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RESEARCH ARTICLE

A RANDOMIZED CONTROLLED TRIAL BETWEEN LOCAL INJECTION OF METHYLENE BLUE VERSUS NORMAL SALINE FOR MANAGEMENT OF PAIN IN POST HEMORRHOIDECTOMY PATIENTS- A COMPARATIVE STUDY

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Abstract

Background: Hemorrhoids have been an ailment to mankind since time immemorial. Treatment of hemorrhoids has evolved since but the constant complaint of the patient with any mode of surgical treatment is the post operative pain. Different analgesics have been tried locally and systemically to relieve the pain. Methylene blue is a well known drug for treating methemoglobinemia and also a dye used for various surgical procedures. Methylene blue is also has analgesic property and is being used in this study to minimize the post operative pain after Milligan Morgan hemorrhoidectomy.

Aims And Objectives: To compare local injection of methylene blue versus normal saline in the post operative pain management along with length of hospital stay in patients undergoing conventional Milligan Morgan hemorrhoidectomy.

Methodology: 51 cases where randomized into 2 groups by systematic randomization; 26 cases were allotted study group who received 4 ml 1% methylene blue and 16 ml 0.5% bupivacaine subcutaneously around the hemorrhoid on table before the procedure and 25 patients were allotted control group will receive 16 ml 0.5% bupivacaine and 4 ml saline without methylene blue similarly and regular Milligan Morgan hemorrhoidectomy is performed after. Each hemorrhoidal pile received 4ml of the titrated mixture. Post operatively pain is assessed by the visual analogue scale and the amount of analgesics required by the patient up to 2 weeks is calculated.

Results: The post operative pain assessed on POD-3 and POD-7 between the two groups was found to be significant with a p value of 0.0001 and 0.0002 respectively with significant. The mean length of hospital stay for study group was 2.269 days and in the control group was 3days with a significant p value of 0.0120. 1 patient in study group needed additional analgesics and 8 patients in control group needed additional analgesics. 2 patients in each of the study and control groups developed acute retention of urine out of the which 1 patient developed greenish discoloration of urine which resolved spontaneously.

Conclusion: Methylene blue acts as a good analgesic which reduces the

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morbidity for the patient and hence the patient can resume daily activities faster.

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Introduction:-

Hemorrhoids are one of the commonest and oldest ailments to afflict mankind with references in ancient texts, dating back to Babylon, Egyptian, Greek and the Hebrew cultures. Although few have died of hemorrhoidal disease, many people wished they had, particularly after therapy because pain is the most frequent complication and the most feared sequela of the procedure from the patient's perspective. A variety of analgesic regimens have been recommended, usually consisting of oral and parenteral analgesics and still is a challenge and research continues in this area. Perianalintradermal injection of methylene blue has shown to ablate nerve endings and bring about temporary pain relief after hemorrhoidectomy as early as the second post operative day[28b].

Hemorrhoids is a term derived from Greek word "hemorrhoid" meaning flow of blood ("Haima" means "Blood" and Rhoos means "Flow"). The word Piles is derived from Latin term "Pila" meaning a pill or a Ball. To be accurate, we should call the disease as 'piles'.

Moolvyadhi is derived as Mool means Anus and Vyadhi for disease and in Sanskrit called "arshashoola", which means "pain from pricking like needles."[4] Classically Hemorrhoids occur at 3 O' clock, 7 O' clock and 11 O' clock position with patient in lithotomy position. Men seem to be affected roughly twice as frequently as women.[5] Hemorrhoids are grossly divided into internal and external hemorrhoids, and the internal variety is further sub divided into four stages, based principally on the degree of the prolapse.

Multiple factors have been claimed to be the etiologies of hemorrhoidal development, including constipation and prolonged straining. The abnormal dilatation and distortion of the vascular channel, together with destructive changes in the supporting connective tissue within the anal cushions, is a paramount finding in hemorrhoidal disease.

In most instances, hemorrhoids are treated conservatively, using many methods such as lifestyle modification, fibre supplementation, suppository delivered anti-inflammatory drugs and administration of venotonic drugs. Non-operative approaches include sclerotherapy and preferably, rubber band ligation. Surgical intervention is indicated when non operative approaches have failed or complications have occurred.

The Milligan Morgan hemorrhoidectomy was originally described in 1937, and its efficacy has been subsequently documented in many series. The technique includes resection of the entire enlarged hemorrhoid complex, ligation of pedicle and preservation of the intervening anoderm. The distal anoderm and external skin is left open to minimize the risk of infection. This technique is safe and effective. However, the fact that the external wounds are left open can be a cause for considerable discomfort and prolonged morbidity. Open hemorrhoidectomy is associated with considerable post operative pain. This leads to patient discomfort, prolonged hospital stay and increased costs. The causes of post hemorrhoidectomy pain ismultifactorial.

Methylene blue has been widely used as a biological dye. However, it also possesses disinfective property and is an inhibitor of soluble guanylatecyclase. It has also been found to reduce cyclo-oxygenase products which are associated with inflammation and pain pathway. It is found that patients with perianal fistula in whom methylene blue was used to delineate the tracks had less postoperative pain. Intradermalmethylene blue has been used successfully in intractable pruritusani. The mechanism of action of methylene blue is likely to be related to the destruction of dermal nerve endings. The administration of subcutaneous methylene blue will thus reduce postoperative pain during the initial period after surgery.

Recently other methods of hemorrhoidectomy like Stapled hemorrhoidectomy, Laser hemorrhoidectomy, Doppler-guided hemorrhoidectomy are gaining popularity. The type of hemorrhoidectomy is to be tailored to the patients.

Aims And Objectives Of The Study:-

1. To assess the efficacy of methylene blue in management of post operative pain after hemorrhoidectomy.
2. To compare local injection of methylene blue versus normal saline in the post operative pain management along with length of hospital stay in patients undergoing conventional Milligan Morgan hemorrhoidectomy.

Materials and Methods:-

Source Of Data and Materials:

Patients undergoing Milligan Morgan hemorrhoidectomy at Karnataka Institute of Medical Sciences, Hubli during the study period from November 2019 to June 2021. The data for this include the following variables

1. Post operative pain (assessed by visual analogue score on POD- 0,3,7,14 days)
2. Intraoperative bleeding (in ml, assessed by number of mops soaked)
3. Length of hospital stay.

Method Of Collection of Data:

A. Study design: Randomized control study

B. Study period: Eighteen months (December 2019 to June 2021)

C. Place of study: Department of General Surgery, KIMS, HUBLI-.580022

D. Sample Size: Based on prevalence of the disease (p=1.23%) and input at our hospital with 95% Confidence Interval with 3% of permissible error (l=0.03) and 10% attrition rates, Sample size is calculated to be 47 rounded off to 50, which will be divided into study group and test group by standard randomization technique.

Sample size $\sqrt{n} = 1.96 \times \sqrt{pq} \div l$

$q = 1-p$

However 52 patients undergoing Milligan Morgan hemorrhoidectomy were enrolled in the study with 26 allotted to study group and 25 allotted to control group where 1 patient in control group was lost for follow up.

Statistical Tests:

The statistical analysis for the study has been conducted using the following formula:

1. Mean.
2. Standard deviation.
3. Chi- square test.
4. Unpaired t test.
5. Fisher's test.
6. Level of significance by 'p' value

Inclusion Criteria

1. Patients willing to give written informed consent.
2. Patients with only grade III and/or grade IV hemorrhoids and grade II hemorrhoids which could not be managed conservatively.
3. Patients of all age groups are included.
4. Patients undergoing only open Milligan Morgan hemorrhoidectomy.

Exclusion Criteria

1. Patients with other anal pathologies like fissure in ano, fistula in ano, etc apart from grade III and IV hemorrhoids.
2. Pregnant and lactating women.
3. Patients who have had allergic reactions to methylene blue previously or any other drug used in the study like tramadol tablet.
4. Patients who are on SSRIs.
5. Acute thrombosed hemorrhoids.

Methodology:-

1. The patient fulfilling the inclusion criteria will be enrolled for the study after obtaining informed consent.
2. All patients meeting the criteria will undergo investigations including complete blood count, coagulation profile, liver function test, renal function test, serum electrolytes, serology,proctoscopy will be done as per general protocol.

3. After admission, patient details such as name, age, sex, IP number, date of admission, date of surgery, along with relevant history, clinical examination will be recorded using standard proforma.
4. Patients undergoing open hemorrhoidectomy are divided into group A-the study group and group B-control group randomly using systematic randomization.
5. 4 ml 1% methylene blue and 16 ml 0.5% bupivacaine is administered to study group patients subcutaneously around the hemorrhoid on table before the procedure and control group will receive 16 ml 0.5% bupivacaine and 4 ml saline without methylene blue similarly and regular Milligan Morgan hemorrhoidectomy is performed after. Each hemorrhoidal pile will receive 4ml of the titrated mixture. Post operatively pain is assessed by the visual analogue scale and the amount of analgesics required by the patient up to 2 weeks is calculated.

Surgical Methods:

Methylene Blue Group:

1. The patient was counselled to take liquid diet 24hrs before surgery, and patient was given enema 2hrs before surgery for bowel preparation. Patient was induced under saddle block/spinal anesthesia and put in lithotomy position.
2. Digital rectal examination was performed. The anal canal was lubricated with 2% lignocaine jelly and proctoscopy was performed using proctoscope to assess the grade of the hemorrhoid and to rule out other lesions.
3. The mixture of methylene blue with 0.5% bupivacaine in the ratio 1:4 i.e., 4ml of methylene blue with 16ml of bupivacaine is loaded into a syringe. The hemorrhoidal tissue is held using artery forceps and the mixture is injected in the subcutaneous plane of about 4ml/ pile taking care that the mixture does not enter any blood vessel directly.
4. After injecting the mixture to the hemorrhoidal tissue, Milligan Morgan hemorrhoidectomy is continued after 2 min.
5. Traction is applied to the external component of the pile using an artery forceps to reveal the internal component which is again held nearer to the pedicle using artery forceps and traction is applied.
6. With scissors or cutting diathermy, a V-shaped cut is made through the skin and those fibers inserting into it around the skin, holding the artery forceps. Traction, combined with careful dissection, will expose the lower border of the internal sphincter.
7. The dissection proceeds up the anal canal, with the sides of the mucosal dissection converging towards the pile apex and with the internal sphincter visible and separate from the dissected pile.
8. A transfixion ligature of strong Vicryl is applied to the pedicle at this level, the pile is excised well distal to the ligature and, after ensuring hemostasis, the ligature is cut long.
9. Each hemorrhoid is dealt with in this manner, taking care to leave mucocutaneous bridges.
10. The raw area is left as it is without suturing and is packed with betadine and lignocaine pack and dressing is done[19].
11. Patient is then followed up for 14 days.
12. Patients were given intravenous paracetamol 1gram, twice daily for 2 days and then tablet diclofenac 50mg and paracetamol 500mg, tiwce daily for the next 3 days for pain. Any additramional requirement of analgesics for pain was documented.

Saline Group:

The patient is prepared similarly, and a mixture of 4ml of normal saline with 16ml of 0.5% Bupivacaine in the ratio 1:4 is made and injected into the subcutaneous tissue and similar to the Methylene blue group, Milligan Morgan hemorrhoidectomy is performed. The control group patients also received similar analgesics as the study group and were followed up for 14 days.

Observation andResults:-

Age Distribution

Age Groups	Case (Number)	Percentage	Control (Number)	Percentage	Total (Number)	Percentage
21-30	2	7.6	2	8	4	7.8
31-40	7	26.9	6	24	13	25.4
41-50	10	38.4	5	20	15	29.4
51-60	6	23	6	24	12	23.5
61-70	0	0	4	16	4	7.8

71-80	1	3.8	2	8	3	5.8
Total	26	100	25	100	51	100

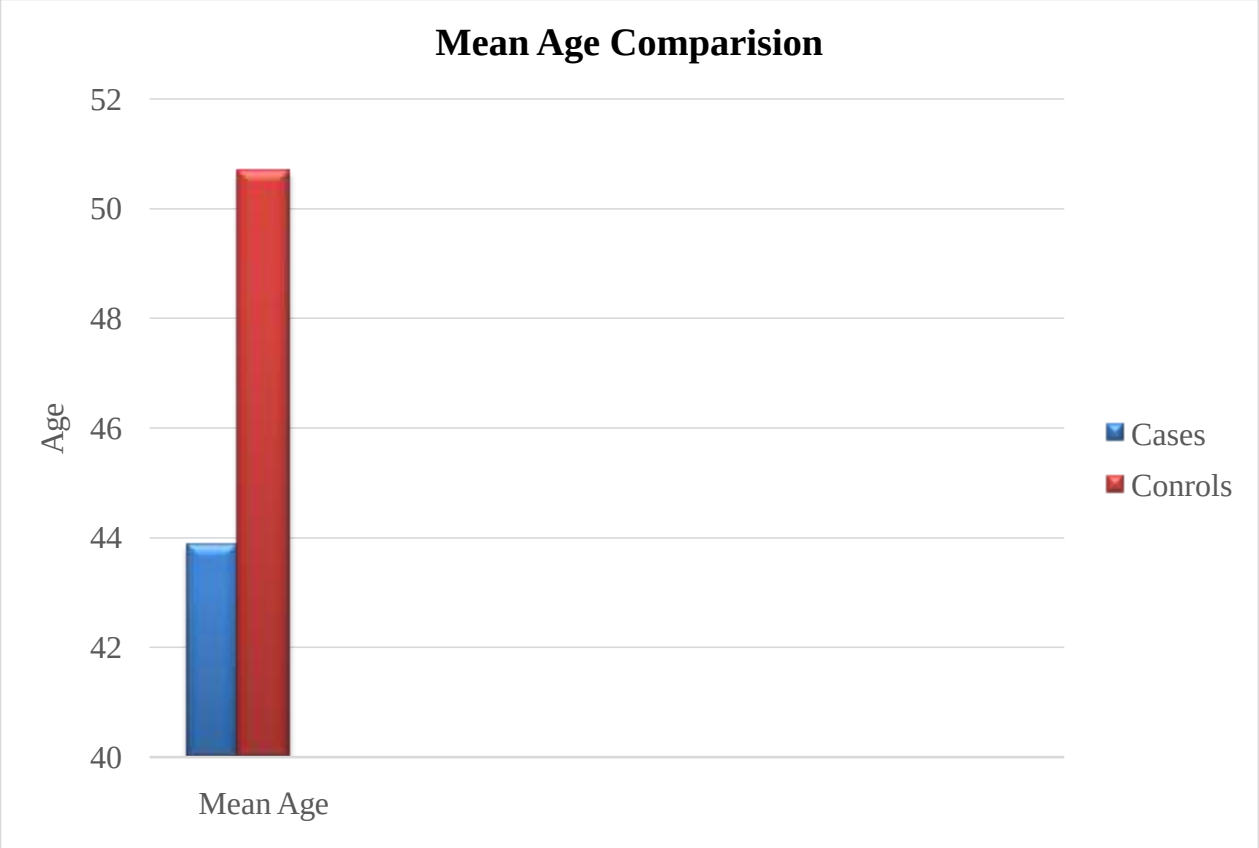
Table No 1:- Comparison of two groups (Methylene blue and Saline) by age groups.

Unpaired T test, p – 0.0580

	Methylene blue group (Case)		**Saline (Control)**	
Age (years)	**Mean**	**SD**	**Mean**	**SD**
	43.88	10.6	50.68	14.21

Table No 2:- Mean age comparison between the two groups.

There was no statistically significant difference in the age between two groups.



Graph 1:- Mean age comparison between each group.

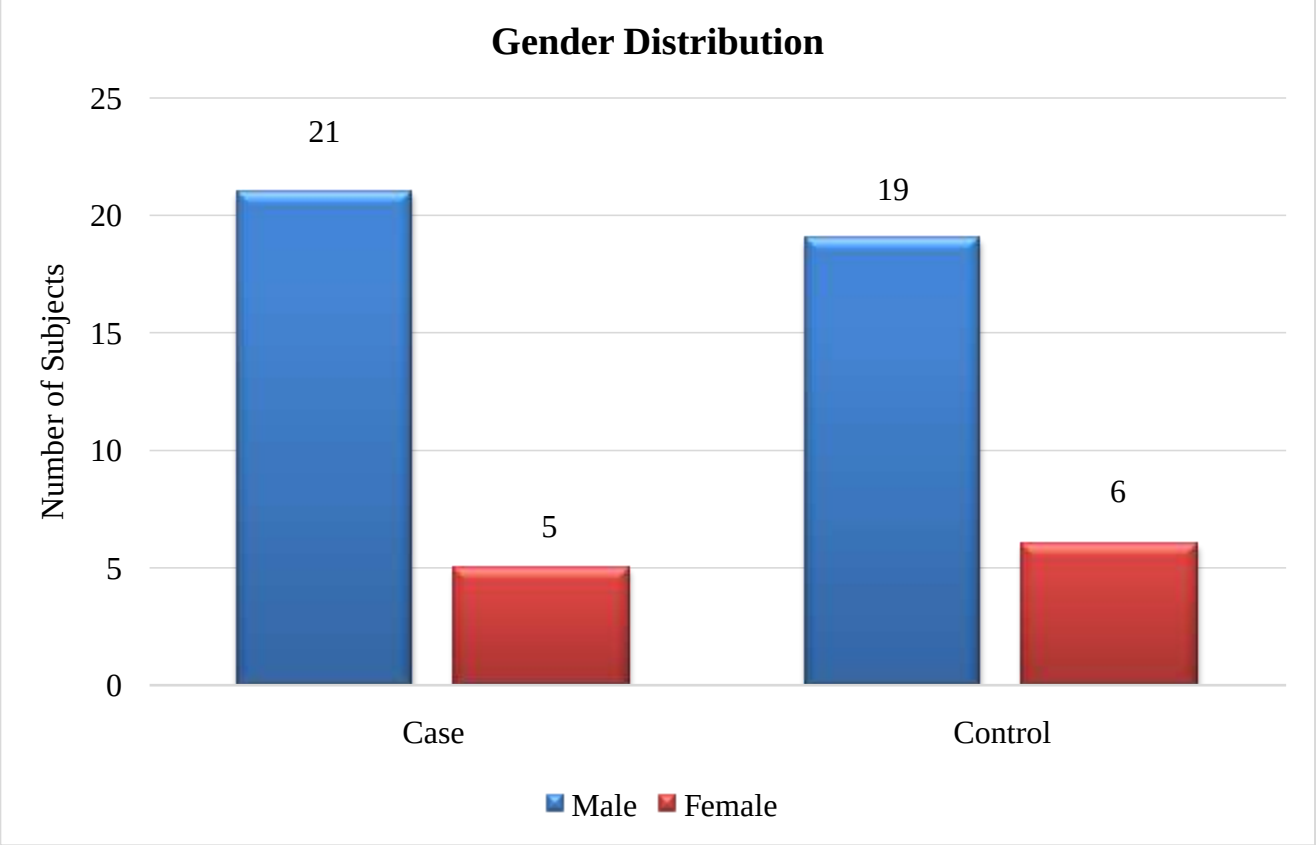
Gender Distribution

		Methylene blue group (Case)		**Saline Group (Control)**	
		Count	**Percentage**	**Count**	**Percentage**
Gender	**Female**	4	19.23	6	24
	Male	22	80.76	19	19

Table No.3:- Gender Distribution between two groups.

Fisher's exact test; p value – 0.743

There was no statistically significant difference in the gender between two groups.



Graph No.2:- Gender Distribution between two groups.

Grade Of Hemorrhoid

		Methylene blue group (Case)		Saline Group (Control)	
		Count	**Percentage**	**Count**	**Percentage**
Grades	**II**	3	11.53	5	20
	III	15	57.69	15	60
	IV	8	30.76	5	20

Table No.4:- Grades of Hemorrhoid distribution in two groups.

Chi-square test: $\chi 2 = 1.173$, df = 2, p = 0.556

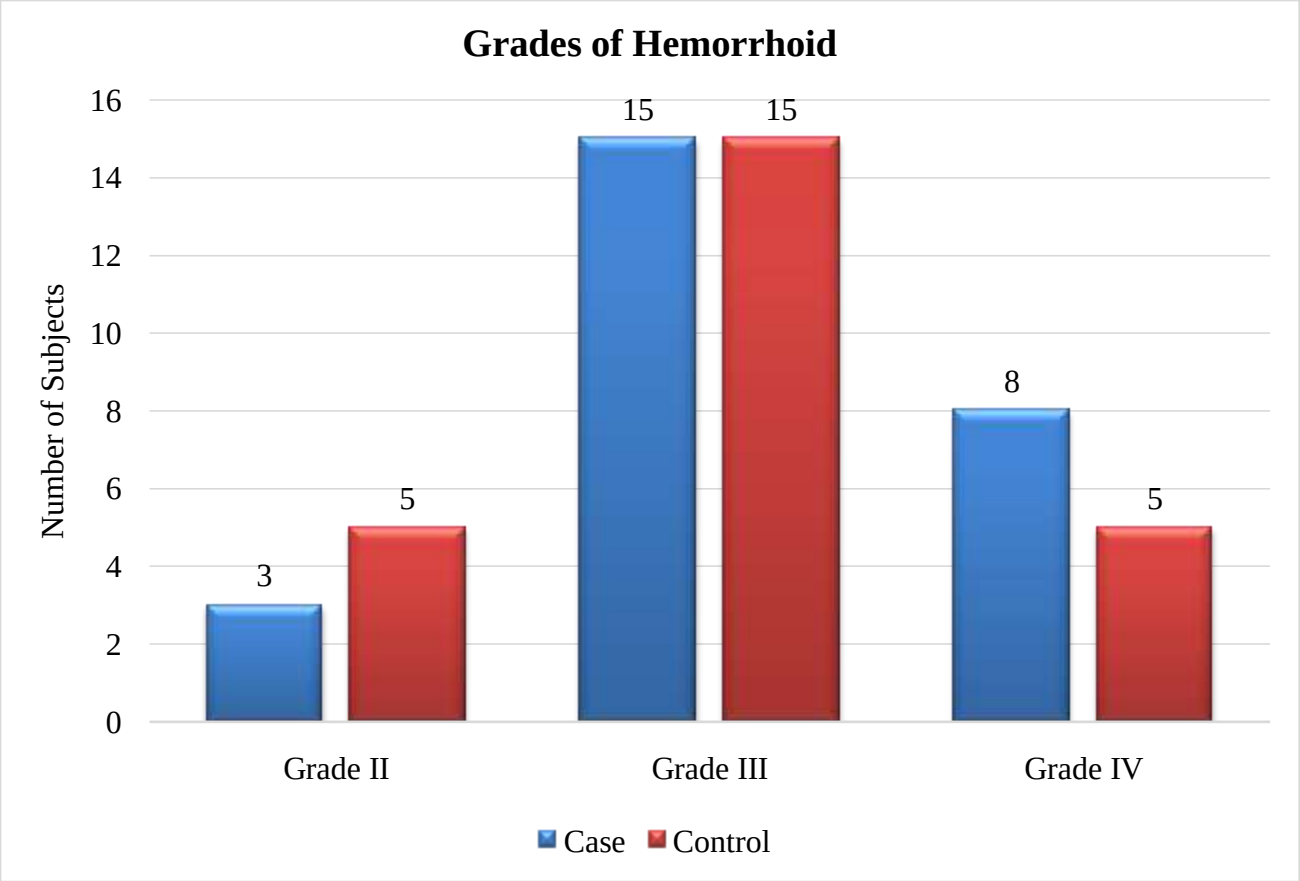
There is no statistically significant difference between the grades of hemorrhoid distribution between the two groups.

Post Operative Pain AtPOD - 3

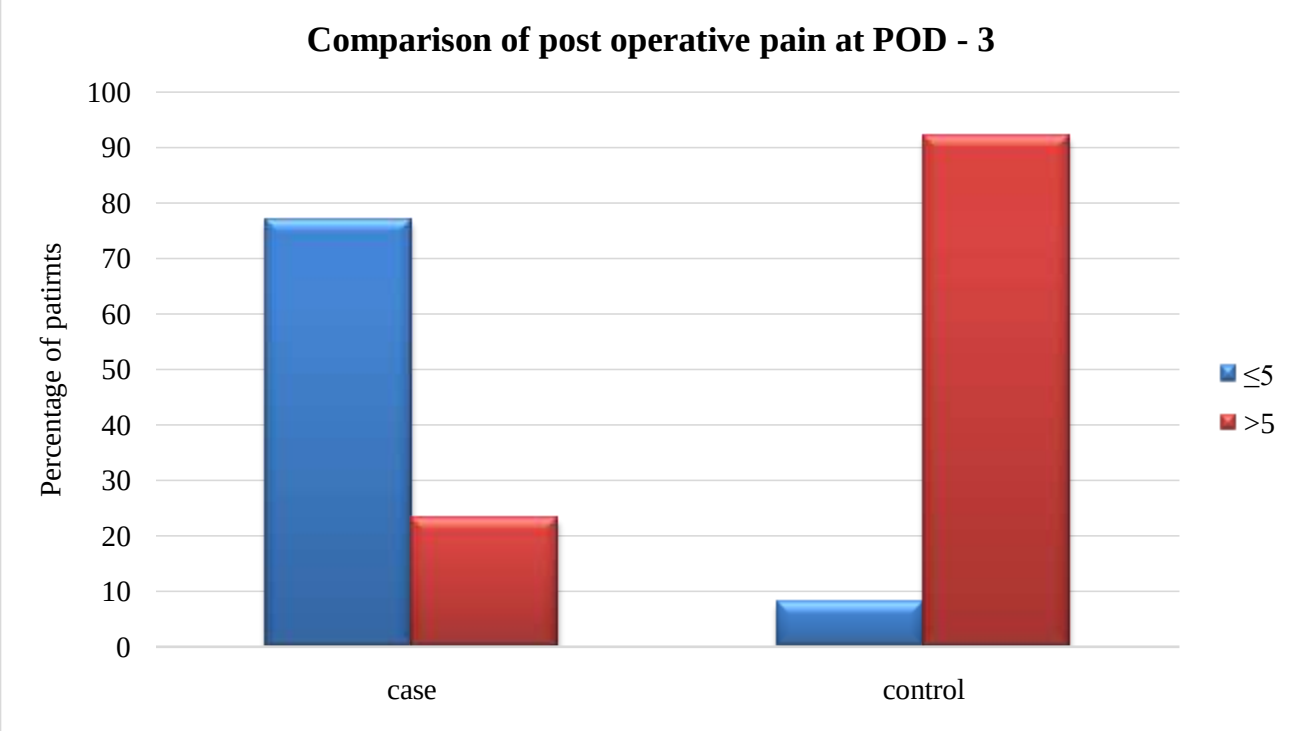
VAS	**Methylene Blue group**	**Percentage**	**Saline Group**	**Percentage**
≤ 5	20	76.9	2	8
>5	6	23.07	23	92

Table No.5:- Post-operative Pain comparison between two groups on POD 3.

Chi Square= 24.6827 P=0.0001*



Graph No.3:- Grades of Hemorrhoid distribution in two groups.



Graph No.4:- Post-op Pain comparison between two groups on POD 3.

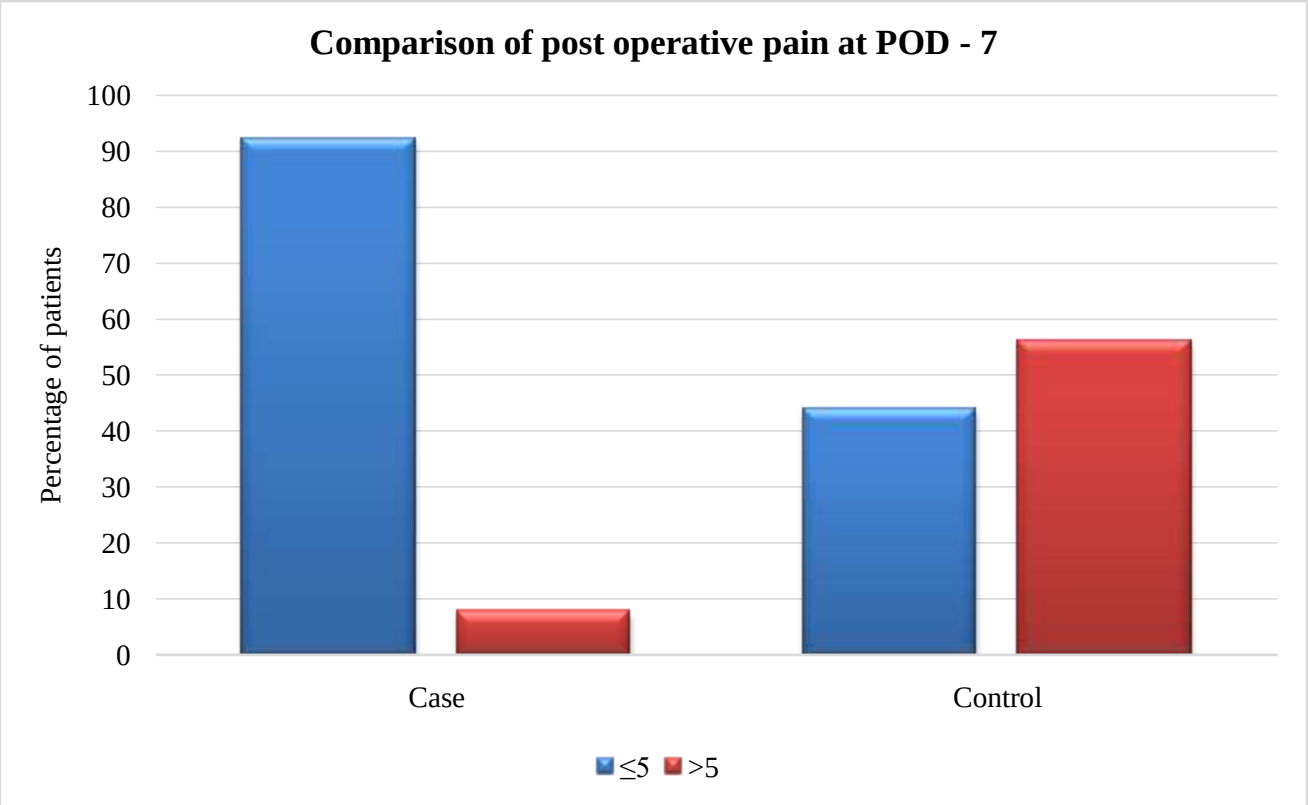
There was a statistically significant difference in post-op pain comparison between two groups on post-op day 3.

Post Operative Pain AtPOD - 7

VAS	Methylene Group	Percentage	Saline Group	Percentage
≤5	24	92.3	11	44
>5	2	7.6	14	56

Table No.6:- Post-op Pain comparison between two groups on POD 7.

Chi- Square= 13.8143, P=0.0002*



Graph No.5:- Post-op Pain comparison between two groups on POD 7.

There was a statistically significant difference in post-op pain comparison between two groups on post-op day 7.

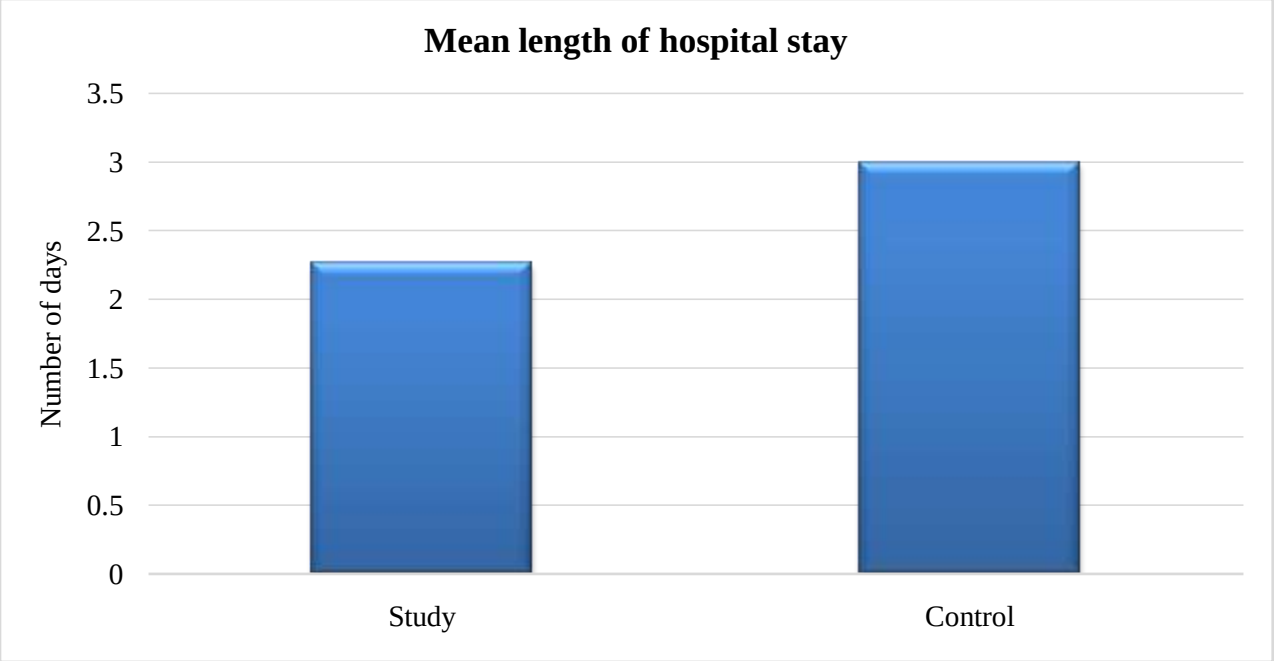
Length Of Hospital Stay

	Methylene Blue group (Case)		Saline Group (Control)	
Hospital stay (days)	Mean	SD	Mean	SD
	2.269	1.041	3.00	0.97

Table No.7:- Hospital Stay comparison between two groups.

Un-paired t test p=0.0120*

The mean hospital stay in case group was lesser when compared to the control group and this difference was statistically significant.



Graph No.6:- Mean Hospital Stay comparison between two groups.

Requirement Of Additional Analgesics

	Methylene Blue Group (Case)		**Saline Group (Control)**	
	Count	**Percentage**	**Count**	**Percentage**
Yes	1	3.8	8	32
No	25	96.2	17	68

Table No.8:- Requirement of additional analgesics in two groups.

Fisher's exact test; p value – 0.019*

The additional analgesic requirement in case group was significantly less when compared to the control group

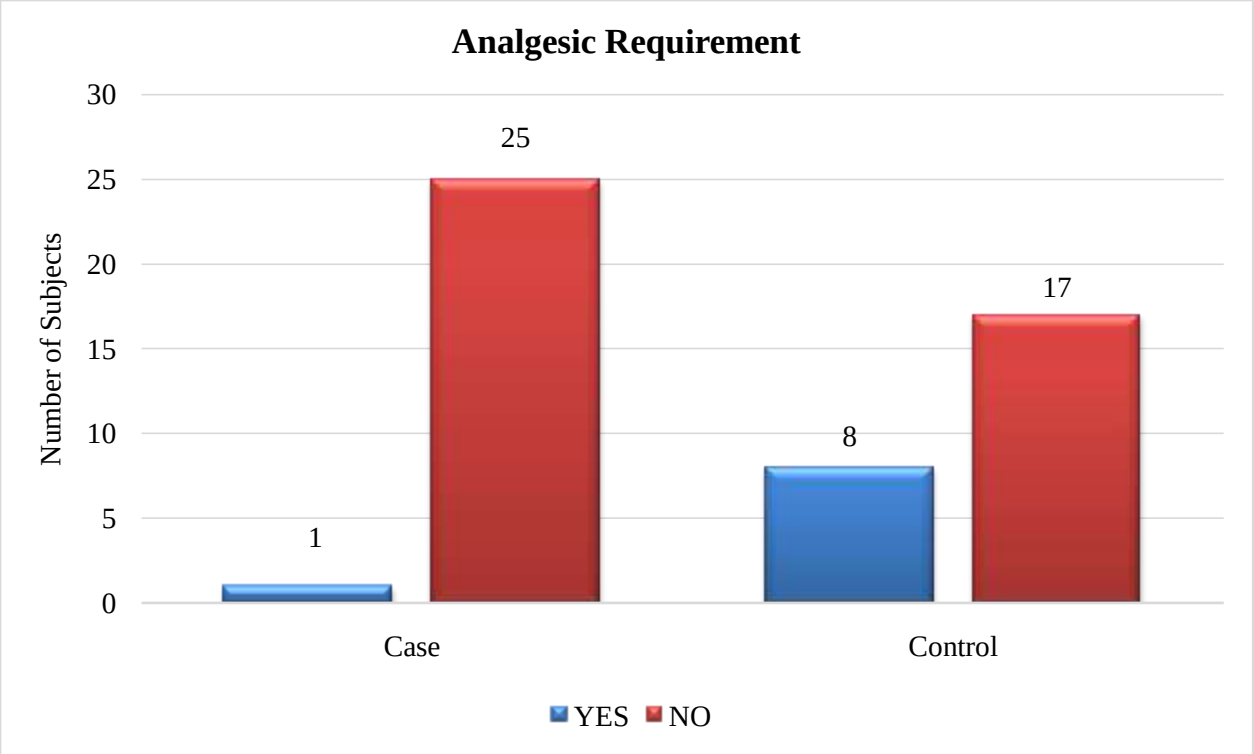
Post Operative Complications

Post op complications	**Methylene blue Group (Case)**		**Saline Group (Control)**	
	Count	**Percentage**	**Count**	**Percentage**
Present	2	7.69	2	8
Not Present	24	92.31	23	92

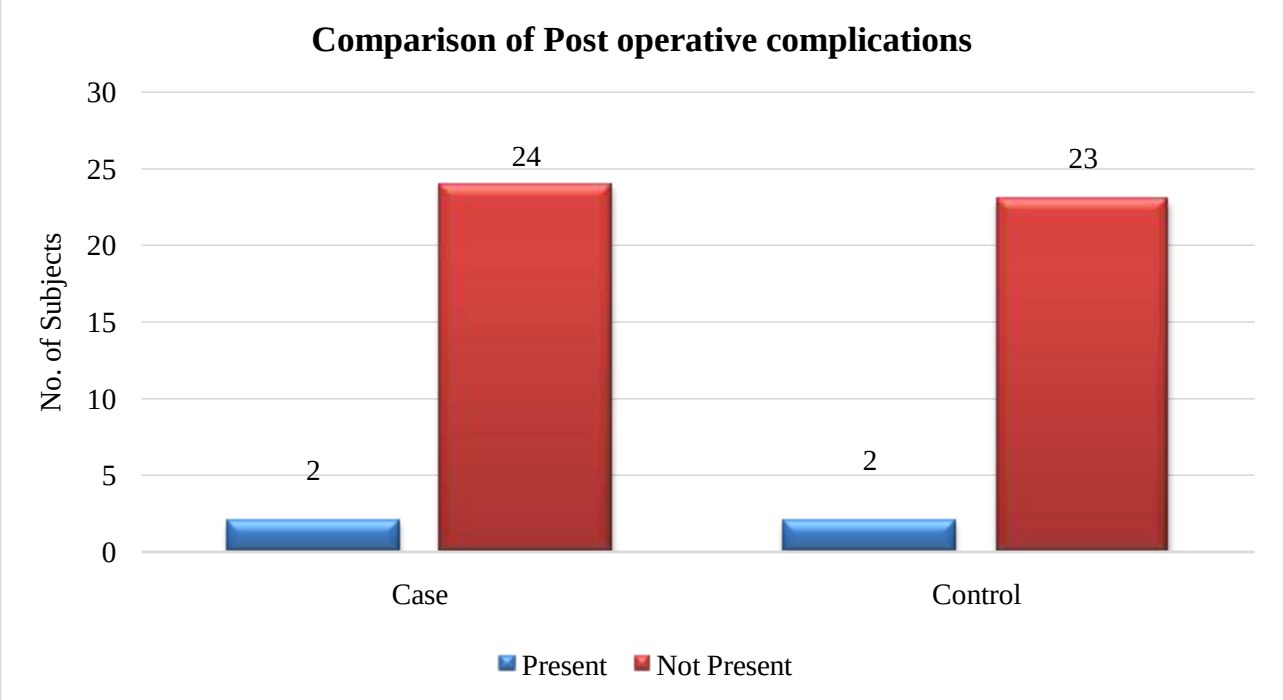
Table No.9:- Comparison of Post-Op Complications between two groups.

Fisher's exact test; p value – >0.999*

The incidence of post of complication in both the groups were not statistically different. Complications such as skin necrosis and skin infections, were not be found in either of the group, where as in methylene group 2 patients had post op urinary retention out of which one patient's urine turned green in color which became normal by POD 3. Even in control group 2 patients had urinary retention.



Graph No.7:- Requirement of additional analgesics in two groups.



Graph. No. 8:- Comparison of post operative complications.

Discussion:-

Pain is an inevitable post operative complication seen after hemorrhoidectomy. It is very troublesome to the patient. Even though different modalities of treatment of hemorrhoids have varying degrees of post operative pain, Milligan Morgan hemorrhoidectomy is still widely practiced. Patients want relief from the hemorrhoidal pain after surgery

which is most often not the case. This study aims at assessing the analgesic effects of methylene blue in reducing the post operative pain along with reduction in intraoperative pain and length of hospital stay.

In this study, the study group received methylene blue with bupivacaine and control group was given normal saline with bupivacaine. In this study, there was significant reduction in the post operative pain, length of hospital stay and reduction in intra operative bleeding in the study group when compared with the control group. Complications like acute retention of urine was noted in both groups with no significance. 1 patient had post op greenish discoloration of urine which resolved spontaneously without morbidity to the patient.

Xiang and Feng and Sim and Tan focused on hemorrhoid. In the study of Xiang and Feng, subcutaneous MB and ropivacaine solution was treated as group of therapy and conventional therapy (consisting of tramadol 100 mg orally twice daily for five days) was treated as control group[28]. Sim and Tan applied intradermal injection of MB and Marcain solution in the treatment group, compared to intradermal injection of Marcain and saline solution in control group[28]. Both of the studies assessed degree of VAS reduction after hemorrhoidectomy that was observed for 14-day period on 151 samples (Xiang and Feng) and 67 samples (Sim and Tan).

The characteristics of age, sex, degree of hemorrhoids in this study is not significant between the two groups (p=0.05; p=0.743; p=0.55). The characteristics of age, sex, degree of hemorrhoids, and the number of incisions in Xiang and Feng study were not significantly different. In Sim and Tan's study, the values of patients' age, genders were 0.281, 0.112. Based on these data we can conclude that there is no statistically significant difference in demographic and clinical characteristics in the study of Sim and Tan.

The present study shows a significant reduction in the pain scores in patients randomized to perianalmethylene blue injection in the first few days after surgery. 1 patient in the methylene blue group even reported pain scores of 0, whereas none in the saline group reported a pain score of 0 during the first 3 days with a p value of <0.0001. At 1 week, most patients in both groups reported much lower pain scores but still there was significant reduction of pain in the methylene group with p value <0.0001. However even though there was reduced pain after 14 days of surgery in the methylene blue group, it was not statistically significant when compared to the saline group.

This is similar to the Xiang and Feng study with p=<0.01 from the POD 1-4 but no significant reduction of pain from 6-14th day.Sim and Tan study had a p value of 0.024 from POD 1-3 which was significant with no significance from POD 4-14 days.

The duration of hospital stay was markedly reduced in the methylene blue group as there was significant post op analgesia with p value of 0.0120 where as in Sim and Tan study the duration of hospital stay was found to be similar between the two groups.

The evidence of post op complications like urinary retention, secondary hemorrhage did not have significant difference in this study. In Sim and Tan study also, complications like acute urinary retention, secondary bleeding, pruritus, and temporary incontinence were not significant between the two groups.

In our study, 1 patient had a complication of greenish discoloration of urine which resolved by POD-3 with no significant derangement of Renal function test and morbidity to the patient which was not observed in any other study.

Conclusion:-

In conclusion, using methylene blue for hemorrhoidectomy is very effective in reducing the post op pain. It not only reduces pain, but also reduces the length of hospital stay and helps the patient to resume daily activities earlier.

Hence it is effective once the operating surgeon gets used to the blue staining of the hemorrhoidal tissue because of the dye. Methylene blue is a known antiseptic and hence will reduce the post operative chances of wound infection.

Although 1 patient had greenish discoloration of urine it resolved with no significant morbidity to the patient. However, more studies with larger cohorts are needed to evaluate the efficacy and safety of methylene blue.

Summary

1. The aim of this study was to evaluate the efficacy of methylene blue in management of post operative pain after hemorrhoidectomy.
2. The objective of this study was to compare local injection of methylene blue versus normal saline in the post operative pain management, intraoperative bleeding and length of hospital stay in patients undergoing conventional Milligan Morgan hemorrhoidectomy.
3. This is a randomized clinical study.
4. 26 patients were allotted methylene blue group and 26 patients were allotted the saline group where 1 patient was lost for follow up.
5. Totally 41 were males 22 in study group and 19 in control group and 10 were females in which 4 were in the study group and 6 in control group.
6. Among the study group, 2 patients had post op acute retention of urine and one of whom had change in color of urine to green which settled by POD 3; in the control group 2 patients had post operative retention of urine. The catheter was reduced by maximum POD-3.

Conclusion of the Study Being:-

1. Methylene blue acts as a local analgesic which reduces post operative pain after hemorrhoidectomy.
2. Due to the reduction in the pain, morbidity reduces and patient can go back to work early.
3. Methylene blue is also an antiseptic, hence postoperative wound infection rates are less.
4. The perianal skin pigmentation stays for 4-6 weeks, which was acceptable to all our patients.
5. Methylene blue can also be used for other anal surgeries like fistula in ano, anal fissures, pruritisani for his analgesic properties.
6. This conclusion is in par with the findings of the conventional studies using methylene blue for post op analgesia after hemorrhoidectomy.

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