

Original Article

Effects of Huhuang Burn Liniment on wound healing and changes in IL-10 and MMP-9 levels in patients with mixed hemorrhoids

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Abstract: Objective: To explore the effects of Huhuang Burn Liniment on wound healing and levels of interleukin-10 (IL-10) and matrix metalloproteinase-9 (MMP-9) in patients with mixed hemorrhoids. Methods: The clinical data of 113 patients with mixed hemorrhoids admitted to Chongqing Sanxia Central Hospital were retrospectively collected. All patients underwent Milligan-Morgan hemorrhoidectomy, and were divided into two groups according to different postoperative treatments. Group A was treated with 1/5000 potassium permanganate sitz bath after surgery, while group B was treated with Huhuang Burn Liniment. The treatment efficacy, wound healing time, level of pain, exudation, edema, granulation scores, anal function index, levels of IL-10 and MMP-9, quality of life scores, and complications were compared between the two groups. Results: The effective rate of group B (94.74%) was higher than that of group A (60.71%) ($P < 0.05$). Group B had shorter length of anorectal hyperbaric zone, higher anal canal resting pressure, anal canal diastolic pressure, and anal canal systolic maximum pressure ($P < 0.05$), lower scores of trauma pain, edema, exudation, and granulation ($P < 0.05$), higher IL-10 levels, and lower MMP-9 levels ($P < 0.05$). The complication rate of group B (8.77%) was lower than that in group A (23.21%) ($P < 0.05$). After treatment, group B had shorter wound healing time and higher quality of life score than group A ($P < 0.05$). Conclusion: The application of Huhuang Burn Liniment in patients with mixed hemorrhoids after surgery could promote wound healing and anal function, reduce trauma pain, exudation and edema, and improve quality of life.

Keywords: Mixed hemorrhoids, Huhuang Burn Liniment, wound healing, treatment efficacy, IL-10, MMP-9

Introduction

Clinically, hemorrhoids are anal diseases with high incidence and recurrence rate, which can occur at any age, and the incidence increases with age [1]. Mixed hemorrhoids are a common type of hemorrhoids that are characterized by anal swelling, bloody stools, which can present as anal pain, foreign body sensation, swelling, and local itching or rectal secretions [2, 3].

The common treatment options for mixed hemorrhoids are conservative therapies and surgery. Conservative therapies include moxibustion, rubbing medicine, drug injection, sitz bath, fumigation with herbal products, etc. Although

the conservative therapies can effectively control the symptoms of early mixed hemorrhoids, long-term studies have shown that these therapies have an extremely high recurrence rate and are ineffective for stage-III and IV mixed hemorrhoids [4, 5]. Surgery is still the main choice for mixed hemorrhoids, with the most common being Milligan-Morgan hemorrhoidectomy (MMH). Trauma, due to the special anatomical structure, is usually subject to repeated irritation by various contaminants, significantly increasing the rate of infection [6, 7]. It has also been shown that the postoperative trauma of mixed hemorrhoids surgery is prone to necrosis and edema, which provides conditions for the culture of a large number of bacterial microor-

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ganisms. As a result of anal sphincter pain, trauma is poorly drained and impaired in circulation, which hinders the wound healing, decreases the quality of life of patients, and increases their physical and mental burden [8, 9]. Therefore, it is necessary to find a scientific and reasonable way of postoperative rehabilitation therapy to promote wound healing.

Sitz bath with potassium permanganate solution (1:5000) is traditionally recommended after mixed hemorrhoid surgery. Although it can relieve pain and promote wound healing, the effect still needs to be improved [10]. With the deepening of traditional Chinese medicine (TCM) research, TCM methods have also been applied in the postoperative treatment of mixed hemorrhoids. TCM believes that deficiency of Qi and blood as well as internal organs are the internal causes of hemorrhoids; the formation of hemorrhoids is ultimately promoted by prolonged sitting and standing, diarrhea and dysentery, poor diet, excessive fatigue, and internal injury by the seven emotions [11]. At present, Huhuang Burn Liniment has been widely applied in the field of burns and has idea effect of promoting wound healing [12]. Studies have indicated that moisture burn ointment is effective in the treatment of anal pain in mixed hemorrhoids [13]. Based on this, Huhuang Burn Liniment was used in this study to further promote postoperative wound healing of mixed hemorrhoids, which has certain innovation and feasibility.

Materials and methods

General data

The general data of 113 patients with mixed hemorrhoids admitted to Chongqing Sanxia Central Hospital were retrospectively collected. All patients underwent MMH and were divided into two groups according to postoperative treatment regimen. Group A (n=56) was treated with fumigation and sitz bath of potassium permanganate solution (1:5000) after surgery, while group B (n=57) was treated with Huhuang Burn Liniment.

Inclusion criteria: Patients who met the relevant diagnostic criteria for mixed hemorrhoids in the Guidelines for the Clinical Management of Hemorrhoids [14]; and patients who were able to follow medical advice strictly. The study

obtained the approval from the Medical Ethics Committee of Chongqing Sanxia Central Hospital (approval number: NCT02563148).

Exclusion criteria: Patients comorbid with anal fistula, anal fissure, and other perianal diseases such as perianal abscess; patients with other organic lesions such as anal polyps; patients with serious cardiovascular diseases; patients with coagulation dysfunction; patients with atopic infections such as ulcerative colitis and Crohn's disease; patients with infectious diseases of the gastrointestinal tract; or patients who were allergic to the treatment drugs.

Methods

Group A: From the first day after surgery, potassium permanganate (Approval No. H2008-4635, Manufacturer: Nanchang Baiyun Pharmaceutical Co., Ltd., Specification: 500 g) was prepared as a solution of 1:5000. Patients were instructed to take a 15 min fumigation sitz bath after defecation or every night before bedtime, once daily, with 7 days as a course of treatment. Two consecutive courses of treatment were carried out.

Group B: From the first day after surgery, patients were treated with fumigation sitz bath every night with Huhuang Burn Liniment (Approval No. Z20010151, Chongqing Xixuan Biotechnology Co., 50 mL/bottle). The liniment (25 mL) was added to 1500 mL of warm water and mixed evenly, and the affected area of the anus was fumigated first, followed by 15 min of sitz bath, once daily, with 7 days as a course of treatment. Two consecutive courses of treatment were administered.

Outcome measurement

(1) Efficacy criteria [15]. Cured: after treatment, symptoms such as redness, swelling and pain of the wound surface disappeared completely, with rectal examination showing smooth mucosa of the anal canal, and there was no swelling and pain in the anus. Improved: after treatment, some clinical symptoms disappeared, the wound surface was bright red with growth of granulation tissue, but the wound surface was not healed completely with occasional mild pain in the anus. Ineffective: after treatment, clinical symptoms were not alleviated,

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the wound surface was dark red, and there was pain in the anus. Total effective rate = (cases of cured + cases of improved)/total cases × 100%.

(2) The criteria for wound healing: no bleeding and pain during defecation and rectal examination.

(3) Anal function was measured in both groups before and 14 days after treatment, including the length of anorectal hyperbaric zone, anal canal resting pressure, anal canal diastolic pressure, and anal canal maximum systolic pressure. The patients were asked to empty the bowel 1-2 h before the examination, so that the examination would not be affected by stool in the rectum. In the meantime, enemas, digital rectal examinations, or anoscopy should not be performed to avoid interference with sphincter function and rectal mucosa, and thus the examination results. The examiner should adjust the instrument beforehand, and put some necessary supplies, such as sterile gloves, syringes, paraffin oil, toilet paper, cloth pads, etc. at convenient places for easy access at any time. The patients were instructed to take the left lateral position. First, the balloon or probe was placed in the anal canal to measure the anal canal resting pressure, anal canal diastolic pressure, and anal canal maximum systolic pressure, and then the balloon was sent into the ampulla of rectum to measure the rectal resting pressure. The catheter was connected to dragging device to measure the length of the anorectal hyperbaric zone of anal canal.

(4) Trauma pain, edema, exudation, and granulation tissue scores [16, 17] were evaluated. Trauma pain was assessed by visual analogue scale (VAS) scores in both groups before and 14 days after treatment, ranging from 0-10, with 0 indicating no pain and 10 indicating severe pain. Exudation was scored 0-3, with exudation penetrating < 4, 4-8, 9-12, and > 12 layers of gauze scoring 0, 1, 2, and 3, respectively. The higher scores represented the severer exudation. The total score for trauma edema was 0-3, with 0 standing for smooth trauma edge, 1 for slightly raised trauma edge but soft to the touch, 2 for translucent, sclerotic and red trauma, and 3 for local necrosis or a mass. The higher scores represented the severer edema. Trauma granulation morphology was scored 0-3 points. 0 point: the trauma was normal,

firm in texture and red in color; 1 point: the trauma was mildly abnormal with evenly distributed granulation in light red color; 2 points: the trauma was moderately abnormal with excessive granulation in crimson color; 3 points: the trauma was severely abnormal with necrosis and erosion in dark red color.

(5) Interleukin-10 (IL-10) and matrix metalloproteinase-9 (MMP-9) levels: The wound granulation tissues were collected from patients in both groups before and 14 days after treatment, and the IL-10 and MMP-9 levels were measured using enzyme-linked immunosorbent assay in strict accordance with kit instructions (Shanghai Enzyme Linked Biotechnology Co., Ltd.). The lot number of kit was 2018-10-12.

(6) Complications: fever, exudation, bleeding, edema, etc., were recorded after 14 days of treatment.

(7) Quality of life [18]: Before and after 14 days of treatment, the Generic Quality of Life Inventory-74 (GQOL-74) scale was used to evaluate the quality of life of patients in both groups, including four dimensions of material life, social function, psychological function and physical function, with 74 items ranging from 0 to 100 points, and the quality of life was proportional to the score.

Statistical methods

Statistical Package for the Social Sciences (SPSS) 22.0 was used to analyze the data. Measurement data (mean ± standard deviation) were examined using *t* test for data conforming to normal distribution, and Mann-Whitney U test was performed for those not conforming to normal distribution. Counting data [n (%)] were examined using χ^2 test. GraphPad Prism 8.0 was used as graphic software. *P* < 0.05 suggested the presence of statistical significance.

Results

Comparison of baseline data

The two groups exhibited no significant differences in terms of baseline data such as sex, age, duration of disease, trauma area, and type

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Table 1. Comparison of baseline data [n (%)]/($\bar{x} \pm sd$)

Data		Group A (n=56)	Group B (n=57)	t/ χ^2	P
Gender (cases)	Male	39 (69.64)	42 (73.68)	0.227	0.634
	Female	17 (30.36)	15 (26.32)		
Age (years)		39.68±3.28	39.71±3.22	0.049	0.961
Duration of illness (months)		9.15±0.19	9.17±0.16	0.606	0.546
Traumatic area (cm ²)		12.29±0.32	12.31±0.29	0.348	0.728
Types of mixed hemorrhoids (cases)					
	Varicose type mixed hemorrhoids	21 (37.50)	22 (38.60)	0.158	0.963
	Connective tissue type mixed hemorrhoids	19 (33.93)	17 (29.82)		
	Ring-shape mixed hemorrhoids	16 (28.57)	18 (31.58)		

Table 2. Comparison of the efficacy [n (%)]

Group	Number of cases	Cured	Improved	Ineffective	Total effective rate
Group A	56	21 (37.50)	13 (23.21)	22 (39.29)	34 (60.71)
Group B	57	35 (61.40)	19 (33.33)	3 (5.26)	54 (94.74)
χ^2	-	-	-	-	18.978
P	-	-	-	-	< 0.001

of mixed hemorrhoids, which were comparable ($P > 0.05$) (**Table 1**).

Comparison of the efficacy

After treatment, 21 cases were cured, 13 were improved, and 22 were ineffective in group A, with a total effective rate of 60.71%; 35 cases were cured, 19 were improved, and 3 were ineffective in group B, with a total effective rate of 94.74%. The total effective rate of treatment in group B was higher than that in group A ($P < 0.05$) (**Table 2**).

Comparison of anal function

Compared with before treatment, the length of anorectal hyperbaric zone was reduced, while the anal canal resting pressure, anal canal diastolic pressure, and anal canal maximal systolic pressure were increased in both groups after treatment (all $P < 0.05$). After treatment, group B had shorter length of anorectal hyperbaric zone and higher anal canal resting pressure, anal canal diastolic pressure, and anal canal maximal systolic pressure than group A (all $P < 0.05$) (**Figure 1**).

Comparison of trauma pain, edema, exudation, and granulation tissue scores

Compared with before treatment, the scores of wound pain, edema, exudation and granulation tissue were reduced in both groups after treat-

ment (all $P < 0.05$). The scores of wound pain, edema, exudation and granulation tissue in group B were lower than those in group A (all $P < 0.05$) (**Figure 2**).

Comparison of IL-10 and MMP-9 levels

Compared with before treatment, IL-10 levels were increased and MMP-9 levels were decreased in both groups after treatment (both $P < 0.05$). After treatment, group B had higher IL-10 levels and lower MMP-9 levels than group A (both $P < 0.05$) (**Figure 3**).

Comparison of complications

The complication rate was 8.77% in group B, which was lower than 23.21% in group A ($P < 0.05$) (**Table 3**).

Comparison of wound healing time and quality of life scores

After treatment, group B had shorter wound healing time and higher quality of life scores than group A ($P < 0.05$) (**Figure 4**).

Discussion

MMH is the preferred surgical procedure for the clinical treatment of mixed hemorrhoids; however due to the specificity of the surgical site, the surgical incision is close to the anal verge to the dentate line, which is easy to stimulate the

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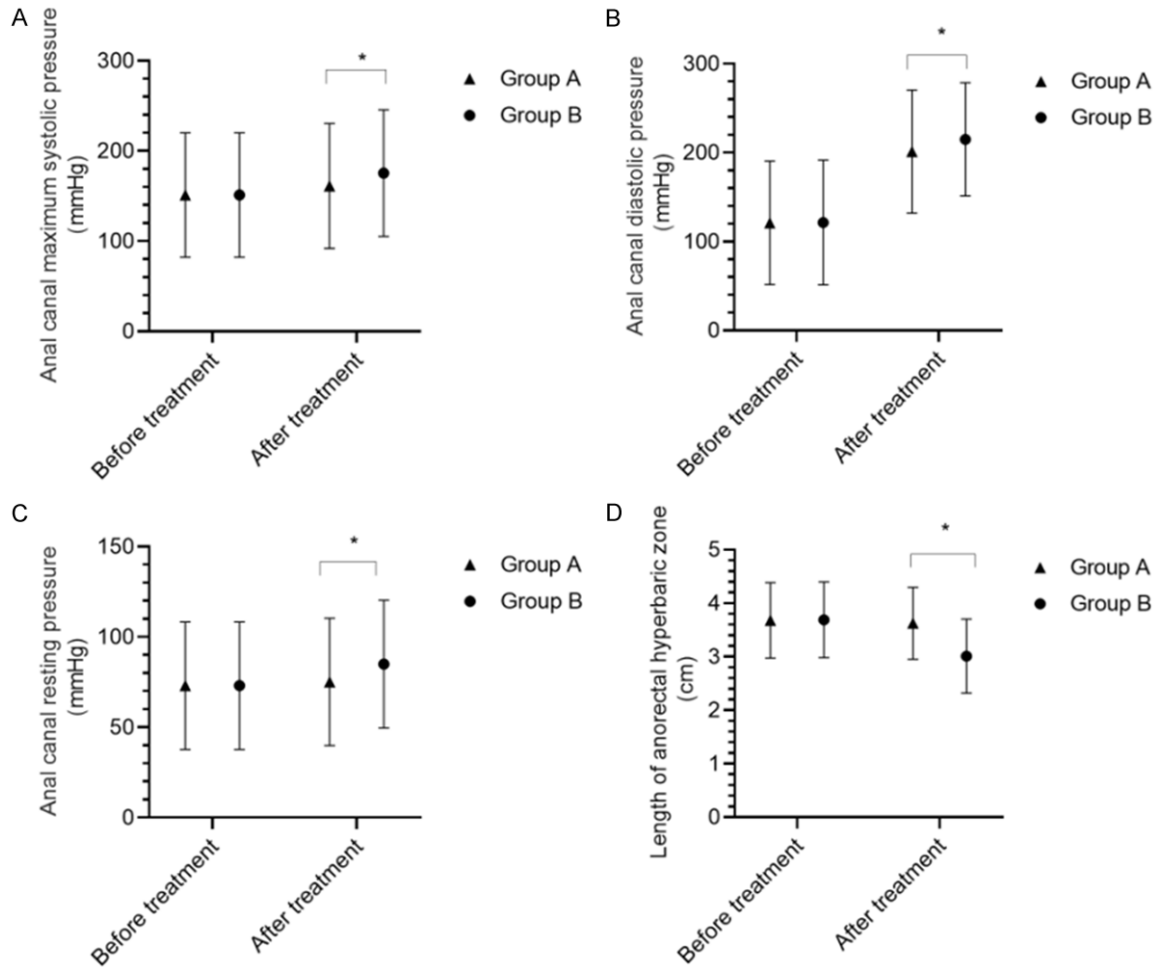


Figure 1. Comparison of anal function. A. Anal canal maximum systolic pressure. B. Anal canal diastolic pressure. C. Anal canal resting pressure. D. Length of anorectal hyperbaric zone. * Denotes comparison with group A, $P < 0.05$.

subdentate tissues and nerves of the surgical wound, causing pain and hindering postoperative wound healing [19]. Postoperative pain can cause accumulation of tissue fluids and complications such as fever, bleeding, exudation, and perianal edema, which seriously affects the healing speed and prolongs the postoperative recovery time [20, 21]. Meanwhile, pain also stimulates the anal sphincter, causes persistent spasm, hinders perianal blood circulation, leads to inflammatory edema and slows down the wound healing [22]. Therefore, it is necessary to find a scientific and reasonable way to promote wound healing and reduce pain of patients after mixed hemorrhoid surgery.

In western medicine, antibiotics or potassium permanganate sitz baths are commonly used to treat mixed hemorrhoids after surgery, but

the overall treatment effect is not satisfactory and may also cause a series of adverse reactions [23, 24]. According to TCM, external factors, such as heat, dampness, dryness and wind, invade the anal area of the large intestine, causing accumulation of dampness, heat and wind around the anus, which leads to stagnation of Qi and blood and poor blood circulation. The main pathogenesis of mixed hemorrhoids is blood stasis, heat and toxicity stagnation, and damp-heat settling downward [25]. Although the hemorrhoids can be removed by surgical treatment, it is difficult to eliminate external pathological factors such as heat, dampness, dryness and wind, so it is believed by TCM that the treatment should be based on drying dampness and relieving pain, invigorating blood and resolving stasis [26]. The results of this study showed that group B exhibited

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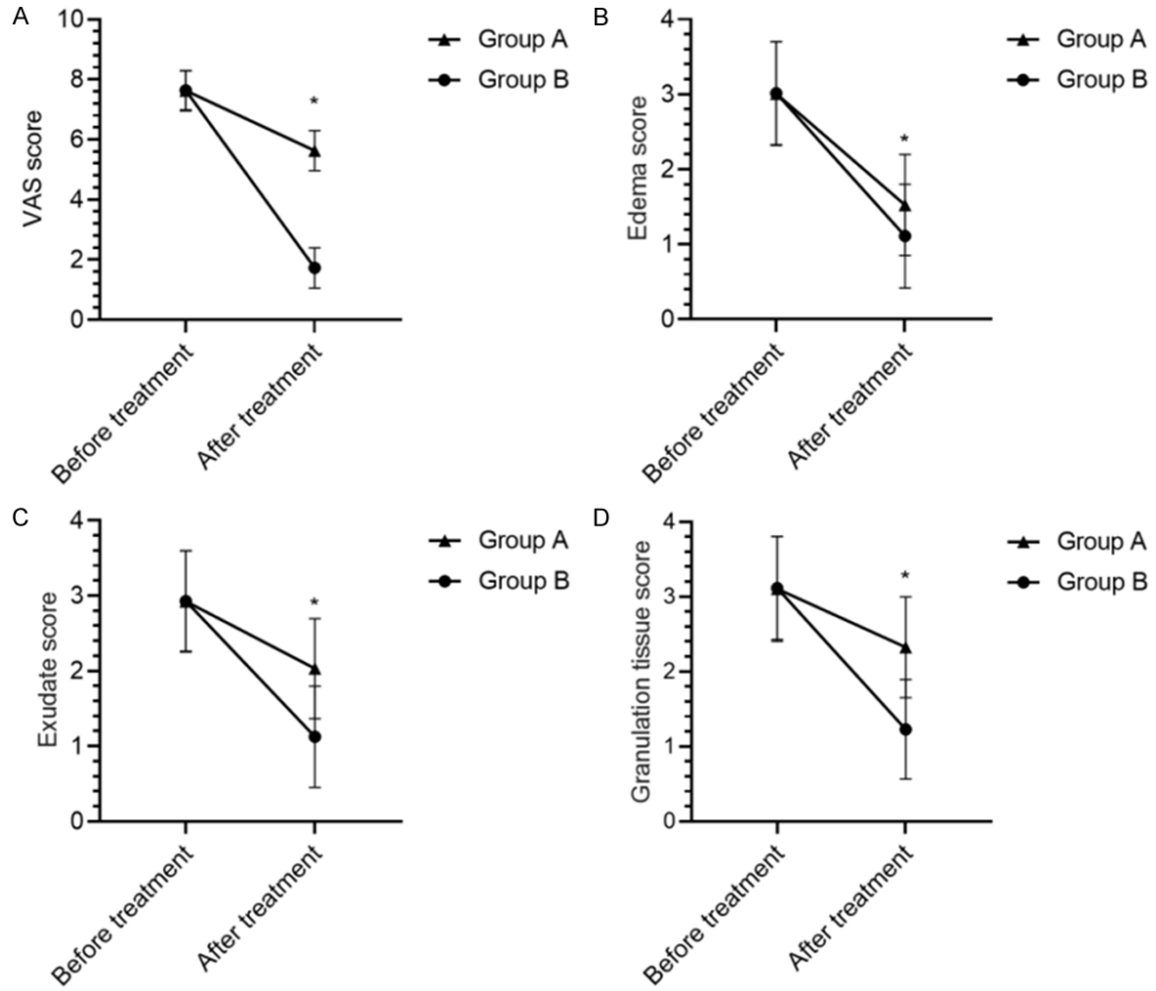


Figure 2. Comparison of pain, edema, exudation, and granulation tissue scores on the trauma surface. A. VAS scores. B. Edema scores. C. Exudation scores. D. Granulation tissue scores. VAS: Visual Analogue Scale. * Denotes comparison with group A, $P < 0.05$.

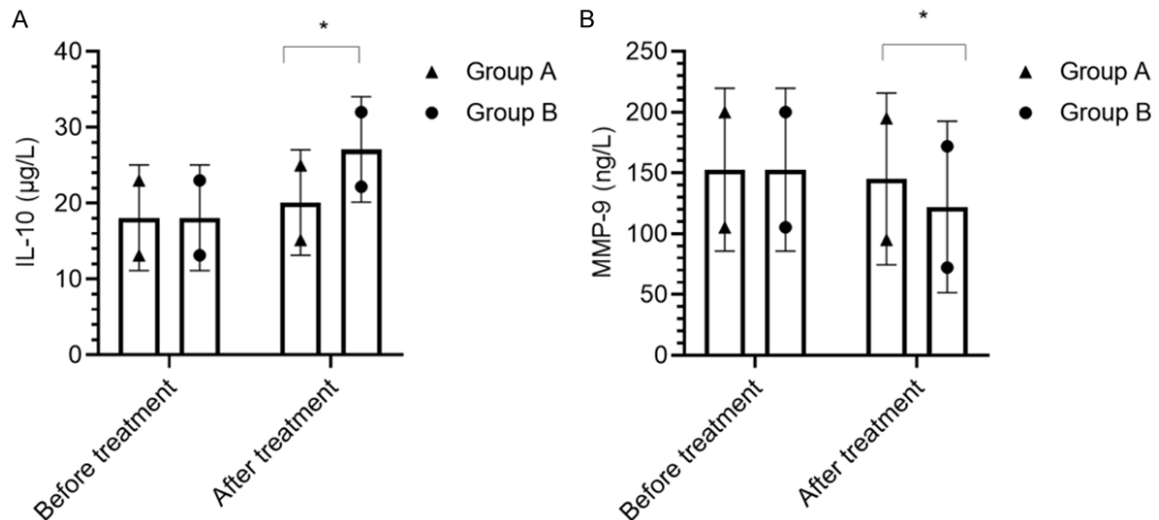


Figure 3. Comparison of IL-10 and MMP-9 levels. (A) IL-10 and (B) MMP-9. IL-10: Interleukin-10; MMP-9: Matrix Metalloproteinase-9. * Denotes comparison with group A, $P < 0.05$.

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Table 3. The incidence of complication [n (%)]

Group	Number of cases	Fever	Exudation	Bleeding	Edema	Total incidence
Group A	56	5 (8.93)	3 (5.36)	2 (3.57)	3 (5.36)	13 (23.21)
Group B	57	2 (3.51)	1 (1.75)	1 (1.75)	1 (1.75)	5 (8.77)
χ^2	-	-	-	-	-	4.399
<i>P</i>	-	-	-	-	-	0.036

higher total effective rate, higher score of quality of life, higher anal canal resting pressure, anal canal diastolic pressure and anal canal maximum systolic pressure, and lower incidence of complications than group A. The healing time and the length of anorectal hyperbaric zone in group B were shorter than those in group A, indicating that Huhuang Burn Liniment could promote wound healing, improve anal function, reduce the degree of trauma pain, exudation and edema, improve patients' quality of life, and reduce the incidence of complications. Huhuang Burn Liniment is composed of eight herbs, including borneol, *Senecio scandens*, *Angelica dahurica*, *Carthamus tinctorius*, Buffalo Horn, Phellodendri Cortex, *Coptis chinensis* and *Reynoutria japonica*, among which borneol has the function of promoting granulation, clearing heat and pain; *Senecio scandens* can cure sores and remove damp-heat, and has the effect of clearing heat and detoxification; *Angelica dahurica* can promote granulation and relieve pain, invigorate blood and promote menstruation; *Carthamus tinctorius* can disperse stasis and relieve pain, invigorate blood and promote menstruation; Buffalo Horn can clear heat and cool blood; Phellodendri Cortex can clear heat and dampness; *Coptis chinensis* can clear away heat and dampness, relieve fire and detoxify, reduce inflammation and eliminate bacteria; *Reynoutria japonica* can dispel blood stasis, relieve pain and clear heat. The combination of all the herbs has the effect of drying dampness and relieving pain, invigorating blood and removing stasis, cooling blood and detoxifying fire. Modern pharmacological studies have shown that *Reynoutria japonica* contains polygonin that can effectively inhibit *Shigella flexneri*, *Salmonella typhi*, *Escherichia coli* and *Staphylococcus aureus*. *Cyperus rotundus* promotes growth of epithelial tissues and accelerates wound healing [27]. Zhao et al. [28] analyzed the treatment effect of Huhuang Burn Liniment on deep II burn

model of rats, and the results showed that the liniment could enhance the antibacterial ability, improve the repair ability and immunity, and promote wound healing of the rats. The extracellular matrix is a key regulator of cell adhesion, proliferation, differentiation, and migration in

the process of skin repair. It has been shown that matrix metalloproteinases (MMPs) play an important role in wound healing and remodeling, while cell and growth factors can affect the expression of MMP [29]. MMP-9 is a collagen that degrades denatured collagen and promotes the hydrolysis of fibronectin, laminin, and elastin. In this study, the levels of MMP-9 in group B were lower than those in group A after treatment, suggesting that Huhuang Burn Liniment could reduce the expression of MMP-9, regulate collagen degradation, block trauma cellular transforming factors, collagen degradation and loss, and promote wound healing. Besides, studies have shown that MMPs expression is regulated by hormones, cellular transforming factors, and inflammatory cytokines. During wound healing, IL-10, as an important cellular inflammatory factor, mediates and activates the expression of MMP-9. In this study, the levels of IL-10 in group B were higher than those in group A after treatment, suggesting that Huhuang Burn Liniment could inhibit the release of inflammatory factors, reduce the expression of MMP-9 and promote wound healing.

There are also some limitations in this study. Although this study confirmed the promoting effect of Huhuang Burn Liniment on postoperative wound healing of mixed hemorrhoids, due to the limited conditions, no pharmacological experiment was conducted. Besides, the sample size was small and should be expanded in the further research.

In conclusion, Huhuang Burn Liniment could promote wound healing, improve anal function, reduce the degree of trauma pain, exudation, and edema, and improve the quality of life of patients.

Disclosure of conflict of interest

None.

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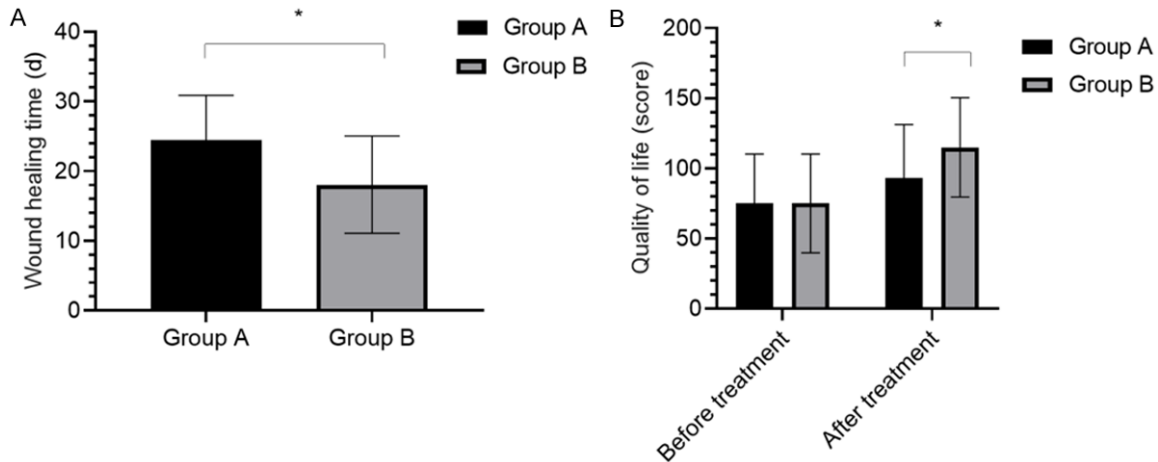


Figure 4. Comparison of wound healing time and quality of life scores between the two groups. (A) Wound healing time and (B) Quality of life scores. * Denotes comparison with group A, $P < 0.05$.

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