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Efficacy and safety evaluation of a novel hemostatic gelatin matrix for intraoperative hemostasis: a prospective, randomized controlled trial

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Borayflo Haemostatic matrix is a new absorbable hemostatic gelatin matrix which can be used for intraoperative assisted hemostasis. In a prospective, multicenter, non-inferiority, randomized controlled trial, a total of 354 subjects were recruited from the departments of hepatobiliary surgery, obstetrics and gynaecology and orthopaedics of 4 hospitals and randomly allocated to test group (Borayflo Haemostatic matrix) or control group (Surgiflo Haemostatic matrix) in a 1:1 ratio. In the modified intention-to-treat population, 163 (93.14%) of 175 subjects in the test group versus 167 (94.89%) of 176 subjects in the control group successfully achieved hemostasis within 5 min ($P > 0.05$). Non-inferiority for effective rates of hemostasis at 5 min to Surgiflo Haemostatic matrix was shown in the study (treatment difference: -1.74% [95%CI, -6.70–3.22%] for modified intention-to-treat population). In terms of efficacy and safety, the new hemostatic gelatin matrix (Borayflo Haemostatic matrix) is equivalent to Surgiflo Haemostatic matrix. There was no significant difference in the incidence of AEs or SAEs between the test and control groups($P > 0.05$). In addition, Borayflo Haemostatic matrix is a domestically produced haemostatic gelatin product, an advantage that will reduce the cost of surgical haemostasis for Chinese patients.

Abbreviations

PT	Prothrombin time
APTT	Activated partial thromboplastin time
TT	Thrombin time
RBC	Red blood cell
Hb	Hemoglobin
T	Temperater
HR	Heart rate
R	Respiration
BP	Blood pressure
WBC	White blood cell
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
ALB	Albumin
TBIL	Total bilirubin
DBIL	Direct bilirubin

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BUN	Blood urea nitrogen
Cr	Creatinine
BMI	Body mass index

Failure to adequately manage intraoperative bleeding can result in prolonged surgical procedures, subsequently augmenting the likelihood of postoperative infection and necessitating blood transfusions, and even lead to death of patients[1,2]. Numerous experiments and clinical studies have demonstrated that the utilization of distinct hemostatic materials for various wound yields disparate outcomes[3–6]. In situations where conventional hemostatic techniques, such as ligation, suturing, and electrocoagulation, prove inadequate or impractical, the utilization of novel wound hemostatic materials becomes imperative for timely bleeding control[7].

Hemostatic gelatin matrix possesses absorbability and hemostatic properties, enabling its direct application at the site of bleeding for hemorrhage control[8–10]. Following its application on a surgical wound, hemostatic gelatin matrix triggers the natural coagulation cascade reaction, effectively halting bleeding[11]. Furthermore, the hemostatic gelatin matrix functions by exerting physical compression and serving as a scaffold for platelet adhesion and aggregation, ultimately leading to hemostasis. When utilized appropriately, this material is fully absorbed within a period of 4–6 weeks in human body[12]. The fluid nature of absorbable hemostatic gelatin matrix enables rapid and efficient distribution around the site of bleeding, facilitating a high level of contact with the bleeding area and expediting the hemostatic process[13]. Therefore, hemostatic gelatin matrix is widely used in neurosurgery, spinal surgery and various other surgical procedures for achieving hemostasis[14–17].

Recently, the Jiangxi Borayer Biotechnology Co., Ltd. from China has successfully developed a new absorbable hemostatic gelatin matrix, which has received approval for application in Chinese hospitals. In comparison to the widely utilized Surgiflo Haemostatic matrix in clinical settings, this particular hemostatic gelatin product shares similar primary components and properties. Nevertheless, no studies have reported the efficacy and safety of Borayflo Haemostatic matrix in assisting hemostasis in surgery. Therefore, in this clinical trial, we chose to compare with Surgiflo Haemostatic matrix to evaluate the efficacy and safety of Borayflo Haemostatic matrix.

Methods

Study design and subjects

This study employed a prospective, multicenter, single-blind, randomized, parallel-controlled trial design to investigate the efficacy and safety of the new absorbable hemostatic gelatin matrix (Jiangxi Borayer Biotechnology Co., Ltd, China) in intraoperative auxiliary hemostasis. The study was conducted from August 2020 to July 2021, with participation from four hospitals in China, including China-Japan Friendship Hospital, Beijing Friendship Hospital, First affiliated Hospital of Nanchang University, and Lishui Municipal Central Hospital. Written informed consent was obtained from all participants, and the study received approval from the ethics committees of each hospital institutions. All recruitment and experimental procedures adhered to the *Declaration of Helsinki*. This clinical study has been registered with the China Clinical Trial Registry (registration number: ChiCTR2400082801, 08/04/2024). Besides, we used the CONSORT reporting guidelines to complete the CONSORT Checklist[18].

Eligible participants were subjects with intraoperative bleeding from capillaries, veins, and small arteries that failed to be controlled by compression, ligation, or other traditional methods and required auxiliary hemostasis. In addition, subjects were required to meet the following criteria to be enrolled. The inclusion criteria were as follows: (1) individuals aged between 18 and 75 years, irrespective of gender; (2) absence of any prior surgical interventions at the designated site; (3) absence of active bleeding pre-operatively, as determined by clinical symptoms, vital signs, and laboratory examination findings; and (4) willingness and capability to attend all subsequent follow-up appointments. The exclusion criteria were as follows: (1) an active infection or a local surgical site infection that may have an impact on hemostasis; (2) coagulation or bleeding disorders characterized by a $\geq$20% increase in prothrombin time (PT), activated partial thromboplastin time (APTT), or other coagulation indexes compared to the normal reference range; (3) recent utilization of platelet receptor antagonists within 48 h prior to the surgical procedure; (4) documented allergy to porcine gelatin; (5) pregnancy or lactation status; (6) involvement in drug clinical trials or clinical trials of other medical devices within the preceding 3 months. The expected duration of participation for each subject was 6 weeks, including a screening (baseline) period (preoperative −7 to 0 days), a treatment period (on the day of surgery, day 0), and a follow-up period (within 48 h after surgery, and 42 days ± 7 days after surgery). The detailed study procedures of the trial are described in Table S1.

Randomization and blinding

Participants who met the inclusion criteria were randomly allocated to either the test group or the control group, in a ratio of 1:1. The Borayflo Haemostatic matrix was used in the test group for intraoperative auxiliary hemostasis, while Surgiflo Haemostatic matrix (Ferrosan medical Devices A/S) was used in the control group. A block randomized design was adopted according to the stratification of the study center and departments. Randomization was facilitated by the interactive network response system (IWRS), which automatically assigned participants to groups based on their order of enrollment.

In this study, subjects and end-point assessors were blind, and surgeons were not blind.

Hemostatic intervention

When there is active bleeding and traditional methods of haemostasis, including electrocoagulation and compression, have failed, the premixed absorbable hemostatic flowable gelatin, approximately 5mL in volume, was uniformly administered into the site of bleeding. Subsequently, a gauze saturated with sterile normal saline was applied to establish direct contact between the hemostatic agent and the bleeding tissue. After 1–2 min, the

gauze was removed to assess the hemostatic effect. Hemostasis was deemed successful in the absence of bleeding; otherwise, it was considered a failure in achieving hemostasis. The researcher employed a standardized stopwatch to document the duration required for hemostasis, encompassing the application of gauze and the point at which visible bleeding ceased. This determination was based on analysis of surgical videos. Three independent reviewers assessed the videos for the time to hemostasis, and the mean of the three assessments was deemed the time to hemostasis. If the duration of bleeding exceeded 5 min, the surgeon autonomously employed a suitable hemostatic technique until bleeding ceased. Once successful hemostasis was achieved, the vascular wound was managed in accordance with established protocols. In the event of any remaining residue in either group after successful hemostasis, the wound was delicately irrigated with sterile normal saline, and any excess blood clot and flowable gelatin were removed via suction.

Outcomes

The primary objective of this study is to evaluate the efficacy of Borayflo Haemostatic matrix compared with Surgiflo Haemostatic matrix. The primary efficacy endpoint was the effective rates of hemostasis at 5 min after the application of the hemostatic product in surgery. Hemostasis was considered successful if there was no noticeable bleeding from the wound within 5 min following the application of hemostatic gelatin matrix, as determined through clinical evaluation. If hemostasis is not achieved within 5 min, the clinical assessment was failure. As predetermined in the statistical analysis plan, the primary efficacy endpoint was tested for non-inferiority subsequent to the determination of the non-inferiority margin. The secondary efficacy endpoint were intraoperative hemostatic time of wound, procedure time, the change in RBC counts and hemoglobin (Hb) from preoperative level, intraoperative blood transfusion volume, intraoperative bleeding volume. The time of intraoperative wound hemostasis was defined as the time when the wound was covered with gauze or brain cotton until there was no obvious bleeding after the application of products. The procedure time was obtained from the anesthesia record.

The secondary objectives were assessment of the safety and performance of Borayflo Haemostatic matrix compared with Surgiflo Haemostatic matrix. Before operation, within 48 h and 6 weeks after operation, vital signs and laboratory examination, including blood routine, blood biochemistry, urine routine, and blood coagulation function, were monitored and adverse events were documented. The safety assessment entailed the evaluation of vital signs, laboratory examination, adverse events, serious adverse events. Adverse events were further classified by severity ("mild", "moderate" and "severe"), the relationship with the hemostatic gelatin matrix (related/unrelated), and whether it caused subjects to withdraw from the study. Doctors would be queried about handling characteristics after applying hemostatic gelatin matrix for aiding hemostasis during surgical procedures. Three inquiries addressed to the ease of product utilization, ability of material to conform to tissue surfaces, and access to locations difficult to reach. A five-point scale is used to rate the answers, ranging from 1 (easy or good) to 5 (difficult or poor).

Statistical analysis

Based on previous studies on similar products, the efficacy of hemostatic gelatin matrix in orthopedic surgery has been reported to range from 83 to 90%. Consequently, it is anticipated that both the test group and the control group will exhibit a 5-minute hemostatic effective rate of approximately 90%. Assuming type I error $\alpha = 0.025$ (one side) and $\beta = 0.20$ (80% power), the non-inferiority margin of -10%, our calculations indicate that a minimum of 142 participants should be recruited for each group. Given the maximum potential loss rate of 20% and the occurrence of additional accidents throughout the study, our intention is to employ a random assignment of 354 subjects, divided equally between the test group and the control group, at a ratio of 1:1. In accordance with the distribution of disease sources among subjects in hepatobiliary surgery, obstetrics and gynecology, and orthopedics, the subject proportion in each department will be 1:1:1, resulting in a sample size of 118 cases for each department.

This study employed modified intention-to-treat (ITT) and per-protocol populations for the primary efficacy analysis. The modified intention-to-treat population encompassed all participants who were assigned randomly and had used hemostatic gelatin matrix at least once. The per-protocol population consisted of participants within the modified intention-to-treat population who did not deviated from the protocol. The institutions underwent block randomization, and the statistical analysis of the effectiveness results for the primary efficacy endpoint was conducted in the intention-to-treat populationr using the Cochran-Mantel-Haenszel test, with stratification by study center. We calculated the difference in effective rates of hemostasis at 5 min between the two groups (Borayflo Haemostatic matrix versus Surgiflo Haemostatic matrix) and the 90% 2-sided CI for this difference on the basis of the stratified (by age group, BMI group, hypertension group and diabetes group). Non-inferiority was considered to have been shown if the lower limit of the two-sided 95% CI for the difference between the two groups was more than − 10%. In addition, we conducted a sensitivity analysis of the primary efficacy endpoints in the modified intention-to-treat population to illustrate the robustness of the conclusion by excluding subjects with missing hemostatic information. Furthermore, we conducted a safety analysis on all randomly assigned participants who had received the study product at least once. The vital signs and laboratory examination results were classified and statistically analyzed according to normal, abnormal and no clinical significance, abnormal and clinical significance, no examination. The changes of vital signs and laboratory examination results relative to the baseline measurement results at each follow-up time were also analyzed.

The data was analyzed using SAS (version 9.4 or higher). Continuous variables were assessed using either Student's t-test (assuming normal distribution and homogeneity of variance) or the Wilcoxon rank sum test (if the conditions for Student's t-test were not met). Classified variables were analyzed using either the chi-square test or Fisher exact test (if the chi-square test was not applicable). Unless otherwise specified, all statistical tests were two-sided, and a significance level of $P < 0.05$ was used to determine statistical significance.

Ethical approval

Written informed consent was obtained from all participants, and the study received approval from the ethics committees of each hospital institutions (China-Japan Friendship Hospital, Beijing Friendship Hospital, First affiliated Hospital of Nanchang University, and Lishui Municipal Central Hospital).

Results

Demographics

From August 2020 to March 2021, a total of 354 subjects were recruited and randomly assigned to either the test group (Borayflo Haemostatic matrix) or the control group (Surgiflo Haemostatic matrix) (Fig. 1). Among these, 175 subjects in the test group and 176 subjects in the control group, who utilized hemostatic gelatin matrix, were included in the modified intention-to-treat population. Notably, 3 subjects were excluded from the analysis set due to reasons such as spontaneous wound hemostasis, hemostatic gelatin matrix contamination, and non-adherence of gelatin matrix to the wound (included in safty analysis set). 168 subjects using Borayflo Haemostatic matrix and 171 subjects using Surgiflo Haemostatic matrix were included in the per-protocol population. 7 subjects using Borayflo Haemostatic matrix and 5 subjects using Surgiflo Haemostatic matrix were excluded from the per-protocol group due to various reasons, including the absence of video recording of

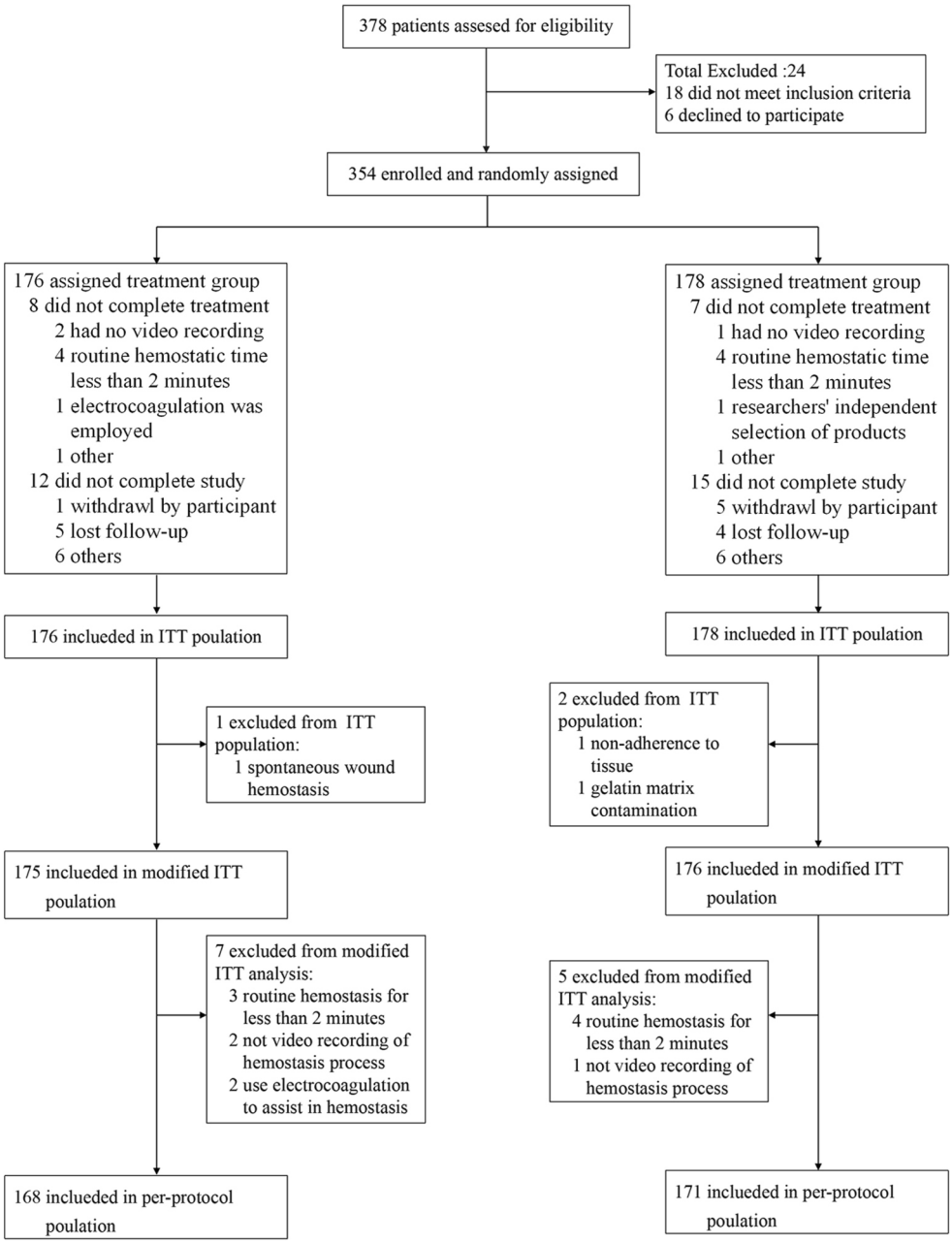

Figure 1. Flow diagram of recruitment and exclusions.

Demographic data	Test group ($n=175$)	Control group ($n=176$)	p value
Age (years)	51.70 ± 12.60	51.89 ± 12.62	0.928
Gender, n(%)			
male	55(31.43%)	59(33.52%)	0.675
female	120(68.57%)	117(66.48%)	
BMI (Kg/m²)	24.64 ± 3.61	24.20 ± 3.61	0.167
Diabetes, n(%)	22(12.57%)	16(9.10%)	0.294
Hypertension, n(%)	44(24.57%)	42(23.30%)	0.781
Medical history within 1 month, n(%)	142	149	0.382
Surgical history, n(%)			
Hepatobiliary surgery	3(1.71%)	2(1.13%)	0.685
Gynecologic surgery	6(3.43%)	4(2.26%)	0.542
Orthopedic surgery	1(0.57%)	1(0.57%)	1.000
Other surgery	6(4.57%)	1(0.57%)	0.067
Previous allergy, n(%)	23(13.14%)	19(10.80%)	0.498
Coagulation indicatiors			
Blood platelet count(10^9/L)	240.45 ± 70.78	241.06 ± 67.18	0.934
PT(s)	11.65 ± 0.96	11.75 ± 0.93	0.209
APTT(s)	30.95 ± 4.38	30.61 ± 4.22	0.448
TT(s)	15.65 ± 1.34	15.77 ± 1.38	0.255
Fibrinogen(g/L)	3.07 ± 0.64	2.99 ± 0.73	0.089
Bleeding severity			
Mild	139(79.43%)	141(80.13%)	0.873
Moderate	34(19.43%)	30(17.05%)	0.563
Severe	2(1.14%)	5(2.84%)	0.448
Life-threatening	0(0.00%)	0(0.00%)	-

Table 1. Baseline characteristics (modified intention-to-treat population). Abbreviation: PT, prothrombin time; APTT, activated partial thromboplastin time; TT, thrombin time.

	Test group	Control group	Treatment difference,%(95% CI)	p value
Modified intention to treat, n	175	176		-
Effective hemostasis, n(%)	163(93.14%)	167(94.89%)	-1.74 (-6.70,3.22)	< 0.001
Sensitivity analysis, n (%)	160(91.43%)	167(94.89%)	-3.46(-8.73,1.81)	0.008
Per-protocol, n	168	171		
Effective hemostasis, n(%)	157(93.45%)	162(94.74%)	-1.28(-6.30,3.73)	< 0.001

Table 2. Primary efficacy outcome in the modified intention-to-treat population and per-protocol population.

the hemostatic process, routine hemostatic time less than 2 min, electrocoagulation was employed to facilitate hemostasis shortly after gelatin matrix applied less than 5 min, and the researchers' independent selection of hemostatic products. Of the 354 subjects, 339 completed the treatment and 327 completed the main study.

As shown in Table 1, there were no notable imbalances in the baseline demographic characteristics, medical history, and blood coagulation function between the test and control groups. However, most of the subjects in the test group (68.57%) and the control group (66.48%) were female. The average age of the test group was 51.70 ± 12.60, while the control group had an average age of 51.89 ± 12.62. In addition, nearly 1/3 subjects in both groups had diabetes and high blood pressure.

Outcomes

In the modified intention-to-treat population, 163 (93.14%) of 175 subjects in the test group (Borayflo Haemostatic matrix) versus 167 (94.89%) of 176 subjects in the control group (Surgiflo Haemostatic matrix) successfully achieved hemostasis within 5 min ($P > 0.05$) (Table 2). The treatment difference between the effective rate of hemostasis within 5 min was − 1.74% (95%CI, -6.70–3.22%; $P < 0.001$), which showed non-inferiority of Borayflo Haemostatic matrix versus Surgiflo Haemostatic matrix (Table 2). In the per-protocol population, 157 (93.45%) of 168 subjects successfully achieved hemostasis within 5 min in the test group (Borayflo Haemostatic matrix) versus 162 (94.74%) of 171 subjects in the control group (Surgiflo Haemostatic matrix) ($P > 0.05$). The treatment difference in the effective rate of hemostasis within 5 min was − 1.28% (95%CI, -6.30–3.73%; $P < 0.001$). The primary endpoint was consistent with the overall outcome in subgroups defined by

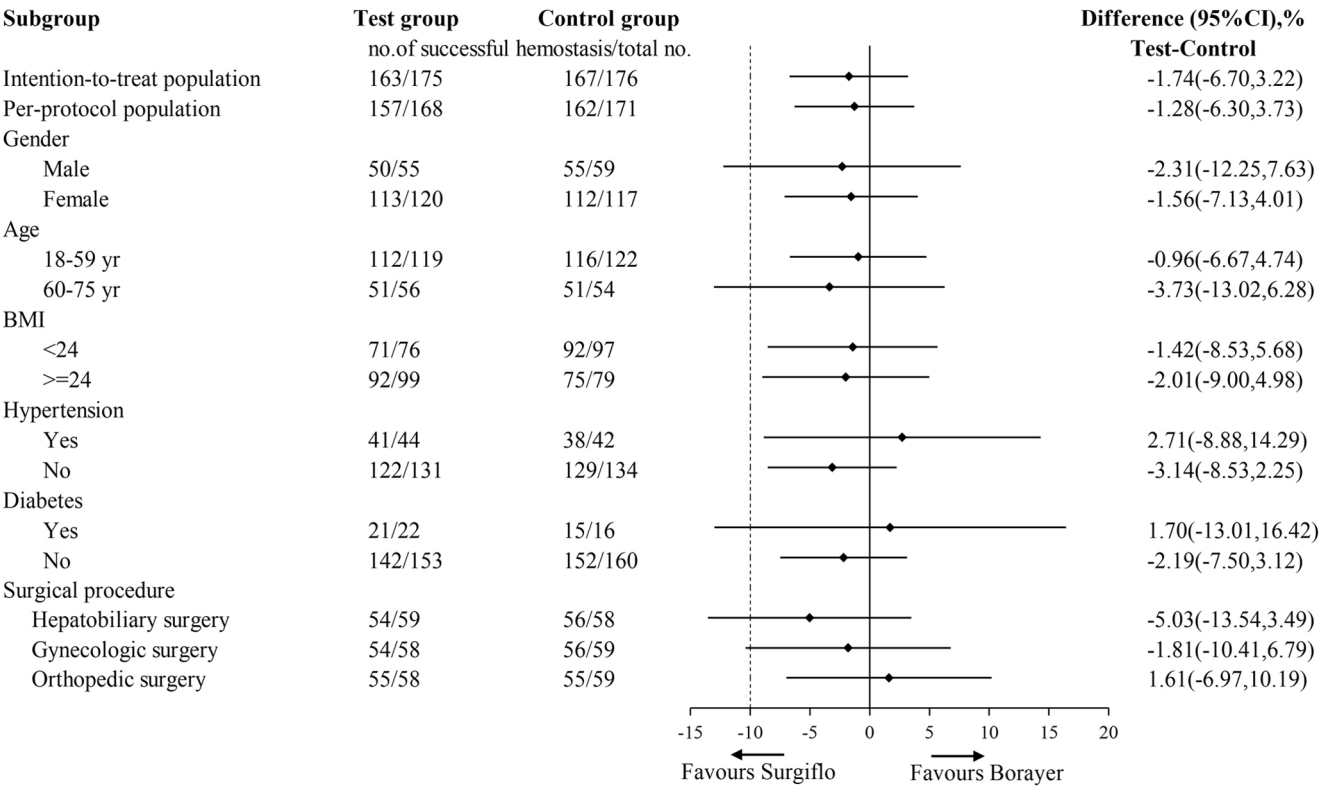

Figure 2. Subgroup analysis of effective rate of hemostasis within 5 min.

	Modified intention-to-treat population, *n*=351			Per-protocol population, *n*=339		
	Test group	Control group	*p* value	Test group	Control group	*p* value
Hemostatic time(s)	171.35±137.14	160.97±80.26	0.742	171.12±139.21	161.37±81.41	0.791
Change in RBC count(10^{12}/L)	-0.37±0.37	-0.42±0.38	0.247	-0.35±0.34	-0.43±0.36	0.235
Change in Hb(g/L)	-10.93±11.07	-12.15±11.40	0.362	-11.13±11.01	-12.20±11.46	0.451
Intraoperative transfusion(mL)	10.86±80.56	26.99±129.74	0.158	11.31±82.20	27.78±131.55	0.164
Intraoperative bleeding(mL)	107.30±163.36	120.04±199.01	0.488	104.74±160.88	122.67±201.21	0.353
Procedure time (minutes)	138.63±71.92	147.24±89.47	<0.001	138.91±72.55	148.84±90.09	<0.001

Table 3. Secondary efficacy outcome in the modified intention-to-treat population and per-protocol population. Abbreviation: RBC, red blood cell; Hb, hemoglobin.

baseline characteristics (Fig. 2). In the modified intention-to-treat population, 3 patiens in the test group were classified as clinical failure due to lack of video recording and hemostatic information. Exclusion of 3 subjects in a stratified sensitivity analysis of study center led to the achievement of successful hemostasis within 5 min in 160 (91.43%) of 175 subjects in the test group (treatment difference − 3.46%, 95%CI -8.73–1.81%) (Table 2). Efficacy analyses in the modified intention-to-treat population and per-protocol populations supported the finding of non-inferiority Borayflo Haemostatic matrix versus Surgiflo Haemostatic matrix.

The secondary efficacy endpoints analytic results was showed in Table 3. In the modified intention-to-treat population, the hemostatic time was 171.35 ± 137.14s in the test group and 160.97 ± 80.26s in the control group ($P=0.742$). In addition, there was no statistically significant difference in the average change of RBC count and hemoglobin, intraoperative blood transfusion volume, and intraoperative blood loss volume between the two groups. In the per-protocol population, the hemostatic time was 171.12 ± 139.21s in the test group and 161.37 ± 81.41s in the control group ($P=0.791$). Furthermore, the average change of RBC count and hemoglobin, intraoperative blood transfusion volume, and intraoperative blood loss volume were similar for the two groups. Notably, in the modified intention-to-treat and per-protocol populations, the procedure time of subjects using Borayflo Haemostatic matrix is shorter than that of subjects using Surgiflo Haemostatic matrix ($P<0.001$).

Adverse events and product-handling characteristics

In general, the majority of adverse events observed during the trial were mild. Specifically, 101 (57.71%) of 175 subjects in the test group reported adverse events (Table 4). Similarly, 109 (61.58%) of 177 subjects in the control group reported adverse events. These adverse events were unrelated to the use of hemostatic gelatin matrix. Statistical analysis revealed no significant difference in the incidence or severity of adverse events between the two groups ($P > 0.05$). Notably, one participant from each group withdrew from the study due to adverse events. In relation to serious adverse events, the test group had 4 subjects (2.29%) while the control group had 5 subjects (2.82%). These occurrences are unrelated to the examination of hemostatic gelatin matrix. There was no statistically significant difference observed in the prevalence of serious adverse events between the two groups. These serious adverse events were unrelated to the use of hemostatic gelatin matrix (Table S3 and S4).

Table 5 presents the results of a quantitative analysis conducted on vital signs (blood pressure, pulse, respiratory rate, body temperature) and laboratory examinations (blood routine, blood biochemistry) (Table 5). The baseline values of vital signs and laboratory examination had no statistically significant difference between the two groups ($P > 0.05$). However, within 48 h post-operation, significant differences were observed in respiratory rate, white blood cell count, and neutrophil count between the two groups ($P < 0.05$). Conversely, no significant differences were found between the two groups after a span of 6 weeks following the operation. To enhance safety assessment, the laboratory test results were categorized into normal, abnormality with clinical significance, abnormality without clinical significance, and non-examination. Subsequently, a qualitative analysis was conducted on the results obtained during each time point visit in relation to the baseline laboratory examination after treatment initiation in both groups (Table 6). Within 48 h post-operation, 109 (62.29%) of 175 subjects in the test group and 91 (51.41%) of 177 subjects in the control group had a statistically significant change in white blood cell count compared to the baseline ($P < 0.05$). The changes in other indices had no statistical significance differences when compared to the baseline ($P > 0.05$).

Table 7 shows the results of the product-handling evaluations. Considering three key factors: ease of use, ability of material to conform to tissue surfaces, and access to locations difficult to reach. The findings demostrated that over 95% of evaluations were categorized as easy or good (1–2 scores), and there was no significant variation observed between the two groups ($P > 0.05$).

Discussion

The efficient management of hemorrhage holds significant importance across various surgical procedures[19,20]. The advantages of promptly and efficiently managing intraoperative bleeding are readily apparent, including the reduction of operation duration, prevention of inadvertent harm to surrounding tissues and organs, diminished reliance on blood transfusions, and decreased incidence of postoperative complications[21–23]. Hemostatic gelatin matrix has several advantages over traditional hemostatic methods and products. Gelatin matrix can be applied to wounds of varying shapes, and it will expand upon contact with blood, thereby enhancing its tamponade effect. This enables the prompt attainment of hemostasis and improved efficiency in managing bleeding at sites with uncertain locations or challenging cessation[24]. Notably, gelatin matrix has favorable biodegradability and biocompatibility, allowing for gradual absorption by the human body during wound healing, obviating the necessity for a secondary surgical intervention[12]. Previous studies have demonstrated the favorable hemostatic efficacy, safety, absence of adverse reactions and postoperative complications associated with the clinical utilization of Surgiflo Haemostatic matrix in various surgical procedures, particularly in spinal surgery, nephrectomy, submandibular gland resection, and neurosurgery[14–17]. The favorable hemostatic effect and safety profile of hemostatic gelatin matrix have led Chinese doctors to frequently opt for Surgiflo Haemostatic matrix as an adjunctive hemostatic agent. However, the high cost of Surgiflo Haemostatic matrix poses a limitation to its widespread utilization in Chinese hospitals.

As the only domestically produced hemostatic gelatin matrix in the Chinese market, the clinical efficacy and safety of Borayflo Haemostatic matrix has been confirmed by this multicenter randomized trial. Regarding the 5-minute hemostatic effective rate, the clinical effectiveness of Borayflo Haemostatic matrix was found to be non-inferior to that of Surgiflo Haemostatic matrix, with rates of 93.14% and 94.89% respectively. The findings

	Test group $n = 175$		Control group $n = 177$		Total $n = 352$		
	n	%	*n*	%	*n*	%	*p* value
Adverse event	101	57.71%	109	61.58%	210	59.66%	0.515
Severity of adverse event							
Mild	88	50.29%	95	53.67%	183	51.99%	0.594
Moderate	27	15.43%	30	16.95%	57	16.19%	0.773
Severe	2	1.14%	2	1.13%	4	1.14%	1.000
Relate to Products	0	0.00%	0	0.00%	0	0.00%	-
Conforming to serious adverse event	4	2.29%	5	2.82%	9	2.56%	1.000
Adverse event leading to discontinuation	1	0.57%	1	0.56%	2	0.57%	1.000
Death	0	0.00%	0	0.00%	0	0.00%	-

Table 4. Adverse evevts.

Time point	Test group	Control group	*p* value
Baseline			
Vital signs			
T( )	36.52(0.31)	36.56(0.27)	0.172
HR	75.28(7.61)	75.89(7.50)	0.200
R	19.14(1.31)	19.40(0.96)	0.152
BP(mmHg)	126.80(12.38)	125.23(11.91)	0.227
Laboratory examinations			
WBC(10^9/L)	6.13 ± 1.65	6.25 ± 1.82	0.888
Neutrophil(10^9/L)	3.75 ± 1.41	3.94 ± 1.65	0.594
Lymphocyte(10^9/L)	1.84 ± 0.59	1.74 ± 0.51	0.250
AST(U/L)	25.90 ± 38.44	25.44 ± 43.23	0.788
ALT(U/L)	34.37 ± 80.98	28.45 ± 47.14	0.620
ALB(g/L)	41.55 ± 4.18	41.40 ± 3.74	0.722
TBIL(umol/L)	15.14 ± 20.17	12.64 ± 7.53	0.293
DBIL(umol/L)	5.56 ± 15.60	3.74 ± 2.89	0.839
BUN(mmol/L)	5.14 ± 1.42	5.03 ± 1.48	0.473
Cr(umol/L)	61.93 ± 15.31	62.24 ± 13.93	0.515
48 h - baseline			
Vital signs			
T( )	0.07(0.43)	0.11(0.48)	0.708
HR	-2.28(12.42)	-2.32(10.83)	0.769
R	0.14(1.41)	-0.23(1.27)	0.022
BP(mmHg)	3.17(16.88)	3.53(16.80)	0.975
Laboratory examinations			
WBC(10^9/L)	5.34 ± 3.10	4.56 ± 3.06	0.018
Neutrophil(10^9/L)	5.94 ± 3.13	5.08 ± 3.14	0.011
Lymphocyte(10^9/L)	-0.68 ± 0.57	-0.57 ± 0.59	0.167
AST(U/L)	12.15 ± 68.21	7.73 ± 79.62	0.777
ALT(U/L)	6.49 ± 91.13	5.46 ± 82.97	0.693
ALB(g/L)	-5.66 ± 4.27	-5.74 ± 4.29	0.854
TBIL(umol/L)	2.64 ± 16.58	2.97 ± 6.45	0.958
DBIL(umol/L)	1.09 ± 11.97	1.25 ± 2.53	0.760
BUN(mmol/L)	-0.93 ± 1.45	-0.96 ± 1.51	0.711
Cr(umol/L)	-0.19 ± 9.25	-2.26 ± 8.83	0.066
6 weeks - baseline			
Vital signs			
T( )	-0.07(0.36)	-0.06(0.31)	0.602
HR	2.90(10.38)	2.59(10.78)	0.798
R	0.36(1.40)	0.07(1.26)	0.056
BP(mmHg)	0.92(13.46)	1.36(13.41)	0.776
Laboratory examinations			
WBC(10^9/L)	0.72 ± 1.66	0.49 ± 2.00	0.320
Neutrophil(10^9/L)	0.56 ± 1.60	0.20 ± 1.91	0.073
Lymphocyte(10^9/L)	0.15 ± 0.55	0.27 ± 0.51	0.032
AST(U/L)	-3.85 ± 38.99	-1.78 ± 45.78	0.385
ALT(U/L)	-11.06 ± 82.00	-0.69 ± 50.57	0.318
ALB(g/L)	2.70 ± 3.74	2.89 ± 3.90	0.661
TBIL(umol/L)	-1.17 ± 22.04	-1.23 ± 6.55	0.774
DBIL(umol/L)	-0.52 ± 16.18	-0.05 ± 2.57	0.741
BUN(mmol/L)	-0.43 ± 1.45	-0.22 ± 1.41	0.195
Cr(umol/L)	-1.75 ± 8.03	-1.44 ± 12.58	0.965

Table 5. Quantitative analysis of vital signs and laboratory examinations. Abbreviation: T, temperater; HR, heart rate; R, respiration; BP, blood pressure; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; BUN, blood urea nitrogen; Cr, creatinine.

	Change	Test group	Control group	*p* value
Baseline → 48 h				
WBC, n(%)	Norm to Abn without CS	109(62.29%)	91(51.41%)	0.048
	Norm to Abn with CS	10(5.71%)	7(3.95%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Neutrophil, n(%)	Norm to Abn without CS	122(69.71%)	113(63.84%)	0.426
	Norm to Abn with CS	9(5.14%)	7(3.95%)	
	Abn without CS to Abn with CS	1(0.57%)	0(0.00%)	
Lymphocyte, n(%)	Norm to Abn without CS	70(40.00%)	71(40.11%)	0.606
	Norm to Abn with CS	6(3.43%)	3(1.69%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
AST, n(%)	Norm to Abn without CS	29(16.57%)	19(10.73%)	0.365
	Norm to Abn with CS	6(3.43%)	5(2.82%)	
	Abn without CS to Abn with CS	1(0.57%)	1(0.57%)	
ALT, n(%)	Norm to Abn without CS	17(9.71%)	18(10.17%)	0.597
	Norm to Abn with CS	6(3.43%)	3(1.69%)	
	Abn without CS to Abn with CS	1(0.57%)	0(0.00%)	
ALB, n(%)	Norm to Abn without CS	75(42.86%)	72(40.68%)	0.721
	Norm to Abn with CS	7(4.00%)	4(2.26%)	
	Abn without CS to Abn with CS	5(2.86%)	7(3.95%)	
TBIL, n(%)	Norm to Abn without CS	21(12.00%)	19(10.73%)	0.645
	Norm to Abn with CS	1(0.57%)	0(0.00%)	
	Abn without CS to Abn with CS	1(0.57%)	0(0.00%)	
DBIL, n(%)	Norm to Abn without CS	21(12.00%)	19(10.73%)	0.659
	Norm to Abn with CS	4(2.29%)	2(1.13%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
BUN, n(%)	Norm to Abn without CS	36(20.57%)	45(25.42%)	0.312
	Norm to Abn with CS	1(0.57%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Cr, n(%)	Norm to Abn without CS	9(5.14%)	11(6.21%)	0.664
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Baseline → 6 weeks				
WBC, n(%)	Norm to Abn without CS	13(7.43%)	8(4.52%)	0.269
	Norm to Abn with CS	0(0.00%)	1(0.56%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Neutrophil, n(%)	Norm to Abn without CS	17(9.71%)	13(7.34%)	0.426
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Lymphocyte, n(%)	Norm to Abn without CS	10(5.71%)	4(2.26%)	0.110
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
AST, n(%)	Norm to Abn without CS	10(5.71%)	12(6.78%)	0.638
	Norm to Abn with CS	1(0.57%)	3(1.69%)	
	Abn without CS to Abn with CS	1(0.57%)	0(0.00%)	
ALT, n(%)	Norm to Abn without CS	16(9.14%)	13(7.34%)	0.836
	Norm to Abn with CS	2(1.14%)	2(1.13%)	
	Abn without CS to Abn with CS	0(0.00%)	1(0.56%)	
ALB, n(%)	Norm to Abn without CS	2(1.14%)	1(0.56%)	0.433
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	1(0.57%)	0(0.00%)	
TBIL, n(%)	Norm to Abn without CS	1(0.57%)	1(0.56%)	1.000
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	1(0.56%)	
DBIL, n(%)	Norm to Abn without CS	4(2.29%)	5(2.82%)	1.000
	Norm to Abn with CS	1(0.57%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	

Continued

	Change	Test group	Control group	*p* value
BUN, n(%)	Norm to Abn without CS	8(4.57%)	6(3.39%)	0.571
	Norm to Abn with CS	0(0.00%)	0(0.00%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	
Cr, n(%)	Norm to Abn without CS	11(6.29%)	8(4.52%)	0.490
	Norm to Abn with CS	0(0.00%)	1(0.56%)	
	Abn without CS to Abn with CS	0(0.00%)	0(0.00%)	

Table 6. Qualitativ analysis of vital signs and laboratory examinations. Abbreviation: Norm, normal; Abn with CS, abnormal with clinical significance; Abn without CS, abnormal without clinical significance.

Variable	Test group *n*(%)	Control group *n*(%)	*p* value
No. of Subjects	168	171	
How easy is the product to apply to the bleeding site?			
1 (easy)	130(77.38%)	137(80.12%)	0.453
2	33(19.64%)	25(14.62%)	
3	4(2.38%)	6(3.51%)	
4	1(0.60%)	3(1.75%)	
5 (difficult)	0(0.00%)	0(0.00%)	
How well did material conform to tissue surfaces?			
1 (well)	135(80.36%)	148(86.55%)	0.166
2	31(18.45%)	20(11.70%)	
3	1(0.60%)	3(1.75%)	
4	1(0.60%)	0(0.00%)	
5 (poor)	0(0.00%)	0(0.00%)	
How easy is product to deliver to hard to reach surfaces?			
1 (easy)	140(83.33%)	149(87.13%)	0.575
2	23(13.69%)	19(11.11%)	
3	5(2.98%)	3(1.75%)	
4	0(0.00%)	0(0.00%)	
5 (difficult)	0(0.00%)	0(0.00%)	

Table 7. Product-handling characteristics.

from the analysis of the modified intention-to-treat and per-protocol populations demonstrated congruity, which was further corroborated by the sensitivity analysis. Moreover, the 5-minute hemostatic efficacy of Surgiflo Haemostatic matrix exhibited consistency with previous research, albeit with a larger sample size and a variety of surgical procedures in our trial, thus affirming the effectiveness of our study[25]. Furthermore, there was no statistically significant difference between Borayflo Haemostatic matrix and Surgiflo Haemostatic matrix when assessing secondary efficiacy endpoints, encompassing hemostatic time, the change in preoperative and postoperative RBC count/Hb, intraoperative blood loss, and intraoperative blood transfusion volume. Nevertheless, the procedure time of Borayflo Haemostatic matrix was shorter than that of Surgiflo Haemostatic matrix (138.63 ± 71.92 vs. 147.24 ± 89.47, $P < 0.001$).

Throughout the clinical trial, the number and types of adverse events in Borayflo Haemostatic matrix group was comparable to that of Surgiflo Haemostatic matrix group, indicating that Borayflo Haemostatic matrix was as safe as Surgiflo Haemostatic matrix which has been used salfly for more than 10 years. During the study period, no subjects died. It is noteworthy to mention that gastrointestinal reactions were observed as the most prevalent adverse events in both the test group and the control group. These findings align with previous clinical trials conducted on similar products, suggesting a potential association with anesthesia and surgery rather than the product itself. Notably, none participants in our study experienced adverse reactions, including allergies and shock, both during and after the surgical procedure. The vital signs and laboratory tests, including blood routine and blood biochemistry, were monitored at two time points: 48 h and 6 weeks after the operation. At the 48-hour and 6-week postoperative time points, the vital signs, blood routine, and blood biochemical findings of Borayflo Haemostatic matrix group were similar to those of Surgiflo Haemostatic matrix group, with the exception of respiratory rate, white blood cell count, and neutrophil count within 48-hour. However, these abnormalities reverted to their baseline levels 6 weeks post-surgery. Surgery, being an invasive procedure, inherently induces tissue damage and inflammation, consequently triggering an elevation in white blood cells and neutrophils. Hence, it was our contention that the observed elevation in respiratory rate, white blood cell

count, and neutrophil count 48 h following the surgical procedure was a typical postoperative response and was unrelated to the application of the hemostatic gelatin matrix.

The product-handling characteristics is a crucial criterion for evaluating product quality. Surgeon responses to all three questions related to product-handling characteristics showed no significant difference between Borayflo Haemostatic matrix and Surgiflo Haemostatic matrix. The fluid characteristics of hemostatic fluid gelatin matrix can be injected into the site of deep bleeding or irregular wounds to stop bleeding, which will expand after contact with blood, further produce tamponade effect and enhance hemostatic effect. Surgeons must exercise caution during the injection process to prevent intravascular coagulation by refraining from injecting hemostatic gelatin matrix into the vascular lumen.

In summary, our research shows non-inferiority of Borayflo Haemostatic matrix compared to Surgiflo Haemostatic matrix in terms of clinical efficacy and safty, which will provide a basis for the use of surgeons. Importantly, Borayflo Haemostatic matrix is a domestic hemostatic gelatin matrix product, offering a comparatively lower price in comparison to similar imported products. The price of Borayflo Haemostatic matrix products of different specification is 15-60% lower than that of Surgiflo Haemostatic matrix, which will help to reduce some of the medical costs for Chinese patients.

Limitations of the study

This study has several limitations. Firstly, the inability to blind the surgeons due to the distinct appearance of the two products may introduce bias in favor of the clinical trail results. Secondly, the absence of statistical analysis on the various types of intraoperative bleeding, along with the differing levels of difficulty in achieving hemostasis for each type, could potentially impact the results. Thirdly, despite our best endeavors, a total of 9 subjects were lost to follow-up. Fourthly, despite the training provided to the evaluators responsible for determining the primary endpoint, there remains the possibility of discrepancies in the recording of hemostatic time and the assessment of hemostatic efficiency based on video information. Additionally, the effectiveness of hemostasis is influenced by numerous factors, and other confounding variables may interfere with the results of research findings. Lastly, the study involved only four centers and exclusively recruited subjects undergoing hepatobiliary surgery, obstetrics and gynecology procedures, and orthopaedic surgeries, thereby potentially compromising the comprehensive evaluation of the efficacy and safety of Borayflo Haemostatic matrix. Henceforth, our intention is to broaden the trial's scope and enroll additional surgical groups for future research, with the aim of enhancing the assessment of Borayflo Haemostatic matrix.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions
BZ, ZY and PY designed the experiments. ZC, LX and BX collected the clinical data. PL, RG and ZC performed data analysis. PL and QL wrote the paper. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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