfactory results in more than 50% of the cases, and "not effective" for satisfactory results in 50% or less of the cases.

Evaluation of safety

Safety was evaluated in terms of the incidence of adverse events.

Evaluation of usefulness

Usefulness was evaluated into 3 levels based on the evaluation of efficacy and safety: very useful, useful, not useful.

RESULTS

Table 2: Subject groups analyzed

Subjects	N	(%)	Samples processed
Enrolled	74	—	79
Evaluated clinically	72	(97.3)	77
Coagulation activity	66	(89.2)	(71)*

* 6 samples excluded due to insufficient testing

Table 3: Number of subjects clinically evaluated by disease (N=72)

Clinical department	Disease	n	(%)
Gastrointestinal surgery	Esophageal cancer	18	(25.0)
Cardiovascular surgery (n=17)	Angina pectoris (coronary bypass grafting: CABG)	10	(13.9)
	Aortic aneurysm	4	(5.6)
	Valvular heart disease	3	(4.2)
Orthopedic surgery (n=19)	Knee joint disease	11	(15.3)
	Malum coxae	4	(5.6)
	Spondylolysis	4	(5.6)
Neurosurgery (n=18)	Brain tumor	10	(13.9)
	Aneurysm	5	(6.9)
	Arteriostenosis	2	(2.9)
	Cerebral vesicle	1	(1.4)

Table 4: Characteristics of subjects evaluated (N=72)

Characteristics	Mean \pm SD	Min - Max
Age (years)	59.5 \pm 12.2	20 - 79
Body weight (kg)	61.3 \pm 11.4	38 - 91
Fibrinogen (mg/dL)	335.9 \pm 108.7	173 - 651

Table 5: Yield of cryoprecipitate and thrombin

	Cryoprecipitate	Thrombin
Number of samples processed	77	77
Yield: Mean \pm SD (mL)	5.1 \pm 1.2	5.1 \pm 1.2
Min - Max (mL)	2.3 - 8.9	2.3 - 8.9

RESULTS -Continued-

Figure 1: Mean concentration of fibrinogen before and after processing by CryoSeal®

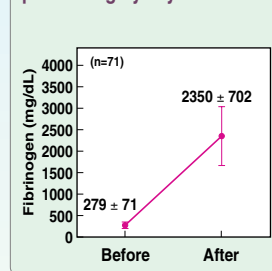


Figure 2: Mean thrombin activity before and after processing by CryoSeal®

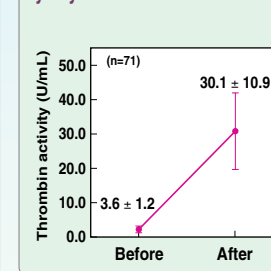


Figure 3: Clinical efficacy by each dosage of cryoprecipitate and thrombin (N=72)

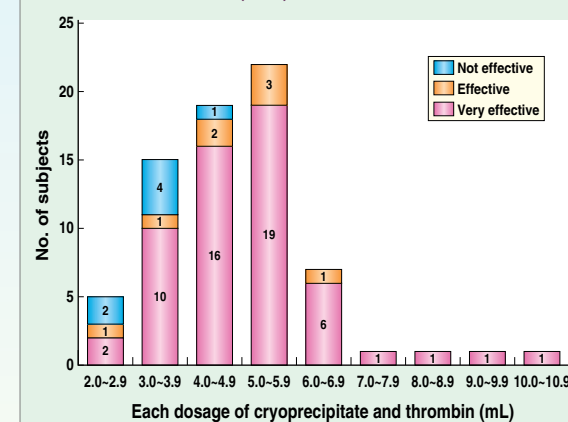


Table 6: Coagulation activity of 71 samples

Efficacy	Time (sec)	n	(%)
Excellent	< 5	46	(64.8)
Good	5 - < 10	16	(22.5)
Fair	10 - < 60	9	(12.7)
Poor	\geq 60	0	(0.0)

Table 7: Evaluation of clinical efficacy by disease

Clinical department	Disease	Number of subjects	Evaluation of efficacy			Effective or better (efficacy rate)
			Very effective	Effective	Not effective	
All		72	57 (79.2)	8 (11.1)	7 (9.7)	65 (90.3)
Gastrointestinal surgery	Esophageal cancer	18	14 (77.8)	2 (11.1)	2 (11.1)	16 (88.9)
Cardiovascular surgery	Angina pectoris (CABG)	17	15 (88.2)	1 (5.9)	1 (5.9)	16 (94.1)
Cardiovascular surgery	Angina pectoris (CABG)	10	8 (80.0)	1 (10.0)	1 (10.0)	9 (90.0)
Cardiovascular surgery	Aortic aneurysm	4	4 (100.0)	0 (0.0)	0 (0.0)	4 (100.0)
Cardiovascular surgery	Valvular heart disease	3	3 (100.0)	0 (0.0)	0 (0.0)	3 (100.0)
Orthopedic surgery	Knee joint disease	19	14 (73.7)	4 (21.1)	1 (5.3)	18 (94.7)
Orthopedic surgery	Malum coxae	4	2 (50.0)	2 (50.0)	0 (0.0)	4 (100.0)
Orthopedic surgery	Spondylolysis	4	3 (75.0)	0 (0.0)	1 (25.0)	3 (75.0)
Neurosurgery	Brain tumor	10	7 (70.0)	1 (10.0)	2 (20.0)	8 (80.0)
Neurosurgery	Aneurysm	5	4 (80.0)	0 (0.0)	1 (20.0)	4 (80.0)
Neurosurgery	Arteriostenosis	2	2 (100.0)	0 (0.0)	0 (0.0)	2 (100.0)
Neurosurgery	Cerebral vesicle	1	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)

DISCUSSION

CryoSeal® is capable of producing the cryoprecipitate and thrombin needed for fibrin sealant in a closed circuit in a short time.

The system is highly effective and is capable of providing safe fully autologous fibrin sealant to surgical patients, where neither bovine nor pooled human plasma are used for production.

Even if yields are small, sufficient amounts of sealant may be prepared by combining multiple preparations.

We compared our results to pooled commercial fibrin sealants and non-commercially produced autologous fibrin sealants in Japan as follows:

Table 8: Composition of commercial fibrin sealants in Japan

	CryoSeal®	Bolheal™ ¹⁾	Beriplast™ ²⁾	Tisseel® ³⁾
Fibrinogen	Autologous	Pooled human	Pooled human	Pooled human
Thrombin	Autologous	Pooled human	Pooled human	Pooled human
Aprotinin	—	Bovine	Bovine	Bovine

Table 9: Composition and production time of the CryoSeal® and non-commercially produced autologous fibrin sealants in Japan

	CryoSeal®	Autologous
Fibrinogen	Autologous	Autologous
Thrombin	Autologous	Pooled human
Production time	1 hour	1 - 2 days

DISCUSSION -Continued-

Table 10: Efficacy of CryoSeal® and commercial fibrin sealants

Clinical department	CryoSeal® (our study)	Bolheal™ ¹⁾	Beriplast™ ²⁾	Tisseel® ³⁾
All	65 / 72 (90.3%)	—	—	971 / 1,044 (93.0%)
Gastrointestinal surgery	16 / 18 (88.9%)	202 / 232 (87.1%)	30 / 37 (81.1%)	31 / 36 (86.1%)
Cardiovascular surgery	16 / 17 (94.1%)	75 / 80 (93.8%)	—	—
Orthopedic surgery	18 / 19 (94.7%)	—	—	249 / 266 (93.6%)
Neurosurgery	15 / 18 (83.3%)	25 / 25 (100%)	39 / 41 (95.1%)	—

Table 11: Dosage and administration of CryoSeal® and commercial fibrin sealants

	CryoSeal®	Bolheal™ ¹⁾	Beriplast™ ²⁾	Tisseel® ³⁾
Dosage (mL)	5.1 \pm 1.2	5.0	5.0	5.0
Fibrinogen (mg/dL)	2,350 \pm 702	8,000	8,000	9,000
Thrombin activity (U/mL)	30.1 \pm 10.9	250	350	500

Table 12: Comparison of CryoSeal® and non-commercially produced autologous fibrin sealants

	CryoSeal®	Tokyo University ⁴⁾	Toho University ⁵⁾	Kagoshima University ⁶⁾
Fibrinogen (mg/dL)	2,350 \pm 702	4,350 \pm 1,720	1,190 \pm 311	2,560 \pm 560
Thrombin activity (U/mL)	30.1 \pm 10.9	588	1,000	200

Our study indicated a sufficient clinical efficacy despite having lower thrombin activity than commercial or non-commercial fibrin sealants.

SUMMARY

An average of 5.1 \pm 1.2 mL (77 samples) of cryoprecipitate and an equal amount of thrombin solution were produced from 200 - 400 mL of plasma.

The average concentration of fibrinogen in the cryoprecipitate produced was 2,350 \pm 702 mg/dL (N=71) and average thrombin activity 30.1 \pm 10.9 U/ml (N=71).

In the clinical trial, the clinical efficacy rate (effective or better) was 90.3% (65/72 subjects) and no adverse events were seen that were causally related to the trial device.

The completely autologous fibrin sealant prepared by the CryoSeal® was shown to be safe and to have excellent performance.

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