# To evaluate the efficacy and safety of novel haemostatic agents in reducing intraoperative bleeding and improving surgical outcomes: a randomized controlled trial

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Introduction. To explore the value of transhemostatic drugs based on randomized controlled trials to reduce intraoperative blood loss and improve surgical outcomes. Methods. 100 elective operation patients admitted from January 2023 to March 2024 were selected and divided into observation group (n=50) and control group (n=50) according to the principle of random number table. Both groups adopted standardized surgical treatment. The observation group injected pit bukistrodon thrombin 30min before surgery, and the control group injected simulated Agkistrodon 30min before surgery. The hemostatic indexes of the two groups were recorded and compared with 30min (T0), 10min (T1), 30min (T2), 30 min (T3), 10min (TT), prothrombin (PT), activated partial thromboplastin time (APTT), and plasma fibrinogen (FIB)], comparing the occurrence of adverse events.

Results. The incision hemostasis time (164.45 ± 46.62) s was shorter than that of the control group, and the bleeding (3.86 ± 0.52) g and bleeding (0.21 ± per unit area 0.04) g / cm2 were less than that of the control group, significant ($P <0.05$). The body temperature, pulse and respiratory rate of the patients at T1 and T2 were lower than that of the control group ($P <0.05$); the coagulation indexes before, 10min and 3d were not different ($P> 0.05$). There was no significant difference between the two groups ($P> 0.05$).

Conclusion. For surgical patients, the hemostasis effectiveness of thrombin is good, which can maintain the stability of intraoperative vital signs, with little impact on body coagulation function and low incidence of adverse events.

Keywords. Surgery; thrombin; haemostasis; vital signs; coagulation function; adverse events

## INTRODUCTION

Bleeding during surgery is one of the common challenges facing surgical procedures, especially for complex or high-risk surgical [1]. Intraoperative bleeding not only increases the risk and complexity of surgery, but may also may lead to the occurrence of postoperative complications, prolong rehabilitation time, and increase the patient hospital stay and medical costs [2]. Therefore, the search of effective hemostatic agents to reduce intraoperative bleeding and improve surgical outcomes is one of the important research topics in the surgical field. At present, there are a variety of intraoperative hemostatic drugs, and thrombin is a protease derived from the snake venom, with strong coagulation effect [3]. It mainly by degrading procoagulation in plasma, promoting thrombosis, thus achieving hemostasis [4]. Clinically, thrombin is widely used in hemostatic agents, especially in the case of reducing intraoperative bleeding, but there is still some controversy and uncertainty about the efficacy and safety of intervention in this hemostatic drug [5]. Based on this, this study used the randomized controlled trial to explore the efficacy and safety of hemostatic drugs to reduce intraoperative bleeding and improve the surgical results, and laid a favorable foundation for the smooth implementation of the operation. The report is as follows.

## 1. DATA AND METHODS

### 1.1 General information

The 100 patients who underwent elective surgical treatment admitted from January 2023 to March 2024 were selected as the study subjects. According to the principle of random number table method, it was divided into observation group and control group, with 50 patients in each group. In the observation group, 28 males and 22 females; 23-70 years, mean age (48.02 ± 3.41); type of surgery: 17 abdominal surgeries and 33 chest surgeries. In the control group, 30 males and 20 females; age 21 to 70 years, mean (47.89 ± 3.26) years; type of surgery: 19 abdominal surgeries and 31 chest surgeries. According to the gender, age and operation type of the two groups, there was no significant difference between the groups ($P > 0.05$). The study was approved by the medical Ethics committee of the hospital.

### 1.2 Inclusion and exclusion criteria

Inclusion criteria: ① Patients with low surgical risk and elective chest and abdominal surgery; patients with bleeding risk during ②; ③ patients over 18 years of age with complete clinical data; ④ normal coagulation function, patients without blood system disease; ⑤ signed surgical consent.

1.1 Exclusion criteria: ① Patients with a history of thrombosis or hemorrhagic disease; ② patients with diabetes, hypertension, hyperthyroidism; ③ patients with heart, liver, kidney and other organic diseases; ④ women during pregnancy or lactation; ⑤ patients with mental disorders, cognitive impairment, or alcohol dependence; and patients with ⑥ patients before surgery.

### 1.3 Methods

The two groups were assigned to experienced medical teams to perform surgical treatment. All patients used electrocardiogram monitoring and recorded vital signs such as heart rate and blood oxygen saturation after entering the operating room. The patient was preoperative disinfected and covered with general anesthesia, routine incision treatment and surgical resection。

Observation group of patients in 30min before the start of the operation, give patients with intravenous injection tip kiss pit snake thrombin (Beijing Kang Chen Pharmaceutical Co., LTD., national medicine approved H20080633, specification 1 unit), mainly injection 2 bottles of thrombin, each bottle of drug application 2ml of saline solution, drug with intravenous injection scheme, according to the patient, the infusion speed can be fast or slow, usually drug choice in push injection within 1min.

In the control group, two bottles of thrombin were injected 30min before the operation, also with 2ml of normal saline, and the mixture was injected by free infusion of the drug for about 1min. The procedure was performed in strict accordance with aseptic specifications, and no other drugs that affect hemostasis were applied during the procedure.

The patients in both groups were sent to the anesthesia awakening room for observation for 30min after surgery. If there was no abnormal conditions, they could be sent to the original ward. After the operation, antibiotics could be used to fight infection, and if the abnormal conditions were found, they could be treated in time.

1.4 Statistical analysis

The relevant indicators of patient hemostasis were recorded, mainly the time of patient incision hemostasis and the time interval between the cessation of incision bleeding and the beginning of the section. In addition to statistics patients incision bleeding and incision bleeding per unit area, specific bleeding of calculation method: patients after successful anesthesia disinfection cloth, with the help of a scalpel, incision continues to cut to the muscle tissue, the length of the incision control in 7-10cm size, and according to the demand of the operation for long incision longer than 10cm, can be considered to extend the surgical incision. The recording time of the clock was corrected, the weighed dry gauze was implanted into the incision site, and the gauze was opened at 15s interval to observe whether there was bleeding. After no bleeding, the gauze was removed and weighed, and the weighing result was the amount of bleeding of the incision. The disinfection steel ruler prepared in advance shall be used to obtain the length and depth of the incision. multiplying the length by the width by 2, the incision per unit area and the amount of bleeding per unit area of the incision by unit area.(2) Vital signs. Vital signs, including body temperature, pulse and respiratory rate, at 30min (T0), 10min (T1), 30min (T2), and postoperative (T3) were recorded in both groups.(3) Coagulation function. In both groups of patients, 10min and 3d before medication, including thrombin time (Thrombin time, TT), prothrombin time (Prothrombin time, PT), activated partial thromboplastin time (Activated partial thromboplastin time, APTT), plasma fibrinogen (Fibrinogen, FIB).(4) Adverse events. The occurrence of surgical and postoperative adverse events, in which clinically significant abnormal changes in laboratory indicators after medication, should also be recorded as adverse events and closely followed up until return to normal or pre-administration level.

1.5 Statistical analysis

The SPSS21.0 software was used for the statistical results analysis, and the measurement data were used（$\bar{x} \pm s$）Representation, using t-test, count data by (%) and $\chi$ 2 test at P <0.05.

2 RESULTS

2.1 Hemostasis index

Compared with the hemostasis related indicators of patients in each group, the observation group was shorter than the control group, and the incision bleeding volume was less per unit area, and the differences were statistically significant (P <0.05), as shown in Table 1.

Table 1 Comparison of hemostasis-related indicators in the two groups（$\bar{x} \pm s$）

| group | n | Incision hemostasis time（s） | Incision bleeding volume（g） | Blood loss from the incision per unit area（$g/cm^2$） |
|---|---|---|---|---|
| observation group | 50 | 164.45±46.62 | 3.86±0.52 | 0.21±0.04 |
| control group；matched group | 50 | 194.47±52.24 | 5.21±0.71 | 0.37±0.07 |
| t | | 4.063 | 13.444 | 16.162 |
| P | | 0.000 | 0.000 | 0.000 |

2.2 Vital signs

In the observation group, the body temperature, pulse and respiratory rate between T 0 and T 3 were not significantly different at each time point (P> 0.05). The body temperature, pulse, and respiratory rate at T1 and T2 decreased than those at TO (P <0.05), while the indicators at T3 were not significantly different from those at T0 (P> 0.05), and the observation group showed lower temperature, pulse, and respiratory rate at T1 and T2 than those at the control group (P <0.05), as shown in Table 2.

Table 2 Comparison of vital signs indicators between the two groups at different times of the surgical process ( $\bar{x} \pm s$ )

| project | group | T0 | T1 | T2 | T3 |
|---|---|---|---|---|---|
| temperature（℃） | observation group （n=50） | 36.24±0.42 | 36.54±0.46 | 36.47±0.45 | 36.32±0.47 |
| | control group；matched group（n=50） | 36.16±0.41 | 37.31±0.36* | 37.26±0.41* | 36.42±0.42 |
| | t | 1.379 | 15.124 | 13.624 | 1.683 |
| | P | 0.170 | 0.000 | 0.000 | 0.095 |
| pulse (Secondary / min) | observation group （n=50） | 78.86±5.15 | 80.11±5.21 | 80.05±5.18 | 78.62±5.04 |
| | control group（n=50） | 79.01±5.42 | 86.65±5.62* | 86.84±5.53* | 79.11±5.17 |
| | t | 0.195 | 8.228 | 8.682 | 0.670 |
| | P | 0.845 | 0.000 | 0.000 | 0.504 |
| Respiratory rate (times / | observation group （n=50） | 15.23±1.62 | 15.75±1.56 | 15.23±1.62 | 15.15±1.41 |
| | control group； | 15.16±1.58 | 21.15±1.02* | 20.87±1.13* | 16.06±41.38 |

| | | | | | |
|---|---|---|---|---|---|
| min) | matched group （n=50） | | | | |
| | t | 0.571 | 9.014 | 9.152 | 0.145 |
| | P | 0.569 | 0.000 | 0.000 | 0.884 |

Note: * P <0.05.

2.3 Coagulation function

In both groups, TT, PT, APTT, and FIB at 10min decreased / increased (P <0.05), but there was no significant difference at 3d (P> 0.05). There were no significant differences in the coagulation function indexes before, 10min and 3d after drug administration (P> 0.05), as shown in Table 3.

Table 3 Comparison of coagulation function indexes at different times in both groups（$\bar{x} \pm s$）

| project | group | Before medication | After medication10min | 3d after surgery |
|---|---|---|---|---|
| TT（s） | observation group （n=50） | 17.15±1.75 | 16.45±1.88# | 17.04±1.81 |
| | control group （n=50） | 17.21±1.77 | 16.51±1.89# | 17.02±1.82 |
| | t | 0.239 | 0.224 | 0.077 |
| | P | 0.811 | 0.822 | 0.938 |
| PT（s） | observation group （n=50） | 11.25±0.89 | 12.04±1.02# | 11.33±0.92 |
| | control group （n=50） | 11.19±0.91 | 12.06±1.04# | 11.36±0.94 |
| | t | 0.466 | 0.135 | 0.225 |
| | P | 0.642 | 0.892 | 0.821 |
| APTT（s） | observation group（n=50） | 26.25±2.62 | 27.14±2.45# | 26.43±2.53 |
| | control group （n=50） | 26.16±2.58 | 27.03±2.51# | 26.41±2.49 |
| | t | 0.246 | 0.309 | 0.056 |
| | P | 0.805 | 0.757 | 0.954 |
| FIB（g/L） | observation group（n=50） | 3.11±0.62 | 2.77±0.58# | 3.16±0.65 |
| | control group （n=50） | 3.14±0.63 | 2.79±0.61# | 3.14±0.66 |
| | t | 0.336 | 0.231 | 0.214 |
| | P | 0.737 | 0.817 | 0.830 |

Note: # P <0.05.

2.4 Adverse events

The patient had mild adverse events during the operation, which did not affect the surgical treatment effect and postoperative recovery, and had no moderate or severe adverse events. In the occurrence of adverse events, the comparative difference was not significant.

## 3 DISCUSSION

Surgery is an effective operation to treat diseases, but bleeding is inevitable in some common and major operations. This is mainly because the cutting, scraping or stitching of the tissue will lead to direct destruction or damage of the blood vessels, making the blood outflow without restraint and forming bleeding [6]. Surgical trauma can cause inflammatory reactions, and the release of inflammatory mediators can also affect the permeability of the blood vessel wall and the aggregation function of platelets, which can then affect the coagulation process, leading to the increase of bleeding during surgery. Intraoperative bleeding often increases the body temperature and pulse, and accelerates the breathing rate, and blood can also affect the surgical field, causing adverse effects on the effect of surgery [7]. Therefore, for patients treated by surgery, effective hemostasis is needed to ensure the smooth operation and ensure the surgical effect, and promote the early recovery of patients' condition.

The application of hemostatic drugs is an important means of hemostasis during the surgical process, and it is important for studying the efficacy and safety studies of hemostasis [8]. The results of this study showed that in terms of effective hemostasis, the observation group had shorter hemostasis time and less bleeding amount, indicating that the application of coagulase was good for intraoperative hemostasis. Conromase is the thromase obtained from the venom in South China. As a hemostatic drug, the main hemostatic route is that it can act fibrinogen to cleave the α subunit, release fibrin peptide A, form soluble fibrin monomer and clot, and play a hemostatic role [9]. The hydrolysis of fibrinogen can generate soluble fibrin monomer, which can promote platelet aggregation in the damaged parts of blood vessels, accelerate the formation of platelet antithrombosis, and play a hemostatic role [10]. In addition, thrombin can also release coagulation factor activators, platelet adhesion, aggregation and release, and play the role of hemostasis [11].

Intraoperative bleeding causes the fluctuation of vital signs, and in addition, the persistence of bleeding can also cause the fluctuation of coagulation factors. In the process of operation, it is necessary to maintain the stability of vital signs and reduce the fluctuation of coagulation function. The results showed that the vital signs of the observation group did not fluctuate from T0 to T 3, while the vital signs of the control group at T1 and T2 were lower than that at T 0, and the body temperature, pulse and respiratory rate of the observation group at T1 and T2 were lower than that of the control group. It shows that the application of hemobin can maintain the stability of intraoperative vital signs. The main reason is that thrombin has a powerful coagulation effect, which can promote thrombosis, thus effectively reducing bleeding [12] during surgery. While reducing the amount of blood loss, it also reduces the impact of blood loss on the patient, which is beneficial to maintain the circulatory stability of the patient. The application of thrombin in A. spinus also reduced the inflammatory response caused by surgical trauma and reduced the release of inflammatory mediators, which to reducing the fluctuation of body temperature, pulse and respiratory rate [13]. The results showed that the coagulation index of 10min after medication fluctuated with that before medication, but there was no difference in the coagulation index measured at each time point between groups, and there was no significant difference in the incidence of adverse events between the two groups, indicating that the application of hemostatic drugs had little impact on the coagulation index of surgical patients, and the incidence of adverse reactions was less. It is mainly manifested by the coagulation effect of thrombin, which is often the bleeding site of damaged blood vessels. In the normal vascular system, because there is no platelet adhesion and aggregation, thrombin and degradation products of them do not induce the aggregation of platelets, so there is no thrombin [14]. The application of thrombin hemostatic drugs has no obvious effect on coagulation function, so it is also small for [15] in the fluctuation of coagulation index. However, the adverse reaction rate and occurrence degree caused by the application of hemostatic drugs are less and the implementation process of surgery is relatively low, which shows that there is no obvious causal relationship between the application of hemostasis drugs and the occurrence of adverse events, which proves that the safety of hemostasis drugs is good, and thus also shows the safety and effectiveness of drug application.

To sum up, for patients undergoing surgical treatment, in the process of surgery, the application of the hemostatic drugs can achieve good hemostatic effect, shorten the hemostasis time and reduce the amount of bleeding, stabilize the operation of vital signs, and drugs for the body coagulation function, the incidence of adverse events is low, is a safe and effective hemostasis scheme.

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