Journal of Artificial Organs (2020) 23:77–84
https://doi.org/10.1007/s10047-019-01135-1

ORIGINAL ARTICLE

Others

Potential utility of new surgical hemostatic film using Hydrofit®: a preliminary study

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Received: 24 July 2019 / Accepted: 19 September 2019 / Published online: 25 September 2019

Abstract

We developed a surgical hemostatic film using Hydrofit® (Hydrofit® film). This film is prepared by reacting Hydrofit® with water in advance, and it can be used in the same way as an accessory silicone sheet. In addition, unlike the silicone sheet, there is no need to remove the Hydrofit® film from the body. In the present study, we describe the hemostatic effect of our new method using Hydrofit® film. We created a pulsatile flow circuit model using a ventricular assist device and a vascular graft. The circuit was filled with water, and the systolic pressure was adjusted to ≥ 130 mmHg. The artificial blood vessel was punctured by an 18-G needle. Operations to prevent water from leaking were attempted through either a conventional method using a silicone sheet or our new method using Hydrofit® film. In the 180-s trial, 14 attempts (93.3%) with the Hydrofit® film were successful. In the silicone sheet group, 13 attempts (86.7%) were successful before the silicone sheet was peeled off, and hemostasis was maintained in 10 (66.5%) cases after the silicone sheet was removed. After short-duration hemostasis for 60 s, good waterproofing was obtained in the Hydrofit® film group (success in 17 cases [85%]). In contrast, in the silicone sheet group, 10 attempts (50%) were successful before the silicone sheet was peeled off, and hemostasis was maintained in only 7 (35%) cases after the silicone sheet was removed. Hydrofit® film showed good hemostatic performance in the pulsatile flow circuit model.

Keywords Hemostasis · Hemorrhage · Hydrofit®

Introduction

Controlling bleeding is an important factor in surgery. Bleeding and the need for transfusions are both associated with increased postoperative morbidity and mortality [1]. In cardiovascular surgery in particular, there are some cases in which severe coagulopathy occurs due to cardiopulmonary bypass and hypothermia [2, 3]. It is often difficult to control bleeding. For oozing after controlling surgical bleeding, hemostasis is often achieved with the aid of a surgical hemostatic sealant [4, 5]. In most cases, successful hemostasis depends on the blood clotting ability of patients. Therefore, in cases of blood coagulation abnormalities, such hemostatic agents sometimes fail to achieve hemostasis. In addition, these hemostatic agents cannot obtain proper hemostasis unless the operative field is dry.

Hydrofit® (Sanyo Chemical Industries, Kyoto, Japan) was first reported by Matsuda et al. [6] in 1986. It does not require any blood components for hemostasis. The synthetic sealant is a hydrophilic urethane prepolymer which reacts with water and then bonds repeatedly with other urethane prepolymers. Finally, these prepolymers react together to form elastic polyurethanes. Because it forms a urethane resin film, it is physically hemostasized. The urethane resin coating firmly adheres to the tissue and forms a flexible and elastic coating, allowing for arterial pulsation [7]. In Japan, it has been approved for use in thoracic aortic surgery and contributes greatly to achieving hemostasis.

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The general usage of Hydrofit® is as follows: first, a syringe prefilled with the sealant liquid is applied to the bleeding point, which is covered with the accessory transparent silicone sheet. The sheet is then pressed with the fingers for about 3 min. After the urethane resin coating film has formed, the silicone sheet is peeled off. However, while this sequence is how the use of Hydrofit® is generally described in official documentation, the silicone sheet sometimes remains stuck to the Hydrofit®, and we often experience cases in which the sealant comes off as well when the silicone sheet is peeled away, resulting in re-bleeding.

As a substitute for the silicone sheet, we examined the possibility of using an already cured film of Hydrofit® sealant (Hydrofit® film). This cured film is prepared by reacting Hydrofit® with water in advance, and it can be used in the same way as a silicone sheet. Because this film is Hydrofit® itself, it does not need to be removed from the body, unlike the silicone sheet. If a good hemostatic effect can be achieved with this film, it could replace the conventional method.

The present study attempted to verify the efficacy of our new method using Hydrofit® film for achieving hemostasis.

Materials and methods

Materials

Hydrofit® sealant (Sanyo Chemical Industries) is a urethane resin-forming prepolymer. The sealant is reacted with water to prepare a cured product [8]. Diisocyanate-capped polyols react with water to convert an isocyanate-amino group with liberation of carbon dioxide (Eq. 1). Potent additional reaction of amino groups with unreacted isocyanate groups leads to polymerization of elastic polyurethanes (Eq. 2)

$$\mathrm{OCN{-}R{-}NCO + H_2O \rightarrow [HOCONH{-}R{-}NCO] \rightarrow H_2N{-}R{-}NCO + CO_2} \quad (1)$$

$$\mathrm{nOCN{-}R{-}NCO + H_2N{-}R{-}NCO + (n+1)H_2O \rightarrow H_2N{-}R{-}(NHCONH{-}R{-})n{-}NH_2 + (N+1)CO_2} \quad (2)$$

–NCO: isocyanate group, $–NH_2$: amino group, –NHCONH–: urea bond.

The prototype Hydrofit® film was prepared by Sanyo Chemical Industries. The silicone sheet (Sanyo Chemical Industries) is a polyalkylalkenylsiloxane crosslinked product made of Hydrofit®. The sheet was 2.5 cm in width, 19 cm in length, and 300 μm in thickness.

Methods

A pulsatile flow circuit model was created using a ventricular assist device (NiproVAS, Nipro Corporation, Osaka, Japan), a ventricular assist device cardiac-driving device (VCT-50χ; YACELEX Corporation, Osaka, Japan) and a vascular graft (Triplex®, 26 mm; Terumo Corporation, Tokyo, Japan) (Fig. 1).

The circuit was filled with water and the systolic pressure was adjusted to be ≥ 130 mmHg. The pressure was displayed on a Life Scope (BSM-6501; Nihon Kohden Corporation, Tokyo, Japan) and the data were recorded. The experimental procedure was as follows (Fig. 2):

1. The leakage of the connections of the circuit and the artificial blood vessel itself over 3 min was recorded as "leakage of the circuit (LC)".
2. The artificial blood vessel was punctured with an 18-G needle (1.2-mm needle outer diameter) to create a spout hole.
3. The total leakage volume over 3 min was measured. We subtracted the LC from the total leakage volume and defined it as the "leakage from the needle hole before hemostasis".
4. Hemostasis was attempted with our new method (using Hydrofit® Film [HF]) and the conventional method (using a silicone sheet [SS]).
5. The amount of leakage for 3 min after hemostasis was measured. We subtracted the LC from this leakage volume and defined it as "leakage after compression hemostasis".
6. In the SS group, the silicone sheet was peeled off.
7. The amount of leakage for 3 min after peeling off the silicone sheet was also measured. We subtracted the LC from this leakage volume and defined it as the "leakage after SS removal".
8. When any leakage remained, an additional waterproofing operation, such as suturing, was performed to move on to the next measurement.

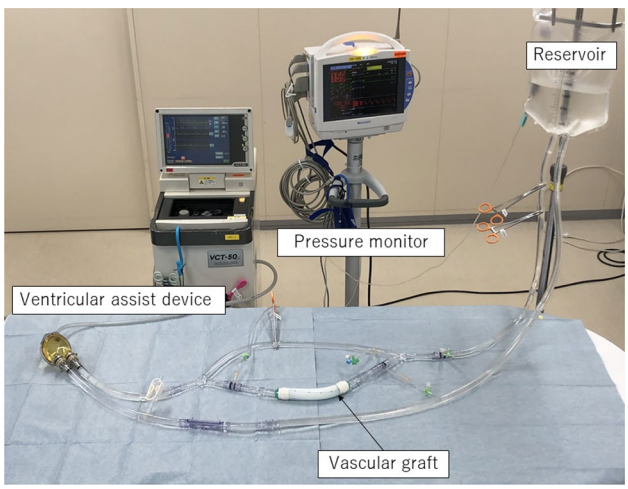

Fig. 1 A pulsatile flow circuit model. We created a pulsatile flow circuit model that pumps constant pressure

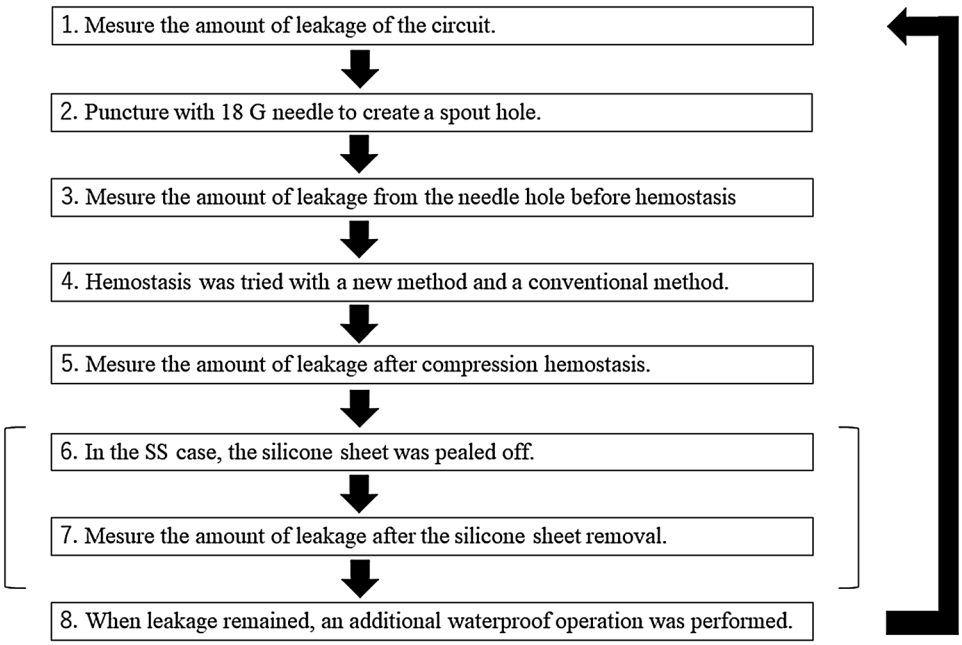

Fig. 2 The experimental procedure. Operations to prevent water from leaking were attempted through either a conventional method using a silicone sheet or our new method using a Hydrofit® film for two time periods per method: 180 s and 60 s. For each vascular graft module, the HF method and SS method were alternately performed 12 times in total and replaced with a new artificial blood vessel module. The same surgeon completed all steps in the series (steps 1–8). *SS* silicone sheet

For each vascular graft module, the HF method and SS method were alternately performed 12 times in total and replaced with a new artificial blood vessel module. These procedures were conducted by five cardiovascular surgeons at Oita University Hospital who were familiar with Hydrofit®'s usage. The same surgeon completed all steps in the series (above steps 1–8).

HF group

HF was placed in a tray filled with saline. After 1 min, the HF was removed from the tray and wiped lightly with gauze. Since the swollen film expands from 2.5 to 3.5 cm in width (Fig. 3), it was molded to 2.5 cm × 2.5 cm. Approximately 0.2 g of Hydrofit® sealant was applied to the film and thinly stretched with the attached spatula. The film was held down over the needle hole with a finger. To promote the reaction, saline was thoroughly sprayed around the film. After the designated time (180 s and 60 s), compression was stopped, and the amount of leakage was measured for 3 min.

SS group

The SS was molded to 2.5 × 2.5 cm. After applying 0.2 g of Hydrofit® sealant, spread thinly with the attached spatula, the sheet was held down over the needle hole with a finger. To promote the reaction, physiological saline was thoroughly sprayed around the sheet. The compression was stopped after the designated time (180 s and 60 s). First, the leakage when the SS was stuck was measured (leakage after compression hemostasis), and then the sheet was peeled off and its leakage was again measured (leakage after SS detachment).

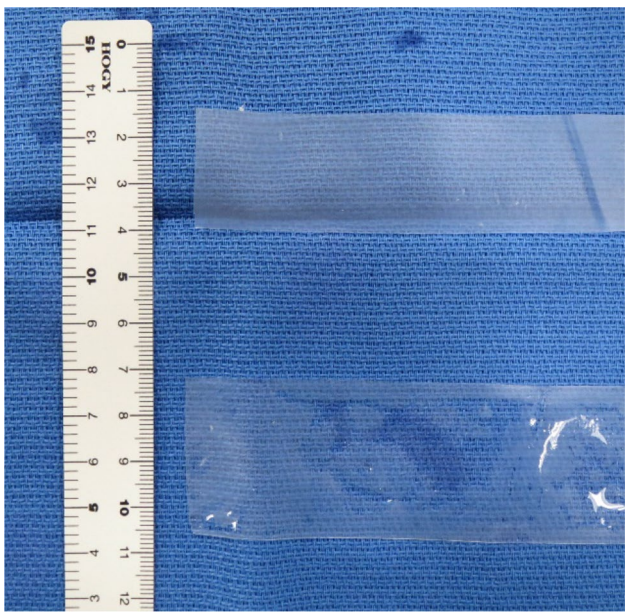

Fig. 3 Hydrofit® film appearance. The top strip is the film before soaking in saline, and the bottom strip is the film after soaking in saline. The film is a hydrophilic substance that swells when it contains saline

In addition, we observed the microscopic findings of two different Hydrofit® resin coatings created in the previous waterproofing experiment. The specimens were stained with hematoxylin and eosin staining.

Evaluation method

Waterproofing experiments at 180 s and 60 s were performed 70 times in total. Since the leakage of water from the artificial blood graft itself could not be completely prevented, a leakage volume ("leakage after compression hemostasis" or "leakage after SS removal") of ≤ 5 ml over 3 min was judged to be a success. Whereas a leakage volume of > 5 ml was judged to be a failure. Since HF cases did not use the SS, we were unable to measure the "leakage after SS detachment". Therefore, in HF cases, we used the same numerical value as "leakage after compression hemostasis" for comparison with the SS group.

Statistical analyses

The success rate of hemostasis was compared by Fisher's exact test. Systolic blood pressure, diastolic blood pressure, mean blood pressure, and basal circuit leakage volume were described as the mean ± standard deviation and evaluated by an unpaired *t* test. The amount of bleeding was described as the median [interquartile range] and judged by the Mann–Whitney *U* test. $P < 0.05$ was judged to indicate a statistically significant difference.

All statistical analyses were conducted using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan). EZR is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) with a modified version R command designed to add statistical functions that are used frequently in biostatistics.

Results

Waterproof experiment

There were no marked differences in the two groups in terms of the systolic pressure, diastolic pressure, mean pressure, leakage of the circuit, and leakage from the needle hole before hemostasis (Table 1a, b).

In the 180-s trial, 14 attempts (93.3%) with the HF were successful. In the SS group, 13 attempts (86.7%) were successful before the sheet was peeled off. In three of these cases, however, water began leaking again after peeling off the sheet. Ultimately, only 10 attempts (66.7%) were successful in the SS group. When comparing the amount of leakage, the HF group had less leakage than the SS group for both times before and after peeling off the SS (Table 2a, Fig. 4a).

Even in the 60-s trial, reliable hemostasis was observed in the HF group with a high hemostasis success rate (85.0%). In contrast, in the SS group, only 10 cases (50%) and 7 cases (35%) showed successful hemostasis before and after peeling off the SS, respectively. In the short-duration waterproof experiments of 60 s in particular, there was a significant

Table 1 Prerequisites

(a) Prerequisites in 180 s	HF group, $n = 15$	SS group, $n = 15$	*P* value
Pressure			
Systolic (mmHg)	134.4 ± 4.8	135.2 ± 2.8	0.585
Diastolic (mmHg)	58.6 ± 4.1	57.2 ± 4.0	0.361
Mean (mmHg)	92.0 ± 4.7	91.2 ± 7.1	0.720
Leakage			
Leakage from the circuit (ml)	5.3 ± 6.5	4.3 ± 4.9	0.642
Leakage from the needle hole (ml)	83.7 ± 35.0	77.5 ± 31.1	0.613
(b) Prerequisites in 60 s	HF group, $n = 20$	SS group, $n = 20$	*P* value
Pressure			
Systolic (mmHg)	135.4 ± 4.5	134.0 ± 3.2	0.329
Diastolic (mmHg)	55.9 ± 7.6	56.2 ± 5.8	0.890
Mean (mmHg)	91.7 ± 6.9	91.0 ± 6.3	0.724
Leakage			
Leakage from the circuit (ml)	4.9 ± 4.5	4.2 ± 4.4	0.651
Leakage from the needle hole (ml)	95.2 ± 34.5	88.7 ± 28.5	0.523

Data given as the mean ± SD

HF Hydrofit® film, *SS* silicone sheet

difference in the hemostasis performance between the two groups (Table 2b, Fig. 4b).

Microscopic findings

In the conventional method, the urethane polymer entered into the interstices of fibers of the artificial blood vessel, forming a firmly adhered film (Fig. 5a). Similarly, with the new method, the urethane polymer infiltrated between the artificial vascular fibers and adhered firmly (Fig. 5b). Furthermore, the sealant infiltrated the sheet to form an integral resin film, resulting in a thicker Hydrofit® layer than with the conventional method. It was thought that this contributed to a stable hemostatic effect.

Discussion

Hydrofit® is a urethane-based hemostatic agent. Using highly reactive isocyanate groups at both ends of the polyurethane precursor, the precursor absorbs the water in the body, undergoing hydrolysis and polymerizing by forming a urea bond while releasing carbon dioxide gas. Finally, it is transformed into a relatively soft rubbery elastomer [9].

This material has many advantages over other hemostatic products. For one, a wet state is required for the reaction to proceed, in contrast to other hemostatic agents. This makes it an exceptionally useful hemostatic agent. In addition, since the hemostatic agent exerts a hemostatic effect regardless of the blood-clotting ability of the patient, it is particularly suitable as a hemostatic agent in cardiovascular surgery. Furthermore, arterial blood vessels stretch and deform every heartbeat, causing repeated stress concentrated at the hemostasis site. If a non-compliant hemostatic agent is used, it may gradually peel away from the blood vessel wall. Therefore, hemostatic agents for arterial walls must fit the deformation of the blood vessel [10, 11]. Hydrofit® reacts with water to form a highly elastic urethane resin film that firmly adheres to the tissue and forms a flexible and elastic coating, which easily follows the arterial pulsation [7].

As mentioned above, Hydrofit® is a hemostatic agent with many advantages, but there are several problems that need to be addressed. In the current standard method of usage, the compatibility between the sealant and the SS is poor. Although the sealant and SS do not chemically react, there are cases where the sealant peels off along with the SS, causing rebleeding. Therefore, several studies have explored methods using Surgicel® (Johnson & Johnson Medical Industry, Ltd., Kyoto, Japan) as an alternative to an SS [7, 12]. Good short-term results with this method have been reported. However, there is a theoretical concern in this method associated with the inclusion of foreign substances during Hydrofit® polymer formation. In addition, long-term clinical results and in vitro studies of this method are missing. In contrast, Hydrofit® has been studied for a long time [6, 13–15]. In animal experiments, it has been reported that problems such as wall thinning and pseudoaneurysm do not occur in the late term [16]. Even in clinical use cases, the Hydrofit® resin coating showed no structural deterioration after removal at 4 years and 8 months after implantation [8]. HF is a form of Hydrofit® sealant that is reacted and cured in advance through basically the same procedure as in cases where the resin coating film is made with Hydrofit® sealant alone.

Table 2 Results

(a) Results in 180 s	HF group, $n=15$	SS group, $n=15$	P value
Hemostasis success			
After compression hemostasis n (%)	14 (93.3%)	13 (86.7%)	1
After silicone sheet removal n (%)	14 (93.3%)	10 (66.7%)	0.169
Leakage			
After compression hemostasis (ml)	0 [0–0]	0 [0–2]	0.047*
After silicone sheet removal (ml)	0 [0–0]	0 [0–14]	0.008*
(b) Results in 60 s	HF group, $n=20$	SS group, $n=20$	P value
Hemostasis success			
After compression hemostasis n (%)	17 (85.0%)	10 (50.0%)	0.041*
After silicone sheet removal n (%)	17 (85.0%)	7 (35.0%)	0.003*
Leakage			
After compression hemostasis (ml)	0 [0–2.5]	6.5 [0–26.0]	0.172
After silicone sheet removal (ml)	0 [0–2.5]	23.5 [0–45.0]	0.016*

Data given as n (%) or median [interquartile range]

HF Hydrofit® film, *SS* silicone sheet

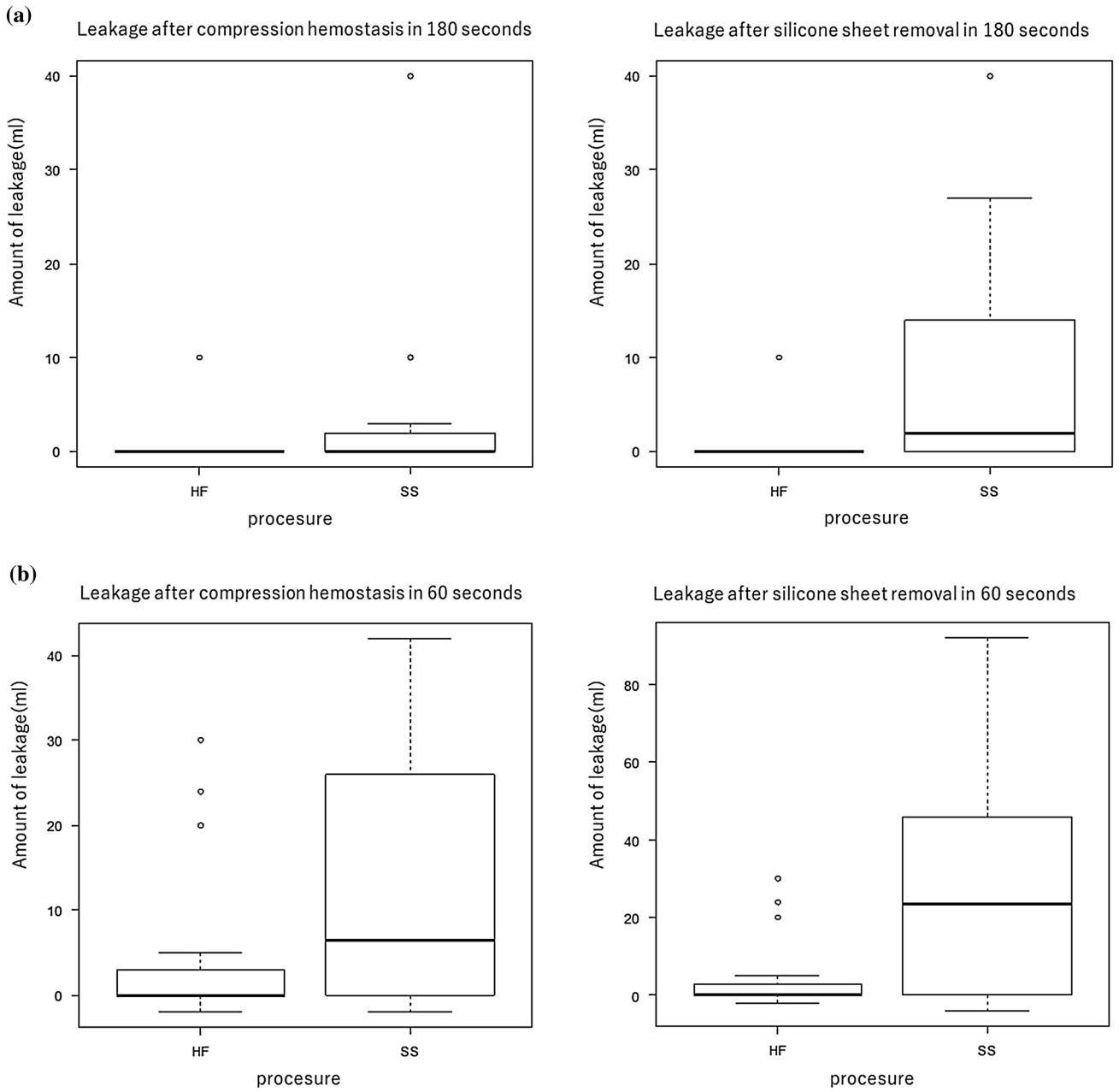

Fig. 4 Results. **a** Results after 180 s, **b** results after 60 s, *HF* Hydrofit® film, *SS* silicone sheet. The HF group had less leakage than the SS group for both times before and after peeling off the silicone sheet

The microscopic findings in the present study also showed that the HF and sealant were sufficiently polymerized. It was thought that good long-term results could be expected for HF.

In this experiment, HF showed better hemostatic performance than the conventional method. Especially for 60-s hemostasis, the difference in the hemostatic performance was remarkable. Our new method using HF was able to stop bleeding quite rapidly in comparison with the conventional method using an SS. Because the HF itself has water retentivity, polymerization was considered to have been promoted not only from the bleeding side but also from the film side through the supply of moisture. This progressive polymerization from both sides likely contributed to the reduction in the curing time. In addition, there were several cases where re-bleeding occurred when the SS was peeled off with the conventional method, as is occasionally noted in the clinical use. The merit of not having to peel off the HF with our new method was therefore considered to be great.

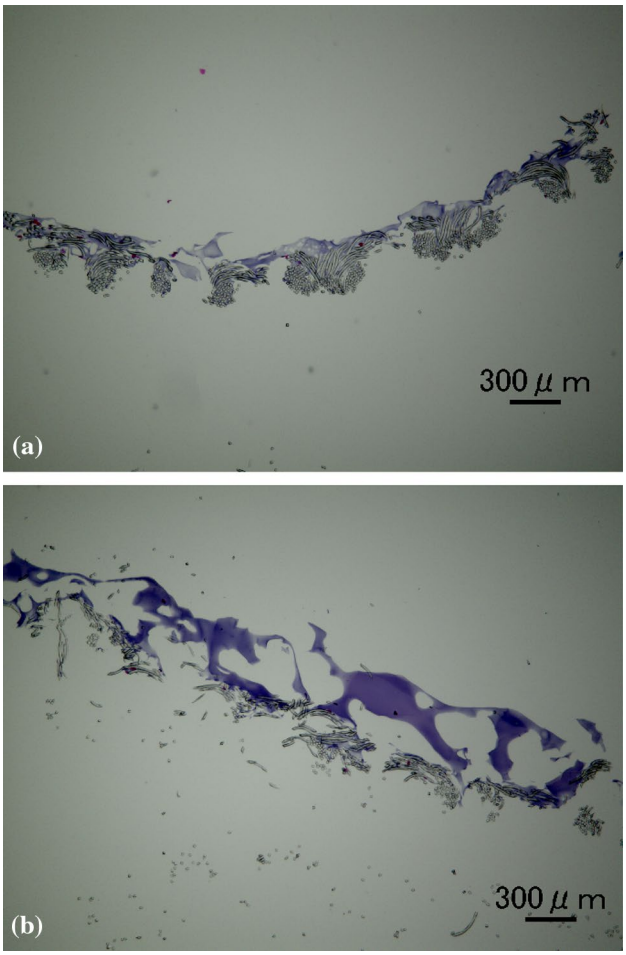

Fig. 5 Histological staining images. **a** Conventional silicone sheet method. The upper layer is the Hydrofit® coating and the lower layer is a vascular graft fiber. **b** The new Hydrofit® film method. The upper layer is the Hydrofit® coating and Hydrofit® film, and the lower layer is a vascular graft fiber. The Hydrofit® film and the sealant are integral and the boundaries are unclear

The HF was immersed in water before its application in this study. One reason for this is to promote the reaction of Hydrofit® sealant with the moisture (water) contained in the film. A second reason is to remove the stickiness of the Hydrofit® film, as it is difficult to handle the films in a dry state, where it sticks to fingers and instruments. Film that has been sufficiently wetted in physiological saline will no longer be sticky and can be more easily handled than dry film.

In this study, a prototype HF was used. The thickness of the film used here was 250 ± 25 μm, as the film thickness of 100 μm used in the previous experiment was considered too thin and fragile. This modification greatly improved the operability and water retentivity of the film. Whether or not the thickness of this film is optimal should be determined by preparing prototypes of different thicknesses and comparing them. Because it takes time to create this film, we had to reduce the number of operations in this waterproof experiment. We are planning to further increase the number in a future study.

Since this experiment requires frequent measurement of the bleeding volume, animal experiments were avoided due to concerns about substantial deaths due to massive bleeding. It was also considered difficult to establish uniform conditions in in vivo experiments. Therefore, experiments were conducted with a simulation circuit. Because this experiment uses water, the results may be different from results obtained with blood. For blood, artificial grafts such as Triplex® would provide sufficient hemostasis for a tiny hole. We intend to conduct animal experiments after confirming key details, such as the ideal film thickness and hemostasis time, and establishing appropriate conditions.

Conclusion

The present study demonstrated good hemostatic performance with the HF and the ability to achieve hemostasis after only a short duration. We hope to conduct further research with the aim of implementing this approach in a clinical setting.

Acknowledgements We are grateful to Dr. Haruto Nishida for helping with this experiment and making the histological specimens and to Sanyo Chemical Industries for providing the prototype of the Hydrofit® film.

Funding None.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with this study.

References

1. Ranucci M, Baryshnikova E, Castelvecchio S, et al. Major bleeding, transfusions, and anemia: the deadly triad of cardiac surgery. Ann Thorac Surg. 2013;96:478–85.
2. Grottke O, Fries D, Nascimento B. Perioperatively acquired disorders of coagulation. Curr Opin Anaesthesiol. 2015;28:113–22.
3. Stein LH, Rubinfeld G, Balsam LB, et al. Too Cold to Clot? Does Intraoperative Hypothermia Contribute to Bleeding After Aortic Surgery? AORTA (Stamford). 2017;5:106–16.
4. Rousou JA. Use of fibrin sealants in cardiovascular surgery: a systematic review. J Card Surg. 2013;28:238–47.
5. Colombo GL, Bettoni D, Di Matteo S, et al. Economic and outcomes consequences of TachoSil®: a systematic review. Vasc Health Risk Manag. 2014;10:569–75.
6. Matsuda T, Itoh T, Yamaguchi T, et al. A novel elastomeric surgical adhesive design, properties, and in vivo performances. Trans Am Soc Artif Intern Organs. 1986;32:151–6.
7. Eto M, Morita S, Sugiura M, Yoshimura T, Tominaga R, Matsuda T. Elastomeric surgical sealant for hemostasis of cardiovascular

anastomosis under full heparinization. Eur J Cardiothorac Surg. 2007;32:730–4.
8. Sonoda H, Ushijima T, Oishi Y, Hinokiyama K, Tatewaki H, Tanoue Y, Shiose A. Long term function of Hydrofit as hemostatic agent. Japanese Soc Cardiovasc Surg. 2018;47:62–5.
9. Yamaguchi T, Matsuda T, Iwata H, Hayashi K, Ando T, Uemura T, Kasegawa H, Adachi S, Nakajima N. Development of novel elastomeric surgical adhesive: compliance matching and in vivo performances. In: proc. ISAO, Artificial Organs. 1887.
10. Matsuda T, Nakajima N. Development of elastameric designed for arterial field. Kyobu Geka. 2013;66:315–9.
11. Morita S, Matsuda T, Eto M, Oda S, Tominaga R. Development of hemostatic sealant for arterial anastomosis: clinical application. Kyobu Geka. 2013;66:395–400.
12. Ishii H, Endo H, Tsuchiya H, Kubota H. Enhanced hemostasis with a sealant consisting of Hydrofit and Surgicel. J Card Surg. 2017;32:576–8.
13. Ishii H, Endo H, Tsuchiya H, Inaba Y, Terakawa K, Kubota H. Off-pump hemostasis for left ventricular rupture after myocardial infarction with Hydrofit and Surgicel. Gen Thorac Cardiovasc Surg. 2018;66:753–5.
14. Matsuda T, Yamaguchi T, Hayashi K, Itoh T, Twata H, Nakajima N. Bio-mechanical design of novel elastomeric vascular adhesive: significance of compliance matching. Adv Biomet. 1988;8:411–6.
15. Matsuda T, Nakajima N, Itoh T, Takakura T. Development of a compliant surgical adhesive derived from novel fluorinated hexamethylene diisocyanate. ASAIO Trans. 1989;35:381–3.
16. Urayama H, Tsuchida K, Ohtake H, Kawasuji M, Watanabe Y. Arterial anastomosis using the telescoping method and an elastomeric adhesive. Artif Organs. 1999;23:347–51.