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Original Article

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Evaluating the Efficacy and Safety of Hemofence (Thorombin Cross-Linked Sodium Hyaluronate Gel Matrix) in Hemostasis for Intractable Exudative Bleeding in Spinal Surgery: A Multicenter, Randomized, Phase III Clinical Trial

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Objective: To demonstrate the noninferiority of the novel hemostatic agent, Hemofence (BMI Korea Co., Ltd., thrombin cross-linked sodium hyaluronate gel matrix) compared to the established agent, Floseal Hemostatic Matrix (Baxter, thrombin-gelatin matrix) in achieving hemostasis for spinal surgeries, with secondary objectives to assess additional efficacy and safety.
Methods: This clinical trial was a multicenter, randomized, subject-blinded, active-controlled, parallel-group, phase 3 study. Investigational drugs were administered to the first and second bleeding sites of each participant (or only to the first site if a second site was absent), evaluating hemostasis success rate within 10 minutes and the time to achieve hemostasis. Subsequent visits were conducted for safety assessments. For noninferiority test, a 97.5% one-sided confidence interval (CI) was used; the test group was deemed noninferior if the lower limit exceeded -10%.
Results: This trial showed a 97.10% success rate in the test group and 96.05% in the control group for primary efficacy. The 95% CI (-4.90% to 7.44%) confirmed the test drug's noninferiority. Time to hemostasis showed no significant difference between groups. All adverse events, adverse drug reactions, and serious adverse events were statistically similar between groups ($p = 1.000$, $p = 0.243$, and $p = 0.966$, respectively).
Conclusion: A novel hemostatic agent, Hemofence, demonstrated an efficacy and safety profile comparable to that of Floseal.

Keywords: Hemostasis, Hemofence, Floseal, Hyaluronic acid, Thrombin, Spin

INTRODUCTION

Surgical bleeding can disrupt operations and negatively affect patient outcomes. Effective hemostasis is crucial, yet standard methods like coagulation, direct compression or suture can fail, particularly in diffuse venous bleeding. This often leads to extended operation time and increased need for transfusions, complicating surgery. Furthermore, continued bleeding during or postoperatively may be caused by coagulation disorders, poor heparin reversal, tissue characteristics, or inaccessible bleeding sites. With the rise of minimally invasive surgeries targeting smaller sites, bleeding control has become an important challenge, prompting the development of various local hemostatic agents.

Among these, thrombin-containing gelatin-based hemostatic agents, introduced in the early 2000s, are increasingly valuable. Baxter Inc.'s Floseal Hemostatic Matrix (Floseal) is a notable example.[1] BMI Korea Co., Ltd., aimed to develop a similar hemostasis product, enhancing their existing freeze-dried thrombin powder 5,000 units (licensed on April 13, 2018) by using cross-linked sodium hyaluronate gel as additive instead of gelatin. Thrombin, vital for blood coagulation, forms a clot by initiating a coagulation cascade, transforming fibrinogen into fibrin which attaches to vascular injury sites.[2] In surgical contexts, where continuous bleeding may wash away thrombin, an additive that ensures the product's stability at the site is essential. Sodium hyaluronate, a biocompatible and safe substance, was chosen for its improved viscosity and elasticity, enhanced by cross-linking with 1,4-butanediol diglycidyl ether.[3] The cross-linked sodium hyaluronic acid gel was mixed with freeze-dried thrombin to create a more effective hemostatic agent, named Hemofence (BMI Korea Co., Ltd., Jeju, Korea). This agent is designed to resist blood flow at the bleeding site, offering improvement over existing agents. Multicenter randomized phase III clinical trial was specifically designed to reveal efficacy and safety. The primary objective was to demonstrate the noninferiority of Hemofence in achieving hemostasis as compared to Floseal. Additionally, the trial aimed to assess and verify the detailed efficacy and safety of Hemofence as secondary outcomes.

MATERIALS AND METHODS

1. Study Design

This is a multicenter, randomized, subject-blinded, active-controlled, parallel-design, phase III study. This clinical trial was conducted across 3 independent academic hospitals and was approved by the Individual Institutional Review Board of the 3 institutions where the experiment was performed. Written informed consent were obtained from all subjects. This study enlisted the expertise of 4 spine surgeons, comprising 2 from 1 center and 1 from each of 2 other independent centers. All participating surgeons possess a minimum of 5 years of experience. Patients scheduled for elective spinal surgery were provided with a comprehensive explanation of the trial. Following their provision of written informed consent, they were assessed for eligibility and subsequently enrolled in the study. This process occurred within 14 days prior to the start of drug administration (visit 1). Subjects confirmed to meet the selection criteria on the day of surgery (visit 2) were randomized in a 1:1 ratio to either the test or control group. The spinal surgeries conducted were standard procedures including endoscopic spinal surgery, lumbar laminectomy and/or discectomy, cervical open surgery, and lumbar spinal fusion. During operations, subjects meeting the final selection criteria received the randomized investigational drug (either Hemofence or Floseal) at the first and second bleeding sites identified as uncontrollable or intractable exudative bleeding. In case the first application of the drug was unsuccessful for the hemostasis, subsequent application was made and documented.

The effectiveness of the investigational drug was assessed within 10 minutes of application to the first and second bleeding sites (or only the first site if no second site was present). Subsequent visits (visit 3 within 6 hours after surgery, visit 4 within 12–24 hours, visit 5 at 7 ± 2 days, and visit 6 at 28 ± 5 days postsurgery) were conducted to further evaluate safety.

2. Eligibility Criteria

In this study, we established specific criteria for participant inclusion and exclusion. The inclusion criteria were: (1) participants aged between 19 and 79, scheduled for nonemergency spinal or orthopedic surgeries, and capable of giving voluntary consent; (2) an International Normalized Ratio of ≤ 1.5 and a satisfactory platelet adhesion collagen/epinephrine test result on the day of surgery; (3) the need for hemostasis in cases of unmanageable exudative bleeding during surgery, without the presence of severe arterial bleeding.

For exclusion, the criteria included: (1) individuals who received platelet or plasma transfusions affecting hemostasis within 3 weeks prior to surgery; (2) administration of medications influencing bleeding/hemostasis, such as anticoagulants, antiplatelet agents, or thrombolytics, within 7 days prior to surgery; (3) a history of active bleeding, platelet or bone marrow disorders, or blood coagulation disorders; (4) the requirement of an-

ticoagulant therapy within 48 hours postsurgery. Additional exclusion criteria encompassed hypersensitivity to medications, abnormal kidney or liver function, history of alcohol or drug abuse, pregnancy during the trial, and recent participation in another clinical trial.

3. Subject Stratification, Random Assignment, and Blinding

The study subjects were enrolled in the outpatient setting and stratified into 3 sets: the safety set (SS), the full analysis set (FAS), and the per-protocol set (PPS). The SS was determined as the study subjected who received the investigational drugs following randomization, FAS as the patients in the SS with the primary efficacy data available, and PPS as the patients in the FAS who completed the trial without major violation of protocol which may affect efficacy evaluation. Efficacy evaluation was analyzed in the PPS group, whereas safety evaluation was analyzed in the SS group.

The random assignment of medication to the participants was revealed to the examiner on the day of surgery through the opening of a random allocation envelope. While participants were blinded, investigator blinding was not feasible due to the distinguishable appearances of the 2 investigational products.

4. Drug Composition, Preparation, and Application

Hemofence kit is mainly comprised of freeze-dried thrombin 5,000 IU in the main vial, along with the additive prefilled syringe of cross-linked sodium hyaluronate gel 2.56 g (3.2 mL), and reconstitution solution (5 mL) of sodium chloride 45 mg. And the control agent, Floseal kit is mainly comprised of freeze-dried thrombin 2,500 IU in the main vial, along with the purified bovine gelatin 704 mg, and reconstitution solution (5 mL) of sodium chloride 45 mg.

For the preparation of Hemofence application in the operating room, 2 mL of the reconstitution solution is drawn and added to the main vial containing freeze-dried thrombin. After gentle rotation of the vial until the thrombin is completely dissolved, thrombin solution is drawn and connected to the prefilled syringe of cross-linked sodium hyaluronate gel. Mixing 2 solutions fully at least 20 times of the syringe-to-syringe pass is required. Final mixture is ready to use up to 8 hours.

During surgical procedures, in cases of uncontrolled exudative bleeding, either Hemofence or Floseal as assigned was applied directly to the bleeding site. The protocol specified that each 3×3 cm^2 of the bleeding area be applied with one kit of the drug. The technique employed for application involved backfilling, starting from the deepest layer and advancing towards the more superficial layers of the bleeding site. In cases where the initial application did not achieve complete hemostasis, a subsequent application was permitted.

5. Efficacy Evaluation

Efficacy evaluation was conducted by 3 independent investigators who were all active neurosurgeons specializing in spine surgery, blinded to each other's evaluation. The hemostasis success was defined as the cessation of the bleeding within 10 minutes following application of the investigational drug. Three investigators independently assessed these parameters based on anonymized video recordings of the surgery. Final determination of hemostasis success or failure relied on a majority consensus among the evaluators. Additionally, the average time to achieve hemostasis, as reported by the evaluators who deemed the hemostasis successful, was calculated. In case bleeding persisted, an additional investigational drug was applied to the affected area as per the operator's discretion and documented accordingly. If hemostasis was not attained with additional application, it was deemed a hemostasis failure.

The primary efficacy was defined as the hemostasis success rate at the first bleeding site within 10 minutes after initial or subsequent drug application. And the secondary efficacy was evaluated as the hemostasis success rate of the second bleeding site following initial or subsequent drug application and the time to hemostasis at each site following drug application.

6. Safety Evaluation

At each visit from visit 3 to visit 6, comprehensive physical examinations were conducted, including assessment of the general appearance, head and neck, thoracic and pulmonary regions, heart, abdomen, urogenital system, limbs, musculoskeletal system, nervous system, and lymph nodes. Vital signs, blood and urine tests, along with electrocardiograms, were performed. Specifically on visit 6, pregnancy test was performed for all women subjects in childbearing age. Unscheduled visits may occur upon study subject's request, or at the investigator's discretion.

Any abnormal findings were collected and classified as treatment emergent adverse event (TEAE) regardless of causality, adverse drug reaction (ADR), serious adverse event (SAE). TEAE regardless of causality was defined as any harmful and unintended sign, symptom, or disease irrespective of its causal relationship with the investigational drug. ADR was defined as any harmful and unintended reaction with possible causal relationship with the investigational drug. SAE includes: (1) death or a life-threatening event, (2) necessity for unplanned hospitalization

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or prolongation of index hospitalization, (3) permanent or significant disability/functional decline, or (4) any other medically significant event as determined by the investigator irrespective of its causal relationship.

7. Statistical Analysis

Statistical significance tests were conducted using a 2-tailed test at a significance level (α) of 5%. For noninferiority test, a 97.5% one-sided confidence interval (CI) was employed. For continuous data, descriptive statistics including the number of subjects, mean, and standard deviation were presented for each treatment group. For categorical data, frequencies and percentages were provided per treatment group. To compare treatment groups, the 2-sample t-test was used for continuous data that satisfied normality. In cases where normality was not met, the Wilcoxon rank-sum test was applied to assess significance. For categorical data, depending on the presence of data with frequencies less than 5, either the chi-square test or Fisher exact test was utilized to evaluate significance. All statistical values were presented to 2 decimal places, while p-values were provided up to three decimal places (with values less than 0.001 reported as <0.001). Frequencies were reported as whole numbers.

For the primary efficacy analysis, the difference in the hemostasis success rate was assessed by calculating the lower limit of the 95% 2-sided CI (equivalent to a 97.5% one-sided CI) utilizing Mantel-Haenszel stratum weights and Sato variance estimation with the type of operation as the stratification factor. If the lower limit of the CI exceeded -10%, the test group was considered noninferior to the control group. And its significance was analyzed using Cochran-Mantel-Haenszel test, also stratified for the type of operation.

For the secondary efficacy analysis, the same statistical method was used as the primary efficacy analysis. In addition, the time taken to achieve hemostasis at each successful site was presented for each group using Kaplan-Meier curves. In cases deemed hemostasis failure, the time taken for hemostasis was set at 10 minutes (600 seconds) for the purpose of censoring. Furthermore, a stratified log-rank test, with the type of surgery as a stratification factor, was employed to compare the 2 groups.

Subgroup analysis was performed based on the initial or subsequent drug application using identical statistical method as the primary and secondary efficacy analysis.

RESULTS

1. Study Subjects

During visit 1, 218 subjects were initially screened. Exclusions were made for those not meeting the inclusion or exclusion criteria, those who withdrew consent, and for other reasons, resulting in 48 patients who failed the screening process. Conse-

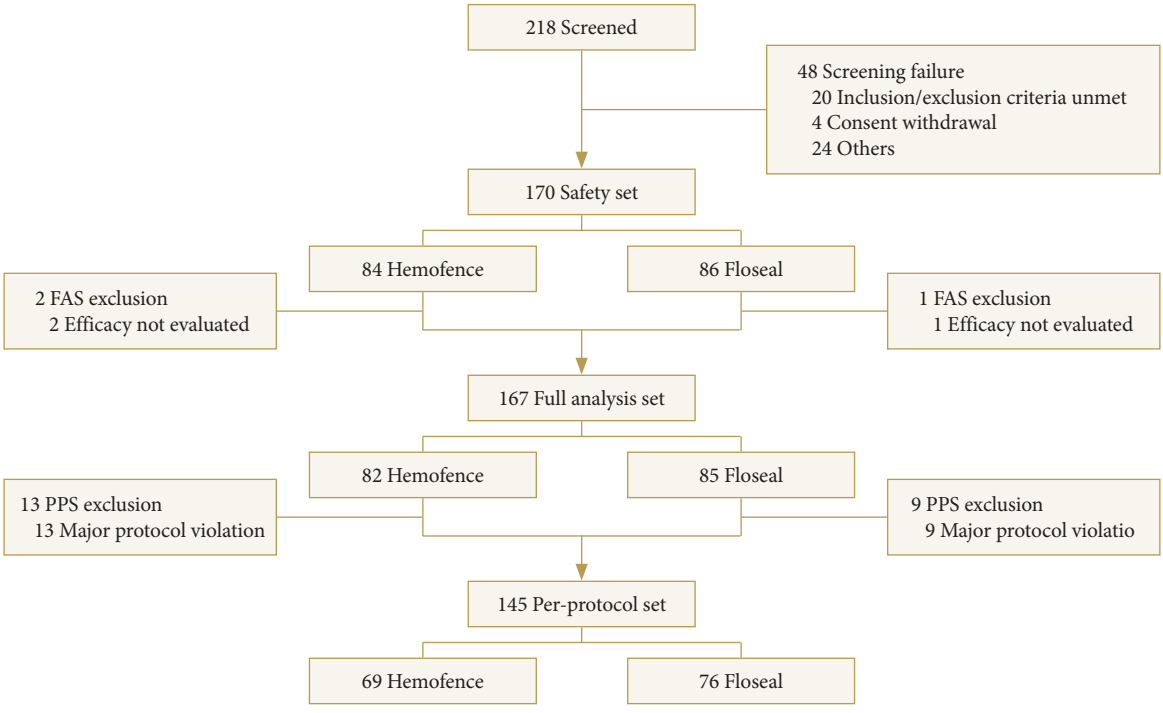

Fig. 1. Flowchart of study recruitment. FAS, full analysis set; PPS, per-protocol set.

Table 1. Demographic characteristics of the safety set

Variable	Total (n = 170)	Hemofence (n = 84)	Floseal (n = 86)	p-value
Male sex	89 (52.35)	42 (50.00)	47 (54.65)	
Age (yr)	59.66 ± 13.16	58.92 ± 13.74	60.40 ± 12.61	0.589
Body weight (kg)	66.56 ± 12.40	66.05 ± 12.88	67.06 ± 11.97	0.595
Height (cm)	162.08 ± 10.06	161.94 ± 10.48	162.22 ± 9.69	0.718
BMI (kg/m^2)	25.26 ± 3.65	25.08 ± 3.64	25.43 ± 3.67	0.450
Diabetes	30 (17.64)	18 (21.43)	12 (13.95)	
Pregnancy	14 (17.28)	6 (14.29)	8 (20.51)	0.459
Type of operation				
Endoscopic spine surgery	47 (27.65)	23 (27.38)	24 (27.91)	0.938
Lumbar laminectomy	29 (29.59)	16 (32.65)	13 (26.53)	0.496
Lumbar laminectomy discectomy	25 (25.51)	15 (30.61)	10 (20.41)	0.252
Lumbar spinal fusion surgery	25 (14.71)	12 (14.29)	13 (15.12)	0.879
Cervical spine surgery	44 (44.90)	18 (36.73)	26 (53.06)	0.190

Values are presented as number (%) or mean ± standard deviation.
BMI, body mass index.

quently, 170 patients were deemed eligible for the study (84 in the test group and 86 in the control group) and stratified as the SS (Fig. 1). Out of the SS, 3 subjects (2 from the test group and 1 from the control group) were excluded due to missing efficacy data, resulting in 167 subjects stratified as the FAS (82 in the test group and 85 in the control group). Out of the FAS, 22 (13 from the test group and 9 from the control group) were excluded due to major violations of the trial protocol, leaving 145 subjects who completed the trial in accordance with the protocol stratified as PPS (69 in the test group and 76 in the control group). The major protocol violations include the perioperative drugs or transfusions that impact hemostasis, deviations from the protocol for the application of investigational hemostatic agents, preoperative abnormalities in platelet adhesion collagen/epinephrine test results, significant alterations in the surgical plan, and failure of recording due to device malfunction.

For the 170 patients in SS, the test group and the control group had insignificant differences in sex, age, body weight, height, body mass index, diabetes, pregnancy, and the type of operations (Table 1).

2. Primary Efficacy Evaluation

The primary efficacy of the investigational drug was evaluated within the PPS. It equals to the hemostasis success within 10 minutes at the primary bleeding site, determined by the majority consensus of the 3 independent investigators. The test group had hemostasis success of 67 out of 69 patients (97.10%), while the control group had 73 out of 76 patients (96.05%), which showed insignificant differences between group (p = 0.676) (Table 2). The difference in hemostasis success rates (test group minus control group) was assessed using the Mantel-Haenszel stratum weights and Sato variance estimation. The 95% 2-sided CI was calculated to be (-4.90% to 7.44%). Since the lower limit of this interval exceeded the pre-set noninferiority margin of -10%, it was confirmed that the test agent was not inferior to the control agent.

3. Secondary Efficacy Evaluation

The secondary efficacy of the investigational drug was also evaluated within the PPS. The hemostasis success rate of the second bleeding site following initial or subsequent drug application was one of the secondary efficacy evaluations. The test group had hemostasis success of 40 out of 43 patients (93.02%), while the control group had 45 out of 46 patients (97.83%), which showed insignificant differences between group (p = 0.257) (Table 2).

Independent investigators assessed the time to achieve hemostasis at each successful bleeding site following the initial or subsequent administration of the investigational drug, along with the corresponding 95% CIs. For the first bleeding site, the median time to hemostasis in the test group was 114.00 seconds, with a 95% CI of (109.67–123.33) seconds. In the control group, the median time was 122.33 seconds, with a 95% CI of (118.00–131.00) seconds. When analyzing the results with 'type of surgery' as a stratification factor, no statistically significant difference was observed between the groups (p = 0.877) (Fig. 2A).

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Table 2. The hemostasis success rate at the first and second bleeding site, assessed within 10 minutes following the initial and subsequent administration of the per-protocol set

Bleeding site	Hemofence					Floseal		
	Total number	No. (%)	95% CI	95% CI of difference†	p-value‡	Total number	No. (%)	95% CI
First								
Combined	69	67 (97.10)	93.14–100.00	-4.9 to 7.44	0.676	76	73 (96.05)	91.67–100.00
Initial	56	55 (98.21)	94.75–100.00	-4.85 to 4.97	0.979	64	63 (98.44)	95.40–100.00
Subsequent	13	12 (92.31)	77.82–100.00	-21.61 to 34.68	0.656	12	10 (83.33)	62.25–100.00
Second								
Combined	43	40 (93.02)	85.41–100.00	-13.72 to 3.69	0.257	46	45 (97.83)	93.61–100.00
Initial	34	33 (97.06)	91.38–100.00	-7.96 to 7.44	0.948	38	37 (97.37)	92.28–100.00
Subsequent	9	7 (77.78)	50.62–100.00	-57.19 to 2.34	0.103	8	8 (100.00)	100.00–100.00

CI, confidence interval.
†Utilizing Mantel-Haenszel stratum weights and Sato variance estimation (stratification factor = type of operation). ‡p-value with Cochran-Mantel-Haenszel test (stratification factor = type of operation).

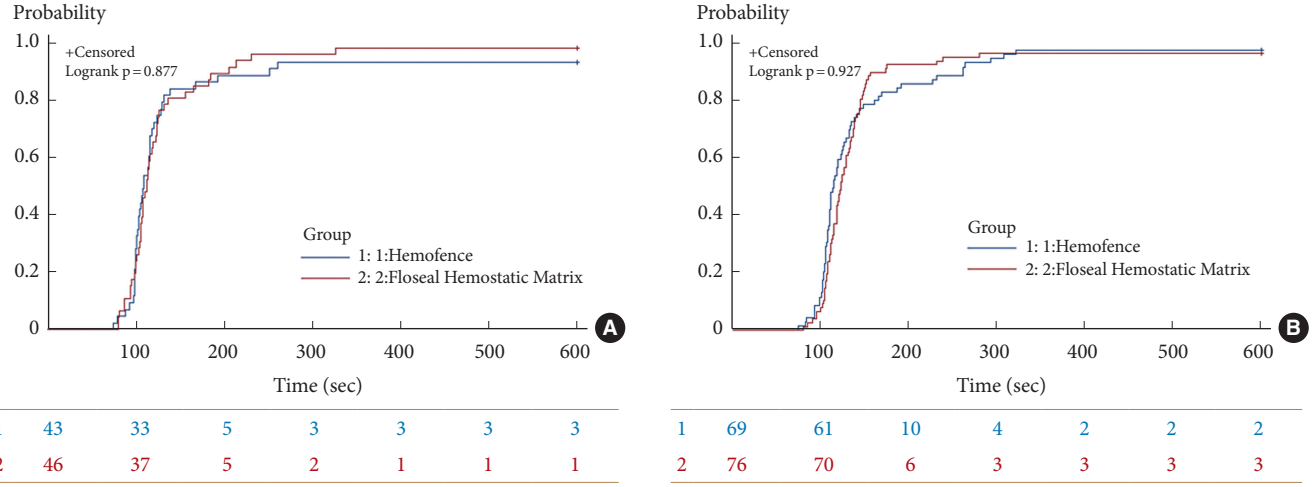

Fig. 2. Kaplan-Meier curve for the time to hemostasis. (A) For the first bleeding site. (B) For the second bleeding site.

For the second bleeding site, the median time to hemostasis in the test group was 109.00 seconds, with a 95% CI of (102.67–116.00) seconds. In the control group, the median time was 112.67 seconds, with a 95% CI of (106.00–119.33) seconds. Again, using 'type of surgery' as a stratification factor, the difference between the 2 groups was not statistically significant (p = 0.927) (Fig. 2B).

4. Safety Evaluation

In a SS of 170 subjects, TEAE occurred in 169. Incidence rates were 100% in the test group (84 of 84, 329 events) and 98.84% in the control group (85 of 86, 347 events), with no significant difference (p = 1.000) (Table 3). TEAE regardless of causality, as defined as any harmful and unintended sign, symptom, or disease, encompasses procedural pain, constipation, pyrexia, and dysuria in the order of incidence. The significant occurrence of TEAE in both groups was primarily attributed to procedural pain, with incidence rates of 100.0% in the test group and 97.67% in the control group.

Among TEAEs, 2 cases of postoperative wound infections in the test group were deemed to have a weak association with the hemostatic agents. Consequently, these were categorized as ADRs, with no significant incidence rate difference between groups (p = 0.243). Both cases were effectively treated with prolonged antibiotic therapy.

SAEs occurred in 12 subjects (15 events), with incidences of 7.14% in the test group (6 of 84, 6 events) and 6.98% in the control group (6 of 86, 9 events), showing no significant difference

Table 3. Safety evaluation of the safety set

Variable	Hemofence (n = 84)		Floseal (n = 86)		p-value
	No. (%)	Events	No. (%)	Events	
TEAE regardless of causality	84 (100)	329	85 (98.84)	347	1.000
ADR	2 (2.38)	2	0 (0)	0	0.243
Postoperative wound infection	2 (2.38)	2	0 (0)	0	
SAE	6 (7.14)	6	6 (6.98)	9	0.966
Infections and infestations	3 (3.57)	3	4 (4.65)	4	
COVID-19	0 (0)	0	2 (2.33)	2	
Postoperative wound infection	2 (2.38)	2	0 (0)	0	
Large intestine infection	0 (0)	0	1 (1.16)	1	
Nephritis bacterial	1 (1.19)	1	0 (0)	0	
Pneumonia	0 (0)	0	1 (1.16)	1	
Musculoskeletal	1 (1.19)	1	2 (2.33)	2	
Muscular weakness	0 (0)	0	2 (2.33)	2	
Back pain	1 (1.19)	1	0 (0)	0	
Investigations	1 (1.19)	1	1 (1.16)	3	
Alanine aminotransferase increase	0 (0)	0	1 (1.16)	1	
Aspartate aminotransferase increase	0 (0)	0	1 (1.16)	1	
Blood alkaline phosphatase increase	0 (0)	0	1 (1.16)	1	
C-reactive protein increase	1 (1.19)	1	0 (0)	0	
Neoplasms	1 (1.19)	1	0 (0)	0	
Prostate cancer	1 (1.19)	1	0 (0)	0	

TEAE, treatment emergent adverse event; ADR, adverse drug reaction; SAE, serious adverse event; COVID-19, coronavirus disease 2019.

(p = 0.966). There were no serious adverse reactions including death which caused stopping of the trial.

DISCUSSION

Perioperative anemia is an independent risk factor for postoperative complications and hospital-related infections in spinal surgeries.[4] This condition, along with the associated need for blood transfusions due to intraoperative blood loss, increases morbidity and medical costs. Current transfusion guidelines generally advocate a restricted approach, recommending transfusion only when hemoglobin levels decrease below 8 to 9 g/dL.[5,6] To mitigate blood loss in spinal surgeries, various strategies have been explored and established. These strategies encompass preoperative discontinuation of anticoagulants, aspirin, and herbal supplements; the administration of erythropoietin and iron supplementation for procedures with high risk of blood loss; and the implementation of intraoperative methods like tranexamic acid infusion and hypotensive anesthesia.[7-11]

However, achieving effective local hemostasis in the surgical field is crucial to directly reduce blood loss. Techniques for local hemostasis are diverse, with thermal/electric cauterization and the use of mechanical/chemical hemostatic agents being common. While thermal/electric cauterization offers a rapid and direct approach, its suitability is limited near sensitive and critical anatomical structures such as nerve roots. In such cases, appropriate use of hemostatic agents becomes important. These agents include solid sponge-type mechanical agents, solution-type active agents, flowables, and fibrin sealants. Advancements in surgical techniques, notably minimally invasive endoscopic spinal surgery, have amplified the importance of gel-type flowable hemostatic agents.[12-14] Floseal, an established hemostatic agent with over 2 decades of clinical use, has been a reference in the development of this agent, Hemofence.[1,15] Both Floseal and Hemofence contain thrombin, a pivotal coagulation factor activated in the final phase of the coagulation cascade, which transforms prothrombin to thrombin, and subsequently converts circulating fibrinogen into fibrin. This process results in the formation of fibrin mesh that adheres to the site of vascular injury, facilitating hemostasis. Thrombin used in these agents is

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extracted and purified from human or bovine blood to provide more rapid hemostasis compared to the natural clotting process. However, the incorporation of additives is required to maintain thrombin at the application site for a certain time, preventing it from being washed away by blood flow. For this purpose, Floseal incorporates gelatin granules as an additive. In contrast, Hemofence incorporates sodium hyaluronate, a biocompatible and safe material already in use in various topical, injectable, and ophthalmic preparations. Its physical properties of high viscosity and elasticity are further enhanced by cross-linking hyaluronic acid molecules with 1,4-butanediol diglycidyl ether.

There are other market-available hemostatic agents of similar properties. Floseal's relative weakness include its higher cost, the potential for rapid displacement from the application site due to blood flow, and a longer preparation time compared to other products. Studies have been conducted comparing the hemostasis efficacy, cost-effectiveness and preparation times between similar products.[9,16-18] As Hemofence is not yet approved for market release, a direct price comparison with Floseal is not currently possible. Nevertheless, existing literature suggests that the cost of Floseal may be considered high relative to its benefits.[19,20] Additionally, Hemofence, utilizing a microbial-derived hyaluronate additive, is likely to offer cost advantages due to its more economical production process compared to Floseal's bovine-derived gelatin matrix. Regarding the preparation time, Floseal requires additional 30 seconds after mixing for the gelatin powder to absorb and stabilize with the thrombin solution before use. In contrast, Hemofence preparation involves the simple mixing of 2 liquid components—hyaluronate and thrombin solution—thus eliminating the need for a stabilization period and significantly reducing preparation time, which could be seen as one of the advantages. From a safety perspective, the bovine-derived gelatin used in Floseal has been associated with fibrosis in a small animal study,[21] and anaphylaxis in a handful of case reports.[22-24] Conversely, 1,4-butanediol diglycidyl ether-crosslinked hyaluronate has been safely used as a implant for approximately 3 decades,[25,26] demonstrating notable safety and biocompatibility.

Current trial initiated with the screening of the first subject on December 3, 2020, and concluded on April 19, 2022, with the final visit of the last participant. As a primary outcome, it demonstrated that a thrombin-based hemostatic agent with cross-linked sodium hyaluronic acid gel as an additive is non-inferior to Floseal in terms of hemostasis success rates for the first bleeding site. Additionally, for the secondary bleeding site, both agents demonstrated similarly high hemostasis success rates. Moreover, the time to achieve hemostasis was consistently around 2 minutes for both agents, a duration deemed clinically acceptable. In terms of safety, 2 instances of surgical site infection occurred in the experimental group (2.38%) as ADRs, both of which improved with antibiotic treatment without necessitating additional operations. Other surgical site-specific ADRs potentially attributable to hemostatic agents were not identified. Additionally, no significant differences were observed in vital signs, physical examinations, and electrocardiograms between groups, indicating a comparable safety profile for Hemofence.

This study recognizes specific limitations. The variability in surgical procedures, encompassing a spectrum from cervical to lumbar and including both open and endoscopic approaches, was evenly distributed among the groups. However, this diversity may have influenced the extent of bleeding, the feasibility of achieving hemostasis, and the duration required to attain hemostasis. Furthermore, regarding the stable attachment of the agent following the washing of the bleeding area, this clinical trial was conducted without predefined protocols for cleaning the site of application. Comparing the hemostatic effect of the 2 agents using an uniform irrigation method would have been more advantageous. Lastly, the local impact on bone sites where the hemostatic agents were applied was not evaluated through postoperative imaging analysis. A comparative assessment between the 2 groups, or against historical controls, would have been advantageous, particularly concerning bony resorption, cyst formation, or other alterations in bone integrity.

CONCLUSION

Hemofence, a newly developed hemostatic material, showed comparable efficacy and safety profile to Floseal, an established market product, when used for hemostasis in patients with intractable exudative bleeding in spinal surgeries.

NOTES

Conflict of Interest: The authors have nothing to disclose.

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Author Contribution: Conceptualization: JWH; Formal analysis: SA, WKK, CI, JBL, JWH; Investigation: WKK, CI, JBL, JK, JWH; Methodology: WKK, CI, JWH; Project administration: WKK, CI, JWH; Writing: SA, JK, JWH.

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