Int J Clin Exp Med 2016;9(3):6302-6308
www.ijcem.com /ISSN:1940-5901/IJCEM0018566

Original Article

Postoperative analgesic effect of methylene blue compound in anal diseases

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Received June 24, 2015; Accepted March 1, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: The postoperative pain associated with haemorrhoidectomy severely affects the life quality of patients. We aimed to explore a method that can partially or even completely eliminate haemorrhoidectomy-associated postoperative pain. Clinical observations showed that subcutaneous injection of methylene blue plus ropivacaine near the haemorrhoidectomy incision could satisfactorily achieve this goal. A retrospective study was conducted to compare the effects between subcutaneous injection of methylene blue plus ropivacaine and conventional analgesic methods after Milligan-Morgan haemorrhoidectomy. A total of 151 patients received the Milligan-Morgan haemorrhoidectomy for the treatment of mixed haemorrhoids between September 2013 and June 2014. Among them, 83 cases were given subcutaneous injection of methylene blue plus ropivacaine adjacent to the surgical incision (treatment group), and 68 cases were given conventional analgesic procedures to relieve pain (control group). Visual analogue scale (VAS) pain scores were used to evaluate the degrees of pain for 14 consecutive days. The clinical results were assessed based on VAS score, healing time and complications. For the treatment group, the VAS scores between postoperative days 1 and 3 were significantly lower than those for the control group ($P < 0.01$), and the VAS scores for the treatment group on postoperative days 4 and 5 were also lower than those for the control group ($P < 0.05$). The VAS scores revealed no significant difference ($P > 0.05$) between the two groups from postoperative days 6 to 14. The control group had a higher use of extra analgesic medications than the treatment group ($P < 0.05$) between the postoperative days 1 and 5. No significant differences were observed between the two groups in wound healing time and postoperative complications ($P > 0.05$). The subcutaneous injection of combined methylene blue and ropivacaine around a haemorrhoidectomy incision can effectively alleviate pain from the haemorrhoid patients during the first 5 days of the postoperative period. The application can achieve a long-acting analgesic effect with minor complications and adverse reactions.

Keywords: Methylene blue, haemorrhoidectomy, postoperative pain

Introduction

Haemorrhoids are common perianal diseases [1]. Milligan-Morgan haemorrhoidectomy operation is a classic haemorrhoid resection procedure that has been widely used as the gold standard for haemorrhoid operations [2, 3]. However, it exhibits a major problem of postoperative pain [4]. Almost all patients experience different degrees of postoperative pain [5], which terrifies the patients. According to a previous report, 12% of the patients who received haemorrhoidectomy had severe postoperative pain [6]. Postoperative pain of patients is a thorny problem, troubling physicians [7] and seriously affecting the life quality of patients. Many patients are reluctant to receive surgical therapy due to the fear of pain, which delays the treatment and aggravates or complicates the disease. The control of postoperative pain is a very important goal for clinical physicians. How to reduce the perianal nerve sensitivity and ease the pain has been a research hotspot and difficulty in the field of perianal postoperative analgesia. Many scholars have conducted studies on perianal postoperative analgesia and hope to explore an effective approach to reduce postoperative pain and even to achieve painless postoperative recovery. Methods including oral administration or intramuscular injection of analgesic drugs, local application of nitroglycerin ointment, and injection of kreotoxin have been commonly used to alleviate postoperative pain [8, 9]. The local use of anaesthetic drugs

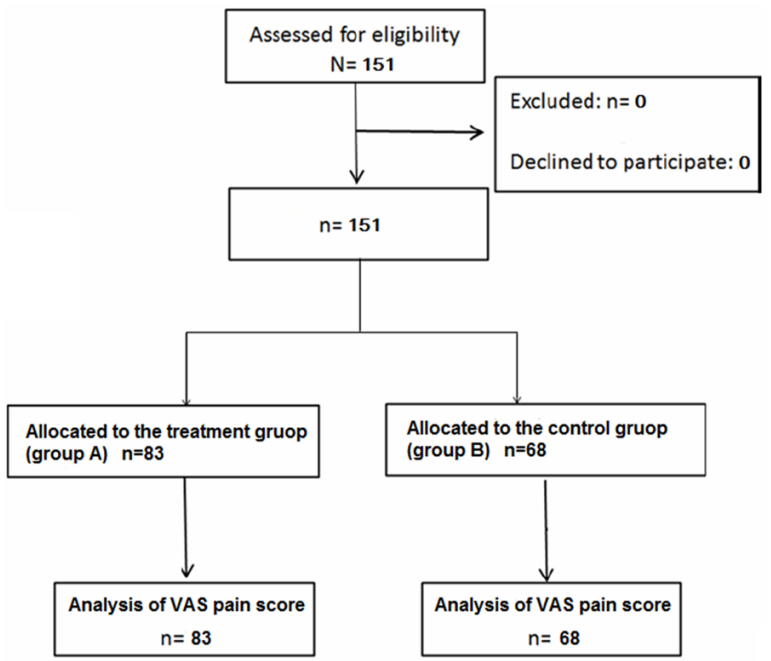

Figure 1. The flow chart for patient selection.

Table 1. Patient demographics and clinical aspects

	Group A (N = 83)	Group B (N = 68)	P
Age, yrs	42.3±11.7	45.4±13.2	0.128
Sex (Male/Female)	38/45	29/39	0.7
Disease stage			0.894
Stage II	24 (28.9%)	19 (27.9%)	
Stage III	41 (49.4%)	36 (52.9%)	
Stage IV	18 (21.7%)	13 (19.2%)	
Number of incisions	3 (1-4)	3 (1-4)	0.774

to control postoperative pain at the wound site has been popular because of its convenience and remarkable efficacy [10]. Clinical observations have shown that subcutaneous injection of methylene blue plus ropivacaine around the incision could achieve relatively long analgesic effect. In China, this method is the most commonly used postoperative analgesic method for anal diseases. We applied this approach after Milligan-Morgan haemorrhoidectomy and realized an excellent analgesic effect. The results are reported as follows.

Materials and methods

Patients

A total of 151 hospitalized patients who received Milligan-Morgan operation between September 2013 and June 2014 in the Anorectal Department of Sichuan Provincial People's Hospital were included in this study. All operations were performed by the same surgical group strictly based on standard Milligan Morgan haemorrhoidectomy. Among the patients, 83 patients received a postoperative subcutaneous injection of methylene blue plus ropivacaine around the incision (treatment group, group A), and 68 patients were treated using conventional methods to relieve pain (control group, group B). A flow chart for patient selection was displayed in **Figure 1**. Disease staging used Goligher's classification method, and statistical analyses were performed between the two groups in terms of gender, age, disease stage and number of incisions. The difference between the two groups was not statistically significant, which confirmed that the two groups were comparable (P > 0.05) (**Table 1**).

Treatment methods

① Methylene blue compound preparation: a 0.167% methylene blue compound solution was prepared by mixing 2 mL (20 mg) of methylene blue injection solution with 10 mL (75 mg) of ropivacaine hydrochloride injection solution. ② Injection method for the treatment group: after the operation was completed, the compound solution was hypodermically injected with a skin test needle around all incisions. The needlepoint was approximately 1 cm away from the incision edge. The needle orientation was approximately 45 degrees from the skin. Uniform injections were given at each injection point in the upper, lower, left and right directions with 0.5 mL of injection drug per injection point. The distance between every two injection points was 1 cm. After the injection, the drug solution was spread evenly by gently rubbing the area with gauze. ③ The control group: 100 mg of tramadol hydrochloride sustained-release tablets were given orally twice a day for 5 days after the surgery. For patients in both groups, if the visual analogue scale (VAS) pain

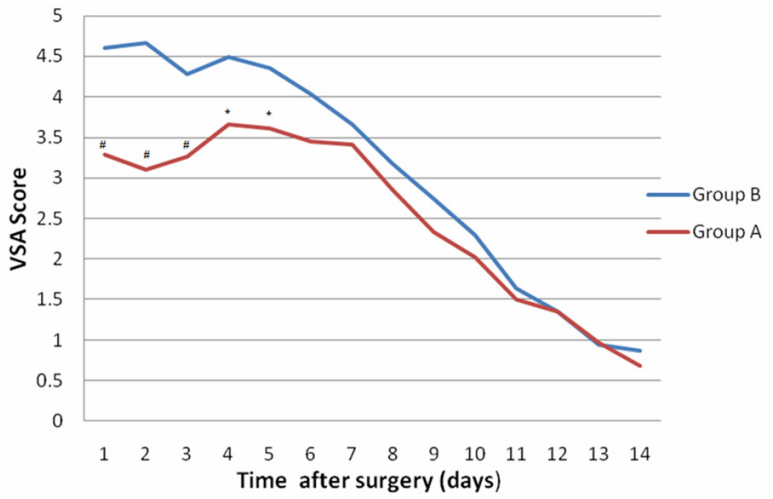

Figure 2. VSA scores after surgery. Compared with group B, $^{*}P < 0.05$, $^{\#}P < 0.01$.

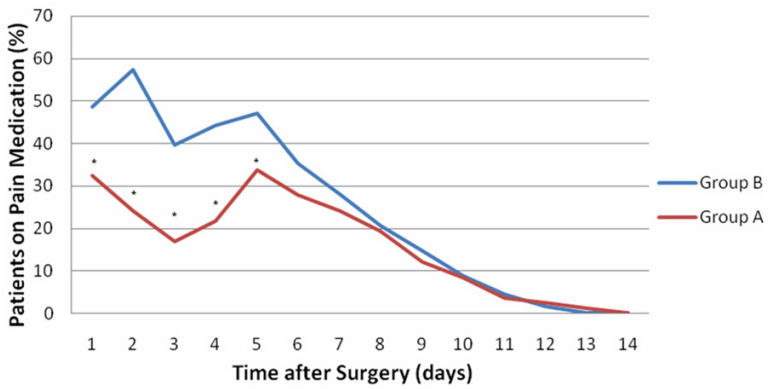

Figure 3. Patients on pain medication after surgery. Compared with group B, $^{*}P < 0.05$.

Table 2. Comparison of postoperative complications

	Group A (N = 83)	Group B (N = 68)	P
Uroschesis	11 (13.3%)	8 (11.7%)	0.784
Crissum skin abnormality	5 (6.0%)	2 (2.9%)	0.459
Anal incontinence temporarily	4 (4.8%)	2 (2.9%)	0.691
Incision oedema	26 (31.3%)	19 (27.9%)	0.651
Skin necrosis	0	0	NA
Wound infection	0	0	NA

NA: not analysis.

score was equal to or greater than 5, an additional 100 mg of tramadol hydrochloride sustained release tablets was provided. If the pain still could not be alleviated, an extra intramuscular injection of pethidine hydrochloride was offered.

Outcome measurements

① VAS pain scores for two groups of patients between days 1 and 14 after the surgery, on a scale between 0 and 10 (VAS, 0 = no pain, 10 = severe pain); ② Number of patients in the two groups who received additional daily oral tramadol tablets or intramuscular injection of pethidine hydrochloride; ③ Wound healing time: the time between the end of the operation and wound healing; and ④ Postoperative complications, including uroschesis, incision oedema, crissum skin abnormality, anal incontinence temporarily, skin necrosis and wound infection.

Statistical analysis

The statistical analysis was performed with SPSS version 19 of Windows (SPSS, Chicago, IL, USA). Categorical variables are given as counts and percentages.

Continuous variables are expressed as mean ± standard deviation (SD). Comparisons between two groups were performed using a sample independent *t* test. A *P* value of < 0.05 was considered statistically significant.

Results

Between the 1st and 3rd postoperative days, VAS scores in the treatment group were significantly lower than those of the control group ($P < 0.01$), and the postoperative VAS scores of postoperative days 4 and 5 were also lower than those of the control group ($P < 0.05$). However, no significant difference was detected in the VAS scores between the two groups from the 6th to the 14th days after the operation ($P > 0.05$) (**Figure 2**).

The proportion of patients who received additional analgesic drugs in the treatment group between days 1 and 5 after the operation was less than that of the control group ($P < 0.05$), and there was no significant difference between the two groups from days 6 to 14 after surgery ($P > 0.05$) (**Figure 3**). There was no significant difference in wound healing time between group A and B (17.69±3.67 vs. 17.56±3.56, $P = 0.855$). In addition, postoperative complications were found not different ($P > 0.05$) between the two groups (**Table 2**).

Discussion

In recent years, many new surgical methods have been developed for the treatment of haemorrhoids, such as circular stapled haemorrhoidopexy and partial stapled haemorrhoidopexy [11, 12], with the advantages of little trauma, minor postoperative pain and few complications. However, these operations still require a traditional excision of the external haemorrhoids when treating mixed haemorrhoids. Although the incision is narrower, the surgical pain from incision is still unavoidable. The anus is very sensitive to the pain from a surgical incision, which results in severe regional postoperative pain with a long duration [13]. There have been many methods for the treatment of postoperative pain [14, 15], but the effective time of pain alleviation was often short, with an obvious effect only lasting from 24 to 48 h after surgery [16, 17]. An effective postoperative analgesia requires at least 72 h of effect [18]. The clinical application of local anaesthetics combined with methylene blue can better achieve this goal with a 72-h or even longer analgesic effect after surgery [19-21].

Methylene blue was first synthesized in 1876 and became widely used in different fields of clinical medicine [22]. It has been more frequently used in the treatment of methemoglobinaemia [23], septic shock [24], intraoperative mapping of intestinal micro-bleeding lesions [25], surgical sentinel lymph node biopsy and mapping in breast cancer [26]. However, methylene blue has been rarely used in analgesia. In recent years, local injection of methylene blue has been evaluated in treatments for various pain diseases and has shown a remarkable long-acting analgesic effect [27-29]. Existing English literature has demonstrated that methylene blue was mainly used in the treatment of anal itching in perianal applications [30-31], and there have been very few studies reporting its application in the postoperative treatment of perianal disease. Only one article introduced the application of methylene blue injection [21] in an open diathermy haemorrhoidectomy. In China, injection of the methylene blue compound as a long-acting analgesic drug after perianal disease surgery has been performed since the 1970s. Clinical observations have revealed its analgesic effect to last 72 h or longer [19, 20].

Methylene blue is a nontoxic dye agent that inhibits the soluble guanylate cyclase and nitric oxide synthase. Nitric oxide regulates physiological functions such as pain and analgesia by activating soluble guanylate cyclase to increase intracellular cyclic guanosine monophosphate [32, 33]. Methylene blue, as an oxidizing-reducing agent, demonstrates a strong affinity to nerve tissues when applied locally, which can directly block the electrical conductivity of nerve fibres, thereby affecting the neural excitability and impulse conductivity. Recent studies have shown that a low dose (0.5% or 1%) of methylene blue may block peripheral nerve fibres at the incision. A local injection of methylene blue could cause reversible damage to the incision and its surrounding subcutaneous nerve terminal medulla, thus achieving a long-acting postoperative analgesic effect [34, 35]. However, the damage will cause a burning sensation between 2 to 4 hours after injection. To eliminate this burning sensation, methylene blue is combined with local anaesthetic drugs. This approach leaves no gaps in the analgesia period; therefore, patients rarely feel any postoperative burning pain. After more than 30 years of development, the choices of local anaesthetics, including traditional Chinese medicine injection, tetracaine, lidocaine, bupivacaine, ropivacaine and other varieties of drugs [19-21], have been explored. Due to such advantages as low toxicity, a long effective time of 4~6 h on local anaesthesia and analgesia, relatively weak motor nerve impediment and separation between feeling and motions, ropivacaine is an ideal local anaesthetic drug currently used in postoperative analgesia [36]. Therefore, we applied a method that involved combining methylene blue with ropivacaine.

The results showed that between the 1st and 3rd days after surgery, the VAS scores of the

treatment group were significantly lower than those of the control group ($P < 0.01$). Some patients in the treatment group only reported the sense of anal pendant expansion but no feeling of anal pain with a VAS score of 0. The anal pendant expansion feeling was likely caused by the ligation of internal haemorrhoids. The mean VAS score of treatment group was approximately 3. In contrast, almost all patients in the control group exhibited varying degrees of pain, with VAS scores ranging from 4 to 5. These results suggested that methylene blue plus ropivacaine has a significant analgesic effect. The VAS scores in both groups on postoperative days 4 and 5 were increased compared to the first three days, but the VAS scores of the treatment group were still lower than those of the control group ($P < 0.05$). The increase of pain in the treatment group may be the result of defecation stimulation or the gradually subsiding analgesic effect of methylene blue, which resulted in a gradually regained sense of pain. Between days 6 and 14 after surgery, the postoperative VAS scores of the two groups decreased gradually, and the difference between the daily VAS scores of the two groups became insignificant ($P > 0.05$). These results indicated that the analgesic effect of 0.167% methylene blue injection was mainly manifested in the first 5 days after surgery. Sim HL et al. [21] reported that the analgesic effect was only significant within the first 3 days after surgery. They used an intradermal injection of methylene blue plus bupivacaine before the incision procedure. Instead, we used subcutaneous injection of methylene blue plus ropivacaine at the end of the operation. Therefore, the disagreement between the two studies was possibly due to differences in medication type, drug concentration and injection site. The commonly used drug concentrations of methylene blue range from 0.1% to 0.33% in China. We used a low concentration (0.167%) of methylene blue in this study. However, the effects from different concentrations have not yet been compared. In addition, the injection sites included the intradermal, subcutaneous, muscular layers of the wound [21, 37], the analgesic effects between which also have not yet been compared. The percentage of patients requesting additional tramadol hydrochloride oral administration or additional intramuscular injection of pethidine hydrochloride for analgesia within the first 5 days after surgery was higher in the control group than in the treatment group ($P < 0.05$). This result also reflects a long-acting analgesic effect of methylene blue plus ropivacaine. There was no significant difference between the two groups in wound healing time ($P > 0.05$). The local injection of the methylene blue compound achieved a remarkable analgesic effect without affecting the wound healing time. In addition, uroschesis, incision oedema, crissum skin abnormality, temporary anal incontinence and other conditions are common postoperative complications of haemorrhoidectomy; there were no significant differences in the complications observed in the two groups ($P > 0.05$). The injection of the methylene blue compound did not result in an increased incidence of complications such as uroschesis, incision oedema and defecation difficulties. In addition, no skin necrosis, wound infection or other serious complications occurred.

Conclusions

In summary, subcutaneous injection of methylene blue plus ropivacaine near the incision effectively alleviated the pain from haemorrhoidectomy for 5 days. The procedure achieved a long-acting analgesic effect with few complications or adverse reactions. This clinical study only used a conventional medication type, drug concentration and injection method with a small number of cases. No study was conducted to separately investigate the effects of different combination of drugs, concentrations and injection methods. In future studies, we will perform randomized and controlled trails and inject methylene blue to surrounding areas of the incision, including archosyrinx and perianal abscess, to observe the corresponding effects, thus providing basis for the development of proper long-acting analgesic applications.

Disclosure of conflict of interest

None.

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