ORIGINAL RESEARCH

Analysis of Hemostatic Effect and Safety of Local Spray Treatment With Hemocoagulase Bothrops Atrox for Injection After Resection of Colon Polyps

Dalei Chen, MM; Yalan Chen, MM; Minhua Wang, MD

ABSTRACT

Context • Postoperative bleeding after resection of colon polyps (CPs) is an extremely common adverse event with endoscopic treatment. Hemocoagulase Bothrops Atrox (HBA) is a newly discovered hemostatic substance that contains thrombin-like and coagulation kinase-like enzymes. However, research is lacking about its use for the treatment of intestinal polyps.

Objective • The study intended to examine the hemostatic efficacy and safety of a local spray treatment with HBA, derived from HBA for injection, after CP resection, to provide a new hemostatic method, support HBA's use, and provide evidence for clinical decision making.

Design • The research team performed a randomized controlled study.

Setting • The study took place at the Affiliated Hospital of Hebei University in Baoding, Hebei, China.

Participants • Participants were 200 patients with CP who received treatment at the hospital between December 2020 and December 2022.

Intervention • The research team divided participants into two groups with 100 participants each, an intervention group and a control group, using the random number expression method. For hemostasis, the intervention group received a local spray treatment that used HBA for injection, and the control group received metal-clip closure or electrocoagulation.

Outcome Measures • The research team measured: (1) the hemostatic efficacy; (2) clinical outcomes—time to hemostasis, hemostasis rate, rebleeding rate, and incidence of late postoperative bleeding; (3) at baseline and at 24h postintervention, the coagulation function—prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB); (4) at baseline and at 24h postintervention, PLT parameters—platelet count (PLT), procalcitonin (PCT), and mean platelet volume (MPV); (5) economic effects—total number of participants with hemostasis, hospital days, and total hospital costs; and (6) adverse reactions.

Results • The total hemostatic efficacy for the intervention group was significantly higher than that of the control group ($P = .027$), and the time to hemostasis was significantly shorter ($P < .001$) and the hemostasis rate, rebleeding rate, and incidence of late postoperative bleeding were all significantly lower than those of the control group, at $P = .009$, $P = .009$, and $P = .048$, respectively. In addition, the intervention group's postoperative PT, TT, APTT, FIB, and MPV were all significantly lower than those of the control group (all $P < .05$), while its PLT and PCT were significantly higher than those of the control group (both $P < .05$). The intervention group's total number of participants with hemostasis, participants with hemostasis, hospital days, and total cost were significantly lower than those of the control group (all $P < .05$), while no significant difference existed between the groups in the incidence of adverse effects ($P > .05$).

Conclusions • HBA has an excellent hemostatic effect on intestinal polypectomy, with convenient use and high safety. In the future, popularizing the use of HBA in the treatment of intestinal polypectomy can not only effectively guarantee the postoperative safety of patients but also could reduce their economic burden and improve the quality of clinical medical services. (*Altern Ther Health Med.* 2023;29(8):406-411).

Dalei Chen, MM, chief physician, and **Yalan Chen,** MM, attending physician, Department of Gastroenterology, Affiliated Hospital of Hebei University, Baoding, Hebei, China. **Minhua Wang,** MD, chief physician, Department of Gastroenterology, Nanwen Community Health Service Center, Rongdong District, Xiongan, Hebei, China.

Corresponding author: Minhua Wang, MD
E-mail: limon_6@163.com

Colon polyps (CPs) are a common clinical condition that infection, age, poor lifestyle habits, and genetics can induce.[1] The disease's clinical manifestations are intermittent blood in the stool or blood on the stool's surface, abdominal stuffiness and discomfort, and vague pain. Without timely treatment, the disease can cause deterioration in the colon, which can greatly increase the risk of intestinal bleeding and CP carcinoma. The incidence of CP is currently on the rise in China.[2]

For patients receiving pharmacological treatments and dietary interventions for CPs, it can take 5-15 years to progress from adenomatous polyps to cancer, and the total cancer rate is 10-20%.[3] Of all bowel cancers, 80%-95% evolve slowly from adenomatous polyps, and any polyp increases the risk of colorectal cancer (CRC).[4] Therefore, excision and removal of polyps can not only effectively relieve patients' adverse clinical symptoms but also reduce the risk of CRC.[5]

Recently, with the continuous advancement of colonoscopy technology, CP endoscopic resection has gradually replaced traditional surgical procedures as an effective treatment for radical CP, with the advantages of being minimally invasive and having a short recovery time.[6]

Postoperative Complications

Concomitantly, the issue of postoperative complications has received increasing clinical focus.[7] Among them, postoperative bleeding after CP resection is an extremely common adverse event with endoscopic treatment.[7] Bleeding after intestinal polypectomy and the protocol of the surgery have a strong relationship; for example, Kawamura et al found that hot- and cold-loop polypectomy can significantly reduce patients' bleeding.[8]

Immediate bleeding can lead to an unclear surgical field, increase the difficulty of surgery, and prolong the operation time.[9,] Delayed bleeding, on the other hand, is extremely unpredictable and can trigger gastrointestinal hemorrhage and induce hemorrhagic shock, endangering patients' lives if not detected and actively managed in time.[10,11] For this reason, hemostasis of intestinal polyps is a focal point in clinical treatment.

Pigo et al found that heparin can effectively alleviate patients' bleeding, but it's not applicable to patients with a hypercoagulable state of blood.[12] Because of its importance, hemostasis after a CP resection has been an important topic in clinical research.

Hemocoagulase Bothrops Atrox (HBA)

HBA is a newly discovered hemostatic substance that various surgical and clinical departments have used widely for hemostatic treatment.[13] HBA is a snake-venom, a hemagglutinating agent for injection, and contains thrombin-like and coagulation kinase-like enzymes. It can promote platelet aggregation at bleeding sites to form white emboli—platelet thrombi, induce the transformation of thromboplastin into thrombin, activate factor V, and affect factor X, which can have a dual effect on blood coagulation and hemostasis.[11] Masuda et al and Amorim et al have established HBA's safety.[14,15]

Waheed et al found that a topical application of HBA to vascular breaks can accelerate the hemostatic effect and doesn't increase the risk of intravascular thrombosis.[16] Currently, surgeons have used HBA widely for intraoperative hemostasis and treatment of bleeding disorders, demonstrating excellent benefits.[17] However, only a few reliable references exist about its use for the treatment of intestinal polyps. Zhu et al and da Silva et al found that patients with intestinal polyps using HBA for injection experienced a significant hemostatic efficiency after resection, confirming excellent results for HBA in intestinal polypectomy.[18,19]

According to Masuda et al, HBA's hemostatic mechanism mainly lies in the fact that it's a coagulation-factor activator that's secreted from the venom of the spearhead pit viper.[14] According to those researchers, it's a single-chain glycoprotein composed of 17 amino acids, with thrombin-like enzymes as the main components, and its mechanism of action is to rapidly cut the A fibrinopeptide at the N-terminal end of fibrinogen's alpha (α)-chain, thus forming an unstable fibrin that effectively promotes vasoconstriction and ultimately coagulation.

In addition, You et al found that HBA's main component could convert to fibrin monomers after corresponding interaction with fibrinogen, promoting increased platelet aggregation and thus rapid hemostasis.[20] Vu et al found that HBA can promote rapid hemostasis, relieve the inhibited state of bone-marrow aggregates, and promote the restoration of normal physiological function of platelets.[21]

Endoscopic spraying, which uses HBA for injection in solution, is effective for hemostasis because it can: (1) provide direct vision of the lesion; (2) accurately apply the drug to the lesion, (3) improve the effective concentration of local drugs, and (4) reduce the damage caused by various digestive fluids' acid and enzyme reactions. It can also overcome the disadvantages of traditional enema treatment that makes it difficult to retain the drug, and it has great advantages for hemostasis of the lesion location at a high level.[22,23]

Current Study

The current study intended to examine the hemostatic efficacy and safety of a local spray treatment with HBA, derived from HBA for injection, after CP resection, to provide a new hemostatic method, support HBA's use, and provide evidence for clinical decision making.

METHODS

Participants

The research team performed a randomized controlled study, which took place at the Affiliated Hospital of Hebei University in Baoding, Hebei, China. Potential participants were patients with CP who received treatment at the hospital between December 2020 and December 2022.

The study included potential participants if: (1) they were 18-70 years of age, regardless of gender; (2) they had received a diagnosis of CP using colonoscopy; (3) their CP size was 0.5-1.0 cm, 1-5 polyps; (4) they required an colonoscopic resection; (5) their main types of preoperative polyp pathology were adenomatous polyps, hyperplastic polyps, misshapen polyps, or inflammatory polyps; (6) their cardiopulmonary function was consistent with the indications for gastrointestinal endoscopy; and (7) they were able to understand and comply with the requirements of the trial's protocols and plan.

The study excluded potential participants if: (1) they had used other medications that can have an effect on coagulation

in the month prior to surgery; (2) they had psychoneurological; serious heart, lung, kidney, immune, or hematologic diseases; or had other serious illnesses affecting their survival; (3) they had clotting disorders or used anticoagulants or couldn't stop using their antiplatelet drugs; (4) they had preoperative pathology suggesting malignant polyps; (5) they were at risk of thrombosis; (6) they were allergic to the intervention or similar products; (7) they planned to become pregnant, were pregnant, or were breastfeeding; (8) they had been participating in other clinical studies during the three months prior to the procedure; or (9) the investigator otherwise deemed them to be unsuitable for participation in the study.

The participants voluntarily signed an informed-consent form. The hospital's ethics committee approved the study's protocols. In addition, we have registered this study with the Center for Clinical Trials and it will be conducted in strict compliance with the Declaration of Helsinki.

Procedures

Groups. The research team randomly divided participants into two groups with 100 participants each, an intervention group and a control group, using the random number expression method. For hemostasis, the intervention group received a local spray treatment with HBA for injection, and the control group received metal-clip closure or electrocoagulation.

Outcome Measures. The research team measured: (1) the hemostatic efficacy; (2) clinical outcomes—time to hemostasis, hemostasis rate, rebleeding rate, and incidence of late postoperative bleeding; (3) at baseline and at 24h postintervention, the coagulation function—prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), and fibrinogen (FIB); (4) at baseline and at 24h postintervention, PLT parameters—platelet count (PLT), procalcitonin (PCT), and mean platelet volume (MPV); (5) economic effects—total number of participants with hemostasis, hospital days, and total hospital costs; and (6) adverse reactions.

Intervention

Intervention group. The research team: (1) after colonoscopic excision of the polyps, dissolved one unit of HBA for injection (H20041419, Penglai Nuokang Pharmaceutical, Yantai, Shandong, China) in 10 mL of 0.9% saline; (2) sprayed it on the wound surface after fully cleaning the bleeding wound; (3) if the bleeding didn't stop within 3 min, again sprayed the wound with one unit of HBA for injection, and (4) after hemostasis occurred, withdrew the scope after 3 min of observation.

Control group. The research team, after excision of the polyps under colonoscopy in the same way as occurred for the intervention group: (1) stopped the bleeding from the trauma using metal clips or thermoelectric coagulation and (2) after hemostasis occurred, withdrew the scope after 3 min of observation.

Outcome Measures

Hemostatic effect.[24] The research team used three conditions of hemostasis: (1) no postoperative signs of fecal, occult blood at 72h after treatment = markedly effective; (2) postoperative signs of fecal occult blood at 72h after treatment but no rebleeding, such as fresh blood in the stool, at 24h later = effective; and (3) postoperative signs, such as active bleeding, that occurred within 24h of surgery = ineffective. Total effective rate = (markedly effective + effective)/total number of cases × 100%.

Clinical outcomes. The research team measured: (1) hemostasis time; (2) hemostasis rate—the number of successful hemostasis cases/total cases; (3) rebleeding rate—the number of reoccurrences of major bleeding within 24 h of surgery/total cases; and (4) incidence of late postoperative bleeding.

Coagulation function. At baseline and 24h postintervention, the research team measured: (1) prothrombin time (PT), (2) activated partial thromboplastin time (APTT), (3) thrombin time (TT), and (4) fibrinogen (FIB The team performed the tests using a coagulation analyzer (Shenzhen Dimai Biotechnology CA520, Shenzhen, Guangdong, China).

PLT parameters. At baseline and 24h postintervention, the research team measured the platelet count (PLT), procalcitonin (PCT), and mean platelet volume (MPV) for both groups, performing the tests using a fully automated blood cell analyzer (Shenzhen Myriad Technology, BC-5800, Shenzhen, Guangdong, China).

Economic effects. The research team calculated: (1) the total number of participants with hemostasis, (2) the number of hospital days, and the total cost of hospitalization for both groups.

Safety. The research team evaluated the incidence of adverse reactions that occurred during the clinical trial.

Statistical Analysis

The research team analyzed the data using SPSS 23.0 statistical software (International Business Machines Corporation, Armonk, New York, USA). The team: (1) expressed qualitative data as numbers (N) and percentages (%) and compared the groups using the Chi-square (χ^2) test and (2) expressed quantitative data as means and standard deviations (SDs) and compared the groups using the t test with the paired *t* test. $P < .05$ indicated a statistically significant difference.

RESULTS

Participants

The research team included and analyzed the data of 200 participants, No participants dropped out or were concurrently enrolled in other trials. 100 in each group (Table 1). The intervention group's demographic characteristics were: (1) mean age—41.2 ± 5.5 y; (2) gender—62 males (62.0%) and 38 females (38.0%); (3) mean body mass index (BMI)—26.2 ± 2.3; (4) living environment—59 urban (59.0%) and 41 rural (41.0%); and (5) ethnicity—91 Han Chinese (91.0%) and 9 a minority (9.0%).

Table 1. Participants' Demographic Characteristics (N = 200)

Group	n	Age, y Mean ± SD	Gender		BMI, kg/m² Mean ± SD	Living Environment		Ethnicity	
			Male n (%)	Female n (%)		Urban n (%)	Rural n (%)	Han Chinese n (%)	Minority n (%)
Intervention group	100	41.2 ± 5.5	62 (62.0)	38 (38.0)	26.2 ± 2.3	59 (59.0)	41 (41.0)	91 (91.0)	9 (9.0)
Control group	100	41.5 ± 5.1	66 (66.0)	34 (34.0)	26.6 ± 2.1	63 (63.0)	37 (37.0)	89 (89.0)	11 (11.0)
χ^2/t		0.400	0.347		1.284	0.336		0.222	
P value		.690	.556		.201	.562		.637	

Abbreviations: BOI, body mass index.

Table 2. Comparison of Clinical Efficacy Between the Intervention and Control Groups (N = 200)

Group	n	Markedly Effective n (%)	Effective n (%)	Ineffective n (%)	Total Effective Rate n (%)
Intervention group	100	58 (58.0)	39 (39.0)	3 (3.0)	97 (97.0)
Control group	100	43 (43.0)	46 (46.0)	11 (11.0)	89 (89.0)
χ^2					4.916
P value					.027[a]

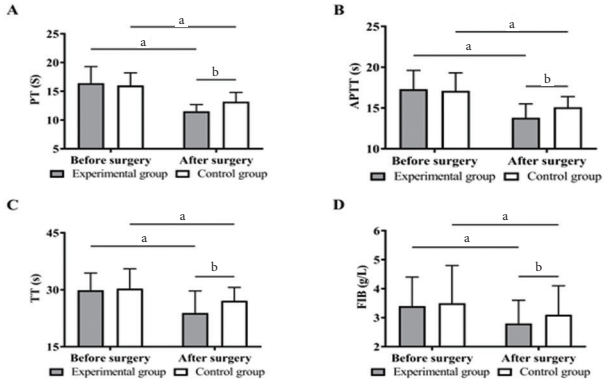
[a]*P* < .05, indicating that the intervention group's total effective rate was significantly higher than that of the control group

Table 3. Comparison of Clinical Outcomes Between the Intervention and Control Groups (N = 200)

Group	n	Hemostasis Time, min Mean ± SD	Hemostasis Rate n (%)	Rebleeding Rates n (%)	Delayed Bleeding Rates n (%)
Intervention group	100	30.2 ± 8.0	99 (99.0)	1 (1.00)	5 (5.00)
Control group	100	35.8 ± 3.7	91 (91.0)	9 (9.00)	13 (13.00)
χ^2/t		6.259	6.737		3.907
P value		<.001[c]	.009[b]		.048[a]

[a]*P* < .05, indicating that the intervention group's delayed bleeding rate was significantly lower than that of the control group
[b]*P* < .01, indicating that the intervention group's hemostasis rate was significantly higher and rebleeding rate was significantly lower than that of the control group
[c]*P* < .001, indicating that the intervention group's hemostasis time was significantly shorter than that of the control group

Figure 1. Comparison of Coagulation Function Between Baseline and Postintervention for the Intervention and Control Groups and Between the Groups. Figures 1A, 1B, 1C, and 1D show the PT, TT, APTT, and FIB, respectively.



*P < .05, indicating that the intervention group's PT, APTT, TT, and FIB were significantly lower than those of the control group postintervention
#P < .05, indicating that both the intervention group's and the control group's PT, APTT, TT, and FIB significantly decreased between baseline and postintervention

Abbreviations: APTT, activated partial thromboplastin time; FIB, fibrinogen; PT, prothrombin time; TT, thrombin time.

The control group's demographic characteristics were: (1) mean age—41.5 ± 5.1 y; (2) gender—66 males (66.0%) and 34 females (34.0%); (3) mean body mass index (BMI)—26.6 ± 2.1; (4) living environment—63 urban 63.0%) and 37 rural (37.0%); and (5) ethnicity—89 Han Chinese (89.0%) and 11 a minority (11.0%).

No significant differences existed between the groups in age, gender, BMI, living environment, or ethnicity (*P* > .05), so the groups were comparable.

Hemostatic Efficacy

In the intervention group, the treatment was markedly effective for 58 participants (58.0%), effective for 39 participants (39.0%), and ineffective for three participants (3.0%), with a total effective rate of 97.0% with 97 participants (Table 2). In the control group, the treatment was markedly effective for 43 participants (43.0%), effective for 46 participants (46.0%), and ineffective for 11 participants (11.0%), with a total effective rate of 89.0% with 89 participants. The intervention group's total effective rate for hemostasis was significantly higher than that of the control group (*P* = .027).

Clinical Outcomes

Table 3 shows that the intervention group's mean hemostasis time was 30.2 ± 8.0 min, which was significantly shorter than that of the control group at 35.8 ± 3.7 (*P* < .001). In the intervention group, 99 participants reached hemostasis (99.0%), one had rebleeding (1.0%), and five had delayed bleeding (5.0%). In the control group, 91 participants reached hemostasis (91.0%), nine had rebleeding (9.0%), and 13 had delayed bleeding (5.0%). The intervention group hemostasis, rebleeding, and delayed bleeding rates were all significantly lower than those of the control group, at *P* = .009, *P* = .009, and *P* = .048, respectively.

Coagulation Function

Figure 1 shows that no significant differences existed between the groups at baseline in the PT, TT, APTT, and FIB (*P* > .05). Postintervention, the PT, TT, APTT, and FIB decreased in both groups (all *P* < .05), but the intervention group's levels were significantly lower in those of the control group (all *P* < .05).

PLT Parameters

Figure 2 shows that no significant differences existed between the groups at baseline in the PLT parameters (*P* > .05). Postintervention, both groups' PLT and PCT were significantly higher than at baseline (all *P* < .05), but the intervention group's levels were significantly higher in those of the control group (both *P* < .05). Postintervention, both groups' MPV were significantly lower than at baseline (both *P* < .05), but the intervention group's MPV was significantly lower than that of the control group (*P* < .05).

Economic Effects

Figure 3 shows that the intervention group's total number of participants with hemostasis, number of hospital days, and total costs were 3.9 ± 2.1 times, 7.1 ± 1.9 d, and 2923.4 ± 314.0 yuan, respectively, and were significantly lower than those of the control group, at 5.8 ± 1.9 times, 8.3 ± 1.2 d, and 3643.5 ± 282.6 yuan, respectively ($P < .05$). These findings indicate a high economic effect (data not shown).

Adverse Reactions

Table 4 shows that four participants in the intervention group had nausea and vomiting (4.0%), three had a loss of appetite (3.0%), and four had fatigue and drowsiness (4.0%), with total incidence of adverse reactions for 11 participants (11.0%). In the control group, two participants had nausea and vomiting (2.0%), three had a loss of appetite (3.0%), and three had fatigue and drowsiness (3.0%), with total incidence of adverse reactions for eight participants (8.0%). No significant differences existed between the groups postintervention in the incidence of adverse reactions ($P > .05$).

DISCUSSION

The present study found that using HBA for injection in an endoscopic spray for patients with intestinal polyps had more significant hemostatic efficacy after resection than metal-clip closure or electrocoagulation did, confirming HBA's excellence for intestinal polypectomy. This result was consistent with the results of several previous studies on the hemostatic application of HBA.[18,19]

The conversion to fibrin monomers after corresponding interaction with fibrinogen, which promoted increased platelet aggregation and thus rapid hemostasis, as Vu et al found,[21] was likely the key reason why the intervention group's TT, PT, APTT, and FIB in the current study were significantly lower than those of the control group. Also, the current study found that the intervention group's PLT and PCT were significantly higher and MPV was significantly lower than those of the control group, which again confirms that HBA can regulate platelet parameters effectively and has an ideal hemostatic effect on patients with intestinal polyps after resection.

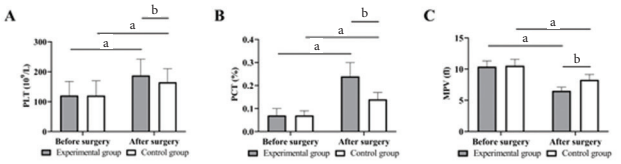
The current research team hypothesizes that the direct vision of the lesion, accurate application of the drug to the lesion, improvement in the effective concentration of local drugs, and reduction in the damage caused by various digestive fluid's acid and enzyme reactions are the main reasons for the reduced time to hemostasis and lower rebleeding rate and increased hemostasis rate in the intervention group compared to the control group.

The current study found that the intervention group had better coagulation signs after surgery and the incidence of adverse reactions was low, which also indicates that HBA has a high safety level and is of high clinical application value.

Finally, the differences in the economic effects between the two groups were significant, which further indicates that the universal use of HBA for injection in intestinal polypectomy could have high economic effects and reductions in the economic burden for patients. This is mainly due to the excellent treatment effect, high tolerability, and more convenient operation of HBA.

The current study had some limitations. The current research team compared only the hemostatic effect of HBA and of metal clip clamping or electrocoagulation for hemostasis, and it's not clear whether HBA also has such a significant advantage when compared with other hemostatic options. In addition, room may exist for optimization and improvement in the dosage and duration of HBA use. Also, the current research team should also initiate a longer follow-up of patients in the current study to further evaluate the prognostic impact of HBA. Meanwhile, researchers could also understand more deeply the hemostatic mechanism and action pathway of HBA through basic experiments and provide a more comprehensive and reliable reference for subsequent studies.

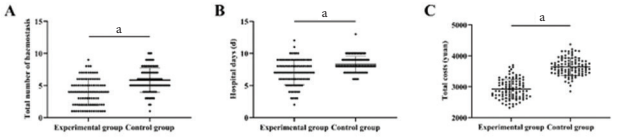
Figure 2. Comparison of PLT Parameters Between Baseline and Postintervention for the Intervention and Control Groups and Between the Groups Postintervention. Figures 2A, 2B, and 2C show the PLT, PCT, and MPV, respectively.



[a]$P < .05$, indicating that the intervention group's PLT and PCT were significantly higher and MPV was significantly lower than those of the control group postintervention
[b]$P < .05$, indicating that both the intervention group's and the control group's PLT and PCT significantly increased and MPV significantly decreased between baseline and postintervention

Abbreviations: MPV, mean platelet volume; PCT, procalcitonin; PLT, platelet count.

Figure 3. Comparison of Economic Effects Between the Intervention and Control Groups Postintervention. Figures 3A, 3B, and 3C show the total number of participants with hemostasis, hospital days, and total costs, respectively.



[a]$P < .05$, indicating that the intervention group's total number of participants with hemostasis, hospital days, and total costs were significantly lower than those of the control group postintervention

Table 4. Comparison of Adverse Reactions Between the Intervention and Control Groups (N = 200)

Group	n	Nausea and Vomiting n (%)	Loss of Appetite n (%)	Fatigue and Drowsiness n (%)	Total Incidence n (%)
Intervention group	100	4 (4.0)	3 (3.0)	4 (4.0)	11 (11.0%)
Control group	100	2 (2.0)	3 (3.0)	3 (3.0)	8 (8.0%)
χ^2					(0.523)
P value					(.469)

CONCLUSIONS

HBA has an excellent hemostatic effect on intestinal polypectomy with convenient operation and high safety. In the future, popularizing the use of HBA in the treatment of intestinal polypectomy can not only effectively guarantee the postoperative safety of patients but also could reduce their economic burden and improve the quality of clinical medical services.

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