

Effect of Bixie combined with perioperative multimodal analgesia management on postoperative pain and wound healing of mixed hemorrhoids

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Abstract: We were to explore the effect of Bixie combined with perioperative multimodal analgesia management on postoperative pain and wound healing of mixed hemorrhoids. A total of 240 patients with mixed hemorrhoids in this hospital from June 2022 to September 2023 were chosen, with 120 in the control group receiving perioperative multimodal analgesia management and 120 in the observation group receiving Bixie combined with perioperative multimodal analgesia management. The results showed that compared with the control group, the observation group had lower visual analogue scale (VAS) scores at 1, 3, 5 and 7 days after the surgery; the 5-hydroxytryptamine (5-HT), prostaglandin E2 (PGE2), nitric oxide (NO), interleukin-2 (IL-2), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) of the observation group at 24 hours and 72 hours after the surgery were lower; the vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and wound healing rate of the observation group at 7 days after the surgery were higher; the total effective rate of the observation group was higher. Therefore, combining Bixie with perioperative multimodal analgesia management could improve postoperative pain, decrease inflammatory factor levels, promote angiogenesis, and accelerate wound healing in patients with mixed hemorrhoids.

Keywords: Mixed hemorrhoids, Bixie, multimodal analgesia, Chinese and Western medicine therapy, postoperative pain, wound healing.

INTRODUCTION

Mixed hemorrhoids are the coexistence of internal hemorrhoids and external hemorrhoids. The varicose veins of the upper and lower hemorrhoids are formed and fused with each other. The main manifestations are anal mass prolapse, accompanied by anal pain, hematochezia, anal swelling, itching, etc., which can be completely cured by surgical resection (Peiq *et al.*, 2021). However, due to the complexity of perianal tissue structure and the particularity of function, wound pain is one of the main problems faced by postoperative patients, which induces a serious stress response and is not conducive to wound healing (Lohsiriwat and Jitmongkarn, 2022). At present, opioid analgesics such as morphine, tramadol, dezocine, codeine, etc., are commonly used for postoperative analgesia of mixed hemorrhoids. They mainly achieve strong effects by damaging sympathetic nerve fibres and nerve endings, but there are also many adverse reactions. With the wide application of enhanced recovery after the surgery in surgical management, more emphasis has been placed on the systematic and comprehensive management of perioperative pain. The multimodal analgesia advocated by ERAS is related to the postoperative pain management guidelines of the American Pain Association, that is, the combined use of analgesic drugs and

techniques with various mechanisms to more effectively rein pain, abate the occurrence of drug resistance and adverse reactions (Cavallaro and Bordeianou, 2019). Traditional Chinese medicine considers that the major etiology and pathogenesis of mixed hemorrhoids are caused by damp heat, wind toxin, or qi and blood stasis. After the surgery, the meridians are blocked, qi and blood are deficient and the meridians are not nourished enough, resulting in postoperative pain. It should be treated with clearing heat and dampness, purging fire detoxification, cooling and activating blood. Bixie (fig. 1) is a traditional folk Chinese herbal medicine in southern China. It is spicy, slightly bitter, mild and mild in nature. It has the functions of draining dampness and turbidity, dispelling wind and removing arthralgia and is mainly used for treating damp-heat sore toxins (He *et al.*, 2020). Modern pharmacological studies have also shown that steroidal saponins (fig. 2) are the main chemical components of Bixie, which can exert anti-inflammatory and analgesic pharmacological activities (Han *et al.*, 2021). Traditional Chinese medicine is safer in the application of postoperative analgesia of mixed hemorrhoids, with fewer adverse reactions, but it works slowly and is less effective when used alone. In view of this, this study applied Bixie combined with multimodal analgesia to the postoperative management of mixed hemorrhoids and aims to serve as a reference for clinical decision-making.

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MATERIALS AND METHODS

Study design

Our study explored the effect of Bixie combined with perioperative multimodal analgesia management in improving postoperative pain and promoting wound healing of mixed hemorrhoids. First of all, we chosen 240 patients with mixed hemorrhoids in this hospital from June 2022 to September 2023 as the research participants, and they were separated into the control group (n=120) and observation group (n=120) by random number table. The Control group accepted perioperative multimodal analgesia management, while the observation group accepted Bixie combined with perioperative multimodal analgesia management. Finally, the preoperative and postoperative pain, Pain medium, inflammatory factors, angiogenesis, wound healing, and curative effect of the two groups were evaluated.

Study object

Inclusion standards: (1) according to the diagnosis for mixed hemorrhoids in the Guidelines for Clinical Diagnosis and Treatment of Hemorrhoids (2006); (2) with surgical indications, the use of external incision and internal sleeve + Xiaozhiling injection; (3) aged between 18-65 years old; (4) Voluntary participation in this study, and sign the informed consent. *Exclusion standards:* (1) suffering from heart, liver, kidney and other vitals malfunction; (2) Combined with colorectal cancer, intestinal tuberculosis, perianal abscess and other colorectal diseases or anal diseases; (3) Having a history of anal trauma; (4) Combined with Crohn's disease, inflammatory bowel disease, diabetes and other consumptive diseases; (5) frequent use of sedative and analgesic drugs in the past month; (6) pregnant or lactating women; (7) Voluntary quitters.

Intervention methods

The control group received multimodal analgesia under the theory of ERAS, as follows. (1) Preoperative management: A pain management team was established, which was composed of surgeons, anesthesiologists, nurses and clinical pharmacists. According to the standardized process of fast-track surgery, unified training was conducted to jointly develop a pain management plan, and the members collaborated with each other to manage postoperative pain. Before the operation, the patients and their families were introduced in detail to the relevant contents of the theory of rapid rehabilitation surgery, so that they could correctly understand the pain and be familiar with and master the VSA scoring criteria.

(2) Operation management: Hydromorphone 1mg was given intramuscularly 30 min before operation. Both groups were operated by the same doctor. Combined spinal-epidural anaesthesia, take the lithotomy position, routine disinfection and towel laying, after the anaesthesia

takes effect, repeatedly expand the anus to 2-3 transverse fingers, after the anal relaxation is good, according to the size and location of the mixed hemorrhoids, the incision is designed. The minimally invasive method of external resection and internal ligation was adopted. The automatic elastic line ligation stapler was used to absorb the internal hemorrhoids and the prolapsed rectal mucosal tissue above them under the direct vision of the anoscope. The elastic line ligation stapler was fired and the elastic line was tightened. The ligation stapler was taken to see that the hemorrhoids ligation was stable without tearing and bleeding, and then the remaining hemorrhoids were treated in the same way. Electric knife resection of external hemorrhoids, high-frequency electric knife electrocoagulation to stop bleeding, Xiaozhiling injection line ligation hemorrhoids injection. Subcutaneous injection of 1% methylene blue injection 1ml + 0.75% ropivacaine hydrochloride injection 6ml, complete hemostasis after filling vaseline gauze drainage, external sterile gauze pressure bandage.

(3) Postoperative management: Immediately after returning to the ward, the local pressure of the controllable T-type pressurizer was applied for 1-2 hours, and the pressure was maintained at a balanced pressure, so as not to feel pain and fall. The direction of pressure was parallel to the longitudinal axis of the anal canal and perpendicular to the wound. Morphine 4mg + ropivacaine 100-150mg + 0.9% sodium chloride solution to 100ml, epidural continuous pumping. 1mg of hydromorphone was given intramuscularly when sudden pain could not be tolerated. Parecoxib sodium 20mg was intravenously injected 15 min before wound dressing change on the first 3 days after the surgery and then a routine dressing change was performed.

The observation group was treated with single prescription Bixie based on perioperative multimodal analgesia management from the second day after the operation. Bixie Chinese herbal medicine was purchased from Anguo Herbal Medicine Market in Hebei Province. It was identified as the dry rhizome of *Dioscorea septemloba* by Chinese pharmacists in our hospital. The 10g of Bixie was accurately weighed and placed in a 250ml round-bottomed flask and refluxed with 10 times the volume of 95% ethanol 3 times, 1 hour each time. The ethanol extract was combined, evaporated to dryness in a water bath, added with an appropriate amount of water, mixed well, extracted twice with an equal amount of petroleum ether, discarded the petroleum ether extract, and extracted twice with an equal amount of water-saturated n-butanol. The n-butanol extract was combined and evaporated to dryness in a water bath to obtain the extract, which was placed in a vacuum drying oven at 60°C after one week, it was taken out and crushed to obtain the dry powder. The method of taking is fasting in the morning, once a day.

Observed indicators

Pain degree: a visual analogue scale (VAS) was applied to assess the degree of resting pain before the surgery and 1d, 3d, 5d and 7d after the surgery, the scores of asymptomatic, mild, moderate and moderate were 0 points, 1-3 points, 4-7 points and 7-10 points, respectively. A higher point indicates more serious pain (Ertlav *et al.*, 2022).

Pain medium: 5ml fasting venous blood was collected from the two groups before the surgery and 24h, 72h after the surgery. After routine separation of serum, the supernatant was taken for testing. The levels of 5-hydroxytryptamine (5-HT), prostaglandin E₂ (PGE₂) and nitric oxide (NO) were detected by enzyme-linked immunosorbent assay (ELISA).

Inflammatory factors: Before the surgery and 24h, 72h after the surgery, the supernatant was taken to be measured after routine separation of serum, the levels of interleukin-2 (IL-2), interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) in serum were examined by ELISA.

Angiogenesis: Before and 7 days after the surgery, the levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) in serum were examined by ELISA.

Wound healing: at 24 hours after and 7 days after the surgery, the wound area was measured and the wound healing rate was computation [(wound area at 24 hours postoperative - wound area at 7 days postoperative)/wound area at 24 hours postoperative \times 100%].

Evaluation criteria of curative effect

The clinical efficacy was evaluated according to the pain relief and wound recovery on the 7th day after the surgery. Significantly effective: Anal pain was significantly reduced, defecation without obstacles, no bleeding and exudation in the wound and the wound healing time was significantly shortened. Effective: anal pain relief, defecation pain relief, no bleeding, exudation, wound healing time shortened. Ineffective: anal pain is not reduced, defecation pain, defecation disorders (excluding constipation factors). The total effective rate = [(effective cases + effective cases) / total cases] \times 100 %.

STATISTICAL ANALYSIS

The data analysis was used with SPSS 26.0. Measurement data according to normal distribution were described as mean \pm standard variance ($\bar{x} \pm s$) and an independent sample t-test was adopted for inter-group comparison. Enumeration data were described by the cases and percentages [n (%)] and compared by chi-square test. The

rank sum test was employed to analyze grading data. $P < 0.05$ indicates difference had a statistical significance.

Ethical approval

This study was approved by the Medical Ethics Committee of Xuchang Central Hospital vide Reference No. 2022-04-001

RESULTS**Common data**

There had no statistically significant in age, sex, BMI, disease course and disease stage between the groups ($P > 0.05$) (table 1).

The degree of pain

Before the surgery, there had no statistical significance in VAS score between the groups ($P > 0.05$). At 1d, 3d, 5d, and 7d after the surgery, the VAS score in the observation group was lower compared with the control group, ($P < 0.05$) (table 2).

Pain medium

Before the surgery, there was no significant difference in the levels of 5-HT, PGE₂ and NO between the groups ($P > 0.05$). At 24 h and 72 h after the surgery, the levels of 5-HT, PGE₂ and NO in the observation group were lower than those in the control group ($P < 0.05$) (fig. 3).

Inflammatory factors

Before the surgery, there had no statistically significant in the levels of IL-2, IL-6 and TNF- α between the groups ($P > 0.05$). At 24 hours after and 72 hours after the surgery, the levels of IL-2, IL-6 and TNF- α in the observation group were less compared with the control group ($P < 0.05$) (fig. 4).

Angiogenesis

Before the surgery, there had no statistical significance in the levels of VEGF, bFGF and PDGF between the groups ($P > 0.05$). At 7 days after the surgery, the levels of VEGF, bFGF, and PDGF in the observation group were higher than compared with the control group ($P < 0.05$) (table 3).

Wound healing

At 24 hours after the surgery, there had no statistical significance in wound area between the groups ($P > 0.05$). At the 7 days after the surgery, the wound area of the observation group was smaller and the wound healing rate of the observation group was higher compared with the control group ($P < 0.05$). See fig. 5.

Determination of curative effect

The total effective rate of the observation group (95.00%) higher than that of the control group (86.67%) and the curative effect was better than that of the control group ($P < 0.05$). See table 4.

Table 1: Common data of the both groups

Data	Control group (n=120)	Observation group (n=120)	$t/\chi^2/Z$	<i>P</i>
Age (years, $\bar{x} \pm s$)	41.75±7.85	39.73±9.52	1.798	0.073
Sex [n(%)]			2.967	0.085
male	40(33.33)	53(44.17)		
femsle	80(66.67)	67(55.83)		
BMI (kg/m ² , $\bar{x} \pm s$)	22.37±2.37	22.63±1.73	0.960	0.338
Course of disease (years, $\bar{x} \pm s$)	2.55±0.73	2.73±0.86	1.740	0.083
Stage of disease [n(%)]			0.583	0.560
II	8(6.67)	15(12.50)		
III	72(60.00)	55(45.83)		
IV	40(33.33)	50(41.67)		

BMI: body mass index

Table 2: Pain degree of the both groups (score, $\bar{x} \pm s$)

Group	T ₀	T ₁	T ₂	T ₃	T ₄
Control group (n=120)	2.57±0.63	5.28±1.04	4.53±0.84	3.58±0.72	2.25±0.81
Observation group (n=120)	2.51±0.78	4.85±0.74	4.11±0.76	2.43±0.65	1.86±0.53
<i>t</i>	0.638	3.654	4.062	12.990	4.414
<i>P</i>	0.524	<0.001	<0.001	<0.001	<0.001

VAS: visual analogue scale; T₀: before the surgery; T₁: 1 day after the surgery; T₂: 3 days after the surgery; T₃: 5 days after the surgery; T₄: 7 days after the surgery



Fig. 1: Chinese herbal medicine Bixie

Table 3: Angiogenesis of the both groups (pg/mL, $\bar{x} \pm s$)

Group	VEGF		bFGF		PDGF	
	T ₀	T ₁	T ₀	T ₁	T ₀	T ₁
Control group (n=120)	81.57±8.66	106.14±13.54	60.26±8.75	89.26±10.51	35.56±6.78	60.37±7.51
Observation group (n=120)	83.88±9.61	134.39±15.26	61.88±6.60	102.76±14.38	36.21±5.97	81.03±6.39
<i>t</i>	1.959	15.172	1.616	8.304	0.779	22.959
<i>P</i>	0.051	<0.001	0.108	<0.001	0.437	<0.001

VEGF: vascular endothelial growth factor. bFGF: basic fibroblast growth factor. PDGF: platelet-derived growth factor. T₀: before the surgery. T₁: 7 days after the surgery

Table 4: Curative effect of the both groups [n(%)]

Group	Significantly effective	Effective	Ineffective	Total
Control group (n=120)	20(16.67)	83 (69.17)	17 (14.16)	104 (86.67)
Observation group (n=120)	35 (29.17)	79 (65.83)	6 (5.00)	114 (95.00)
Z/ χ^2		2.401		5.716
<i>P</i>		0.016		0.017

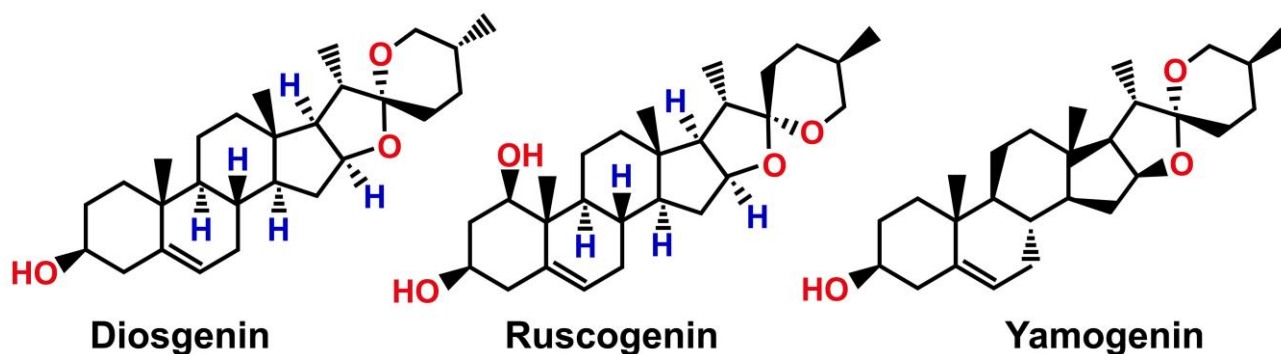


Fig. 2: Steroidal saponins in Bixie

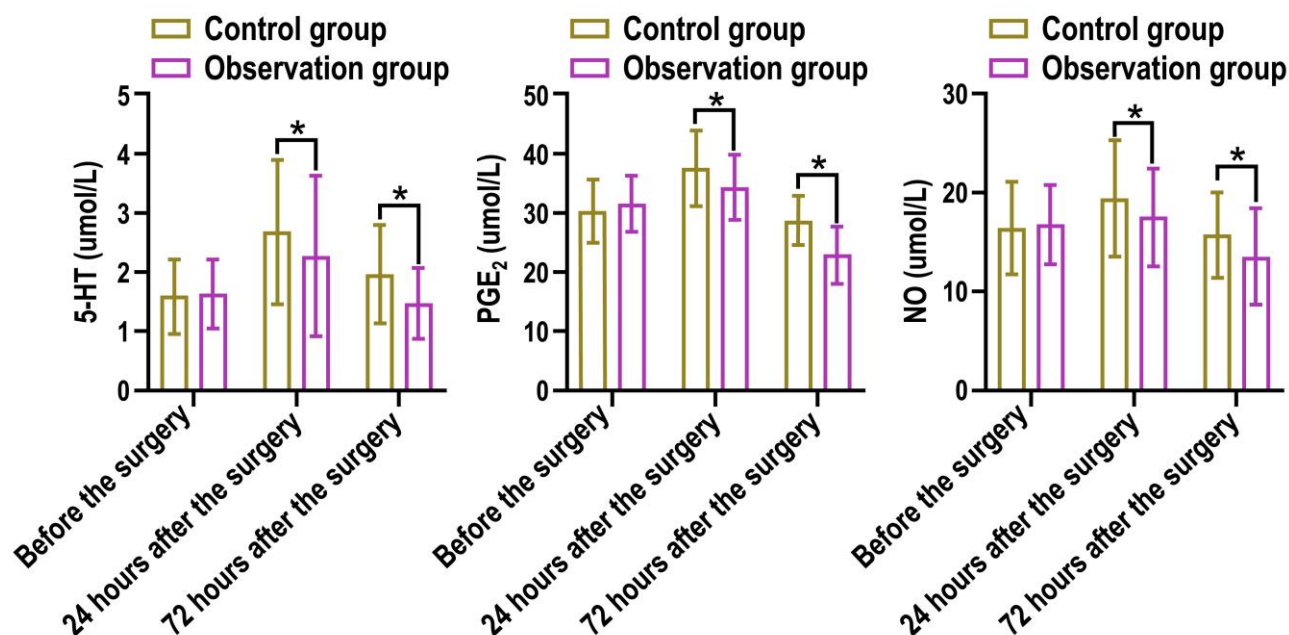


Fig. 3: Pain medium of the both groups. 5-HT: 5-hydroxytryptamine; PGE₂: prostaglandin E₂; NO: nitric oxide

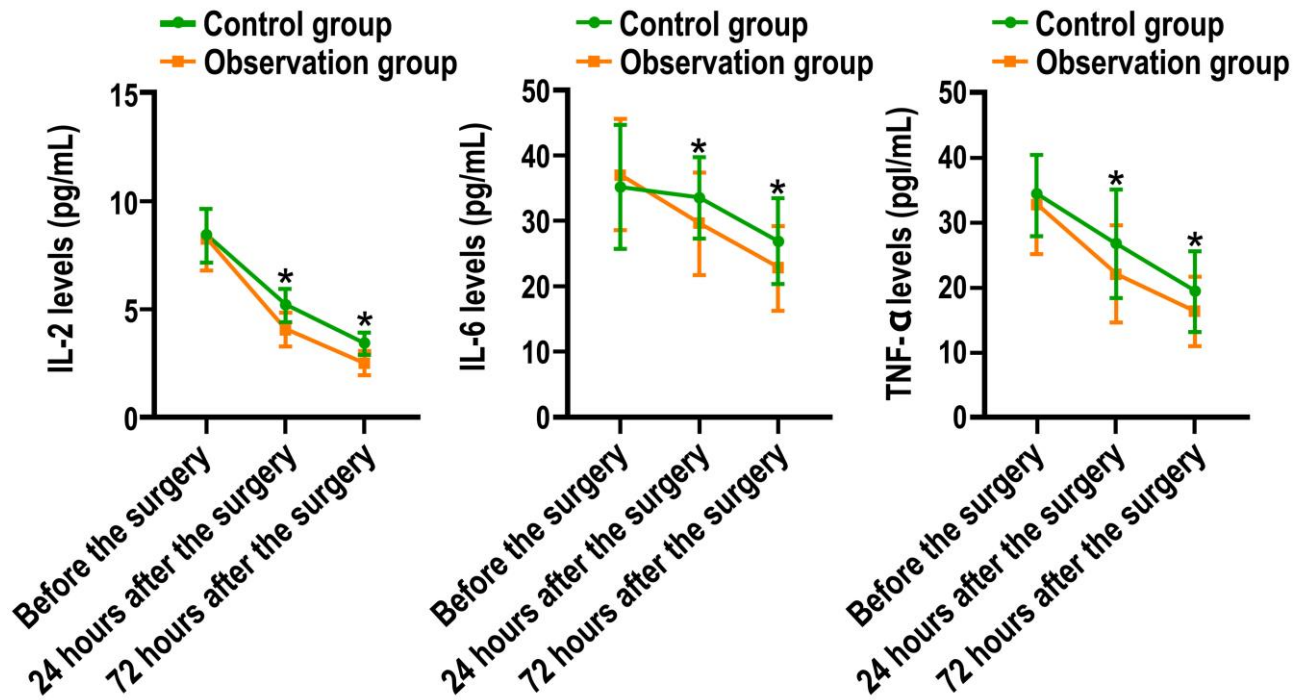


Fig. 4: Inflammatory factors of the both groups. IL-2: interleukin-2. IL-6: interleukin-6. TNF-α: tumor necrosis factor-α

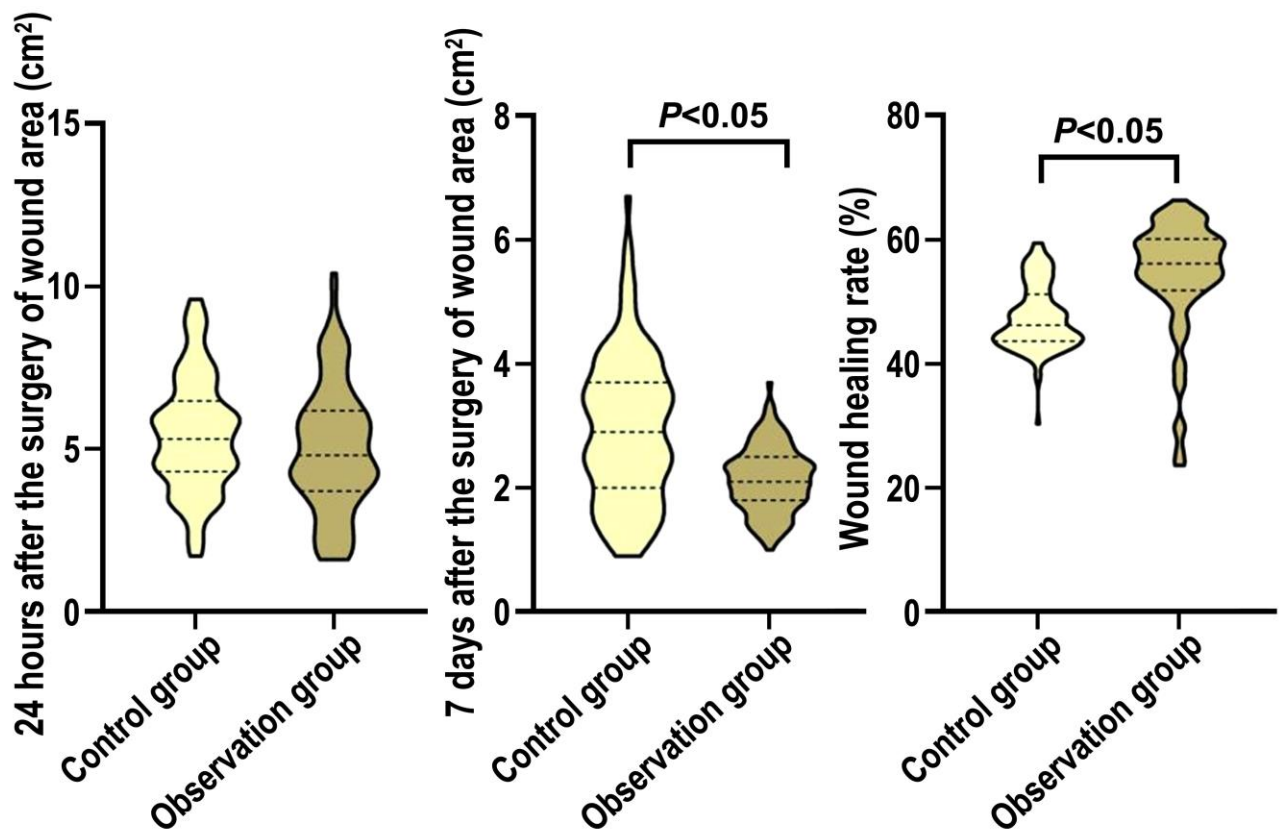


Fig. 5: Wound healing of the both groups.

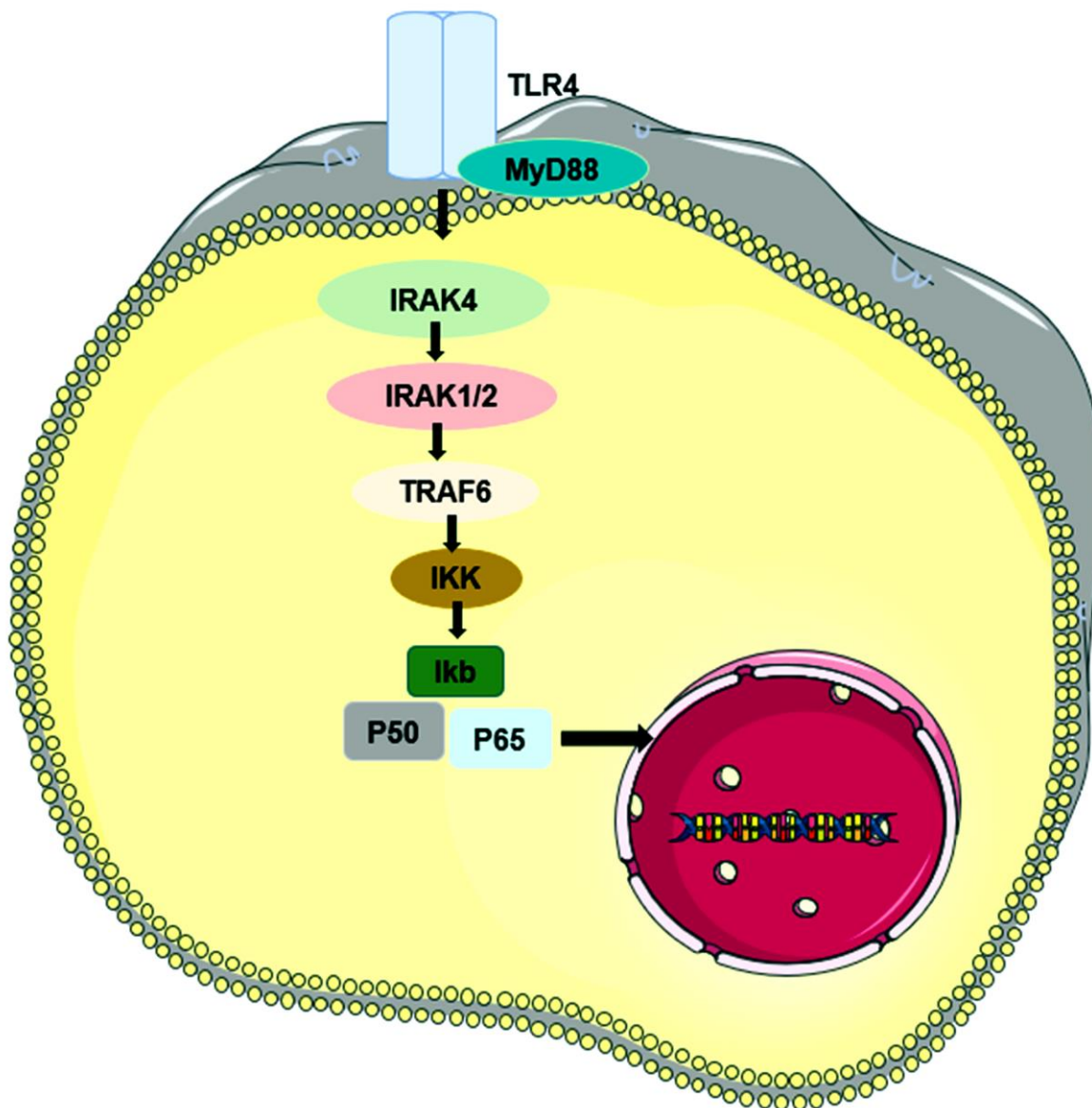


Fig. 6: Specific mechanism diagram

DISCUSSION

At present, there is no consensus on the pathogenesis of hemorrhoids. the surgery is the radical treatment of hemorrhoids, but almost every patient will experience moderate to severe pain after the surgery and about 12% of patients will experience severe pain throughout the recovery period (Kazachenko *et al.*, 2022). The anorectal is divided into two different innervations by the dentate line. The spinal nerve below the dentate line is more sensitive to pain and most of the wounds formed after the surgery are located on the anal skin below the dentate line and the incision pain is obvious. Pain can also stimulate internal sphincter spasm, resulting in poor local blood and lymphatic circulation and increased release of inflammatory substances, causing anal margin and local

tissue oedema, which in turn stimulates local nerves, aggravates pain and delays wound healing (Du *et al.*, 2022).

Traditional Chinese medicine doctors believe that hemorrhoids occur in the anus and intestines, but are closely related to the viscera. Most of them are thanks to the deficiency of the viscera, the wind-damp heat dryness forcing the large intestine and the tendons and veins being scattered and weak to form hemorrhoids (Sha *et al.*, 2022). Hemorrhoids for a long time, the evil poison for a long time in the anus, qi movement is not smooth, combined with surgical injury skin flesh blood vessels, qi stagnation and blood stasis, meridian block, impassable pain, can lead to postoperative pain; blood stasis does not go, new blood does not grow, the wound is lost in glory, resulting in slow wound healing (Wang *et al.*, 2020^a).

At present, there is no specific scheme for postoperative pain of hemorrhoids in the clinic. There are many choices and progress in Chinese and Western medicine. However, each method has its advantages and disadvantages. Combining the advantages of the two can bring a better treatment experience to patients. Enhanced recovery after the surgery is a concept of multidisciplinary and multimode therapy based on evidence-based evidence. It takes patients as the main body, pays attention to humanistic care, and multidisciplinary comprehensive surgery to reduce postoperative physiological and psychological discomfort and accelerate recovery (Grilo *et al.*, 2024). In this study, perioperative multimode analgesia management was performed under the theory of ERAS. The observation group was given an intramuscular injection of hydromorphone 30min before the surgery, a subcutaneous injection of methylene blue injection + ropivacaine hydrochloride injection during the surgery and an intravenous injection of parecoxib sodium 15 min before dressing change to stop peripheral or central sensitization, which had preemptive analgesic effect (Ma *et al.*, 2023). The minimally invasive method of external resection and internal sleeve surgery is used to reduce the pain caused by the surgery itself and avoid oedema caused by excessive postoperative tissue damage. Immediately after the surgery, the T-type compression technique was used to improve postoperative pain and perianal edema by giving external force to the wound, preventing or reducing gravity, vasodilation, anal sphincter spasm, anal venous congestion, etc. Through the above series of management methods, combined with a variety of analgesic drugs, methods, reduce the body's sensitivity to pain, optimize the postoperative stress state and regulate the purpose of the micro-inflammatory state.

The monarch drug is Bixie, which was first recorded in Shennong Baicao Jing. It has an old history of medicine and has the effects of draining dampness and turbidity, dispelling wind and removing arthralgia. There are many chemical components in Bixie, main extract is the total saponins of Dioscorea, total saponins of Dioscorea and its active ingredient dioscin are the main material basis for Dioscorea to exert analgesic and anti-inflammatory effects (Wang *et al.*, 2020^b; Chan *et al.*, 2023; Adoménienė and Venskutonis, 2022). Local inflammatory response is an important cause of postoperative pain in anorectal diseases. IL-2, IL-6 and TNF- α are important cytokines mediating inflammatory response, which can stimulate the abnormal proliferation and differentiation of immune cells, leading to local immune inflammatory response. 5-HT, PGE₂ and NO are all pain mediators, which can directly or indirectly excite the nociceptors, resulting in pain. The higher the expression level of the above substances, the more serious the body pain. In this study, the levels of 5-HT, PGE₂, NO, IL-2, IL-6 and TNF- α in the observation group were lower than those in the control group at 24h and 72h after operation, indicating

that Bixie can inhibit the release of 5-HT, PGE₂, NO, IL-2, IL-6 and TNF- α to play an analgesic role and the decrease of inflammatory factor level has a significant reduction effect on postoperative oedema. It has been reported that dioscin can inhibit the activation of the TLR4 / NF- κ B signalling pathway to reduce the production of inflammatory factors (Li *et al.*, 2021). Postoperative pain of mixed hemorrhoids is often chronic inflammatory pain, manifested as persistent noxious hypersensitivity. TLR4 is a material mode recognition receptor in congenital immunity, which can promote the expressed of proinflammatory cytokines by activating the expression of related transcription factors. NF- κ B plays a key function downstream of the TLR4 signaling pathway (Zhao *et al.*, 2019). TLR4 will cause the NF- κ B protein complex to release NF- κ B after stimulation, and the free NF- κ B enters the nucleus, binds to the correlation reaction elements, activates the expression of inflammation-related factors and aggravates inflammation. On the contrary, the decrease in NF- κ B activity can alleviate the inflammatory response (Liu *et al.*, 2024; Xiao *et al.*, 2024). It can be inferred that the total saponins of Bixie relieved the pain response induced by inflammatory mediators by inhibiting TLR4/NF- κ B signaling pathway (See fig. 6 for the specific mechanism).

There was some boundedness to our study: It was a one-centre study with a small number of samples, also was a lack of long-term observation, resulting in a certain bias in the results. Next, the selection range of research participants should be magnified and multi-center and large-sample surveys should be conducted to further verify the research results. Currently, there is still a shortage of sufficient studies on the chemical constituents and pharmacological effects of Bixie and its potential is to be further searched.

CONCLUSION

In summary, Bixie can clear heat and dampness, purging fire detoxification, cooling and activating blood. The total saponins in Bixie may reduce anti-inflammatory and analgesic effects by arresting the TLR4/NF- κ B signaling pathway. Perioperative multimode analgesia management combined with various pain-causing factors, using a variety of methods to minimize the pain of patients. Bixie combined with multimode analgesia management could improve postoperative pain, decrease inflammatory factor levels, promote angiogenesis and accelerate wound healing in patients with mixed hemorrhoids.

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