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To know efficacy of methylene blue as local analgesics in perianal surgeries

[1]Dr.Jayeshkumar B. Bagada, M.S., Assistant Professor, Department of General Surgery, PSMC and Shree Krishna Hospital, Karamsad-388325,Dist-Anand, Gujarat.

[2]Dr. Gazal B. Patel, Third Year Resident, Department of General Surgery, PSMC and Shree Krishna Hospital, Karamsad-388325,Dist-Anand, Gujarat.

[3]Dr. Jignesh B. Rathod, M.S., F.M.A.S, Professor, Department of General Surgery, PSMC and Shree Krishna Hospital, Karamsad-388325, Dist-Anand, Gujarat.

Corresponding Author: Dr. Jayeshkumar B. Bagada, M.S., Assistant Professor, Department of General Surgery, PSMC And Shree Krishna Hospital, Karamsad-388325,Dist-Anand, Gujarat.

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Abstract

Background: Through temporary impairment of sensory nerve conduction, methylene blue (MB) has been demonstrated to have particular analgesic characteristics. The biologic stain MB is often used in anorectal surgery. The application of highly concentrated topical MB during anorectal surgery not only stains the tip and nerve fibres but also temporarily impairs their function.

Aims: To compare the effectiveness of MB as a local analgesic after peri-anal surgeries with those receiving conventional analgesics.

Materials and methods: The present study was conducted with a population of 81 patients and was conducted in the Department of Surgery of Shree Krishna Hospital Karamsad, Anand and Anand Laparoscopy Centre and Hospital, Anand. With Consent, all the patients were operated on for peri-anal surgery were divided into 3 groups A, B and C, in which group A (27 patients) were given methylene blue + ropivacaine subcutaneously around the incision, Group B (27 patients) -only ropivacaine subcutaneously around the incision and group C (27 patients) -routine post-operative analgesics. Comparison of pain will be done on a post-operative day 2 with VAS (visual analogue scale) pain score from 0 to 10, where 0 implies no pain at all and 10 means severe pain.

Results: Out of the total 81 cases,51 patients had VAS Score below 5, and 31 of the patients' VAS Score was 5 or more 5. It showed that all the patients in group A had

a VAS Score below 5 compared to other groups. VAS Score was low in the methylene blue group compared to the controls with conventional analgesics.

Conclusions: The present study concludes that injection of methylene blue can effectively alleviate pain after peri-anal surgeries. However, a large-scale multi-centric trial is needed to validate our findings further.

Keywords: Methylene Blue, Ropivacaine, Post-operative Pain.

Introduction

Through brief impairment of sensory nerve transmission, methylene blue (MB) has been demonstrated to have particular analgesic characteristics. MB is often used as a biological stain in anorectal surgery [1]. The application of highly concentrated topical MB during anorectal surgery not only stains the tip and nerve fibres but also temporarily impairs their function. As far as is known, MB has been used for analgesia after anorectal surgery, to lessen pruritus and to treat neuritis [2].

The papillary layer of the skin contains nerve endings for itch and pain, with the dermis and epidermis being the highest in number. These nerve ends are not myelinated. When the receptors are stimulated, the excitatory neurons transmit the impulses to the spinal cost dorsal horn and then continue to the central nervous system to develop s sensation of itch or pain [3]. This mechanism explains why MB is effective in reducing pain and itching.

When the tract is injected with MB in subjects with peri-anal fistulas as opposed to those without, the post-operative discomfort is reduced [4]; after lateral anal sphincterotomy and haemorrhoidectomy, studies in China and Singapore found that peri-anal intradermal injection of MB gives momentary pain alleviation [4,5]. According to other research, those who had an intradermal MB injection for severe anal pruritus (intractable anal pruritus) had improved symptom scores [6, 7].

Anorectal disorders affect the rectum and anus. The most prevalent anorectal problems are haemorrhoids, condyloma, fistulas and fissures. Anorectal pathology is widespread; however, most anorectal problems are temporary and don't need a thorough medical assessment. For individuals who need surgery to treat their anorectal disease, the procedure may often be performed safely and with little morbidity in an outpatient environment. However, no treatment comes without danger, and problems after anorectal surgery are common, with rates as high as 50% in certain studies [8]. Certain symptoms, such as itchiness, pain, bleeding, swelling, and burning, may substantially impact a patient's way of life [9]. Most patients have post-operative discomfort in varying degrees, which scares the patients [10]. In a prior study, 12 percent of Hemorrhoidectomy individuals experienced significant post-operative discomfort [11]. Patient's post-operative pain is a complex issue that bothers doctors and significantly lowers their quality of life [12]. The fear of pain prevents many patients from undergoing surgical treatments, which prolongs the healing process and worsens or complicates the condition. For surgeons, reducing post-operative discomfort is a primary priority.

According to published literature, methylene blue's effectiveness in anorectal surgery is still unknown. Therefore, the purpose of the current research was to determine if giving methylene blue to patients will lessen their post-operative discomfort and pain in the early post-operative period.

Material and Methods

Study Area

- Department of Surgery of a Shree Krishna Hospital Karamsad, Anand. (Tertiary Care Hospital)
- Anand Laparoscopy Centre and Hospital, Anand.
- Study Population: All the 81 patients who signed the informed consent form before the study underwent surgery for peri-anal diseases (peri-anal abscess, anal fissure, fistula in ano, haemorrhoids).

Study Design

- Prospective study
- Sample Size Calculation: The below-given formula was used for calculation:
  n= (Zα/2 + Zβ) 2 * (SD * 2) / d2
- The visual analogue score reported in methylene blue is 3-3.2
- While in conventional treatment, it is between 4.5-4.7
- Considering the deviation of 1 on the VAS scale at:
- Type-1 Error α =0.5
- Type-2 Error β=0.5
- The minimum sample size for an expected difference of 1.5 units is 17 in each group
- Assessing last year's data and the number of operated cases at our centre, we have chosen 27 as the sample size for every group.
- The cases were distributed in three groups as per computer-generated random numbers.
- Group A (27 patients) will be given methylene blue + ropivacaine subcutaneously around the incision.
- Group B (27 patients) will be given only ropivacaine subcutaneously around the incision
- Group C (27 patients) was given routine post-operative analgesics.

Inclusion Criteria

• Females and Males 18 to 65 years of age

• Patients with the peri-anal disease who are undergoing surgery.

• Patients with no mental retardation or cognitive impairment condition.

Exclusion Criteria

• Patients with a known allergy to methylene blue

• Pregnant women

This research was commenced after institutional ethical committee approval. All the patients were informed about the study. This study involved 27 patients undergoing peri-anal surgery. All the patients operated on for peri-anal surgery were divided into 3 groups, A, B and C, in which group A (27 patients) were given methylene blue + ropivacaine subcutaneously around the incision.

Group B (27 patients) were given only ropivacaine subcutaneously around the incision, and group C (27 patients) was given routine post-operative analgesics. The methylene blue sensitivity test was done pre-operatively in patients in whom the dye was injected intraoperatively. Patients from Group A(case) (27 patients) will be given a combination of 1% methylene blue 2 ml and 10 ml Ropivacaine hydrochloride injection solution subcutaneously around the incision immediately post-operatively and will not give any iv analgesic (or SOS) up to post-operative day 1 patient. Group B (27 patients) will be given 8 ml ropivacaine hydrochloride injection solution subcutaneously around the incision immediately post-operatively and will not give any IV analgesic (or sos) up to post-operative day 1, and Group C (27 patients) will be given routine post-operative analgesics. Comparison of pain will be done on a post-operative day 2 with VAS (visual analogue scale) pain

score from 0 to 10, where 0 implies no pain and 10 means severe pain.

Statistical Analysis

The data was estimated in terms of mean ± SD. The nominal and categorical data were presented in percentage values. For estimating the quantitative data, a t-test was used, and the non-parametric data were analyzed with the help of the Mann-Whitney test. Analysis of categorical data was done using the chi-square test. The p-value significance threshold was set for <0.05. SPSS Software Version 21 was used for all of the analyses.

Results

Out of the total 81 cases, 26 (32.1%) were females, and 55 (67.9%) were males, with a mean age of 45.26 years and a standard deviation of 17.96. The maximum age was 94, and the minimum age was 3 years. Group A consisted of 27 participants; the mean age was 40.67±14.47 years. The maximum age was 68 years, and the minimum was 10 years. Group B consisted of 27 participants; the mean age was 39.85±12.52 years. The maximum age was 64 years, and the minimum age was 17 years. Group C consisted of 27 participants; the mean age was 55.26 ± 21.74 years. The maximum age was 94, and the minimum age was 3 years.

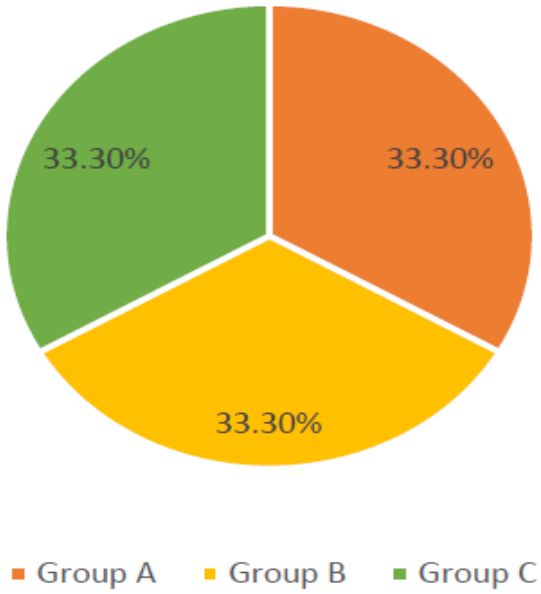

Figure 1: Distribution of cases as per study groups (n = 81)

On reviewing other studies, the mean age for the subjects considered for the research was 43.75 years, with no variations (p-0.44) between the two study groups. Among the 50 cases, 5 (10%) were females, and 45 (90%) were males, with no variation (p-1.0) between study groups. In the same kind of research**, Vinay G et al. [13]** concluded that the mean age group of study subjects was 41.3±9.71 and 44.6±8.34 years among LIFT procedure and fistulotomy groups, respectively. The distribution of gender was: 12 females (24%) and 38 (76%) males. In another gender-based research by **Ayyar P.V. et al.** [14], the distribution was 9 women and 51 men with an age range of 19-65years (Median 35 years). **Dhanraj M. et.al,** [15]. Their research observed that the mean age was 44.5 years, with a 4:1 male-to-female ratio.

In our study, several procedures were done for peri-anal diseases. Out of the total 81 Patients, 2 (2.5%) patients underwent Anal fistulectomy, 1 (1.2) patient for Anoplasty, 2 (2.5%) patients of EUA & Fistulectomy, 1 (1.2%) patients of EUA & Peri-anal incision and

drainage, 20 (24.7%) patients of haemorrhoidectomy,23 (28.4%)of LAS, 1 (1.2%) of LAS with Haemorrhoidectomy,2 (2.5%) of Marsupialization of anal fistula, 7 (1.2%) of MIPH, 1 (1.2%) patients of Perianal Fistulectomy, 12 (14.8%) patients of Perianal Incision & drainage, 2 (2.5%) of Peri-anal sinus tract excision,4 (4.9%) patients of Piles banding, 1 (1.25) of Pilonidal sinus.

Table 1: Distribution of cases as per procedure (n = 81)

Procedure	Frequency %
Anal Fistulectomy	2 (2.5)
Anoplasty	1 (1.2)
EUA & Fistulectomy	2 (2.5)
EUA & Perianal Incision and Drainage	1 (1.2)
Haemorrhoidectomy	20 (24.7)
LAS	23 (28.4)
LAS with Haemorrhoidectomy	1 (1.2)
Marsupialization of anal fistula	2 (2.5)
MIPH	7 (1.2)
Perianal Fistulectomy	1 (1.2)
Perianal Incision and Drainage	12 (14.8)
Peri-anal sinus tract excision	2 (2.5)
Piles Banding	4 (4.9)
Pilonidal Sinus Excision	1 (1.2)
Rectopexy	1 (1.2)
STARR Procedure	1 (1.2)
Total	81 (100)

In the present study, the most common presenting complaint was anal discharge (94%), swelling (86%) and pain (68%). No differences were seen in the study groups regarding presenting complaints (p>0.05). The mean duration of symptoms was 8.1 months in the methylene blue group and 6.7 months in the control group (p-0.71).

Ayyar PV et al. [14] observed the most common presenting complaint as discharge (88.3%), followed by swelling (71.7%) and pain (35%). **Dhanraj M et al.** [15] also report that discharge from the external opening is a common symptom of fistula, followed by pain and swelling. In the Tan K et al [16] study, the most common symptom was Peri-anal discharge coming from the external opening.

A total of 81 patients participated in the study. Of these, 51 (61.7%) of the patients had VAS Score below 5, and 31 (38.3%) of the patient's VAS Score was 5 or more than 5. As mentioned in the description of table number 4, 50 (61.7%) of the patients had VAS Scores below 5. Out of these, the majority of the patients were from group A, 27 (54%), followed by group C, 12 (24%) and group B, 11 (22%). Group A patients were treated with methylene blue with ropivacaine. It showed that all the patients in group A had a VAS Score below 5 compared to other groups. The VAS score was low in the MB injected group compared to the controls with conventional analgesics (p<0.05).

People undergoing or undergoing peri-anal surgeries and were treated with methylene blue – post-operatively had a significant impact on relieving post-operative pain. F (2,78)= 7.255, P= 0.001. The mean difference, post-Hoc Test, was significant at 0.05 level.

As shown in the above table, the first Test is between Group A with Group B, and the P value is 0.858. The P value was >0.05, so no difference was detected among the groups. In comparison, Group A with Group C shows a significant difference in the groups as the P value is <0.05. Comparing the groups B and C, a

significant difference was detected, as the P value is <0.05.

In another study, the mean VAS score was 2.48 in the methylene blue group on day 1, which reduced to 2.40 by day 5, while 7.92 and 3.84 in controls on day 1 and 5, respectively. However, pain scores fell significantly in both groups (p<0.01), for the MB group, the VAS scores on post-operative 4 and 5 days were less as compared to the (P<0.05) control group.

Table 2: Distribution of cases among groups as per VAS Score (n = 81)

VAS Score	Groups			Total
	Group A	Group B	Group C	
Less than 5	27	11	12	50
	100 %	40.74 %	44.44 %	61.72 %
5 and more than 5	00	16	15	31
	00 %	59.25 %	55.55 %	38.21 %
Total	27	27	27	81
	100%	100%	100%	100%

The VAS score estimated no such variations (P>0.05) exist in the two groups after 6-14 days post-operation. The Control group uses extra analgesic medications more than the MB group (P<0.05) between 1-5 post-operative days. Thus, to summarize, injection of methylene blue near the incision effectively alleviated the pain in cases undergoing surgery for peri-anal diseases. This helped achieve a long-acting analgesic impact with few side effects or complications and is thus recommended.

Discussion

Surgery for peri-anal diseases is considered essential for acute decomposing abscesses for fistula and preventing the spread of infection. Peri-anal surgery is also linked with considerable post-operative discomfort and pain that simple analgesics do not generally relieve. Nitric oxide synthase and soluble guanylate cyclase are both inhibited by the non-toxic agent methylene blue. Nitric Oxide regulates physical functions like analgesia and pain with the activation of soluble guanylate cyclase for increasing the intra-cellular guanosine monophosphate. As an oxidizing reducing agent, Methylene blue shows a strong affinity to the nerve tissues when locally applied, which can block nerve fibres electric conductivity directly, affecting impulse conductivity and neural excitability. Some of the latest research has concluded that MB may block the peripheral nerve fibres at the incision.

The application of highly concentrated topical MB during anorectal surgery stains the tip and nerve fibres and momentarily impairs their function. Methylene Blue has reportedly been used for analgesia during anorectal surgery, to treat neuritis, and to lessen pruritus. In a present hospital-based randomized control trial, we aimed to compare the effectiveness of MB as a local analgesic after fistulectomy with those receiving conventional analgesics.

Our study included a total of 81 cases undergoing peri-anal surgery. All the patients operated on for peri-anal surgery were divided into 3 groups, A, B and C, in which Group A (27 patients) were given methylene blue + ropivacaine subcutaneously around the incision. Group B (27 patients) were given only ropivacaine subcutaneously around the incision, and Group C (27 patients) were given routine post-operative analgesics.

Reviewing other studies, the study included 50 cases undergoing surgery for fistulectomy. Of these 50 cases, 25 patients were injected with methylene blue intraoperatively, while 25 were injected with distilled water and conventional analgesics for pain relief [13]. In the study by **Tan k et al.** [16]. The median post-

operative pain score was less than 2.5 for the first four days and 0 on the fifth day. **Fransiska D et al [1]**. Conducted a systemic review to determine methylene blue's efficacy as an analgesic in anal surgeries.

Table 3: Statistical comparison among study groups (Post Hoc Test) (n = 81)

Groups		Mean Difference	Standard Error	Significant	95% Confidence Interval for Mean	
					Lower Bound	Upper Bound
Group A	Group B	0.815	4.552	0.858	-8.25	9.88
	Group C	-14.593	4.552	0.02	-23.66	- 5.53
Group B	Group A	-0.815	4.552	0.858	-9.88	8.25
	Group C	- 15.407	4.552	0.001	-24.47	- 6.34
Group C	Group A	14.593	4.552	0.002	5.53	23.66
	Group B	15.407	4.552	0.001	6.34	24.47

Table 4: Multiple Comparison Table

Study Groups	P Value	Significant
Group A vs Group B	0.858	No
Group A vs Group C	0.02	Yes
Group B vs Group C	0.001	Yes

Table 5: Table Mean

Group A	Group B	Group C
40.67	39.85	55.26

The study concluded that methylene blue effectively reduces the VAS (pain degree) with strong evidence of 2 levels [1]. Thus, to summarize, injection of methylene blue near the incision effectively alleviated the pain in cases undergoing surgery for peri-anal diseases. The technique had minimal problems or unfavourable reactions, although it did have a long-lasting analgesic effect and is thus recommended.

Conclusion

The present study concludes that injection of methylene blue can effectively alleviate pain after peri-anal surgeries. With very few complications and minimal side effects, the application may provide a long-lasting analgesic effect. It may lead to shorter hospital stays and decreased analgesic consumption, among the other advantages of methylene blue injection. The present study thus recommends using methylene blue as a local analgesic after peri-anal surgeries in all cases. However, a further large-scale multi-centric trial is required to validate the outcomes of the study further

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