



Outcomes of Vancomycin Enema vs Normal Saline Enema in Patients with Hirschsprung's Associated Enterocolitis

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ABSTRACT

OBJECTIVE: This research was designed to compare the outcomes between vancomycin enema and normal saline enema in the treatment of HAEC in terms of full remission of symptoms of HAEC and length of hospital stay.

METHODOLOGY: This randomized controlled trial was carried out from March 2020 to March 2021 in the Department of Pediatric Surgery Lady Reading Hospital Peshawar. A total of 40 patients were randomly assigned in two groups; A (vancomycin enema) and B (normal saline enema), with 20 patients in each group. After the diagnosis was established, patients were randomly assigned to one of two groups by balloting method. SPSS 24 was used for data entry and analysis.

RESULTS: In our research, men outnumbered females. In both groups, the HAEC score decreased significantly after treatment from pre-treatment score (12.31 and 11.15) to post-treatment score (7.73 and 7.61) with significant P-values 0.013 & 0.015 respectively. The average hospital stay between vancomycin enema and normal saline enema group was 7.91 days as opposed to 6.89 days with a p-value (0.031). Overall, 7.33 ± 2.426 days were required for full remission of HAEC symptoms in the study. A p-value of 0.251 suggested that there was no difference between groups in terms of symptom relief.

CONCLUSION: We conclude that there is no difference between the normal saline and vancomycin enema in terms of symptom resolutions and hospital stay in patients of HAEC.

Keywords: Hirschsprung's disease, Enterocolitis, Vancomycin, Normal Saline Enema

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INTRODUCTION

Hirschsprung disease is a developmental abnormality defined by the lack of distal colonic ganglion cells (intestinal nerve cells), which causes a functional obstruction.¹ The majority of Hirschsprung disease cases are diagnosed in newborns. If a baby does not pass meconium within 24 to 48 hours after delivery, Hirschsprung disease should be suspected. Although contrast enema helps to establish the diagnosis, full-thickness rectal biopsies continue to be the gold standard. Once the diagnosis is established, the ultimate treatment consists of removing the aganglionic bowel and restoring continuity with the rectum, with or without a

temporary intestinal stoma. Hirschsprung-associated enterocolitis (HAEC) is a frequent and sometimes fatal consequence of Hirschsprung disease (HD). It may manifest either before or after the final HD surgery.² There is evidence that 15%-50% of people may develop enterocolitis before being diagnosed with Hirschsprung's disease. 20% to 50% of diagnosed patients may die because of it. Enterocolitis occurs in 2 to 33 percent of the times after surgical reconstruction, with a mortality rate of 0 to 30 percent.³ Abdominal distension, discomfort, explosive watery diarrhea, and fever, are clinical symptoms of HAEC.¹ Abdominal distension occurs in 99 percent of cases in children with HAEC, along with explosive diarrhea in 82 percent of cases, vomiting in 61 percent, fever in 40 percent

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of the cases, lethargy in 32 percent of cases, rectal bleeding in 6 % of cases, and shock in 6% of cases.⁴ Pastor created and validated a scoring system based on a Delphi analysis and developed standardized diagnostic criteria for HAEC.⁵ Plain abdomen radiographs are the most often used diagnostic imaging for HAEC. The "cutoff" mark in the recto sigmoid colon, dilated loops of intestine, air-fluid level, pneumatosis intestinalis, and "saw tooth" appearance with uneven intestinal lining are found on the x-ray. Other methods, such as colonoscopy or capsule endoscopy, have been documented to assess for HAEC in clinically stable patients when the diagnosis of HAEC is ambiguous.⁶

Therapeutic interventions for acute HAEC include prompt resuscitations, colonic decompression, and intravenous antibiotics. If the bowel cannot be adequately decompressed using washouts and antibiotic medication, the patient may need a laparotomy and the creation of a stoma near the transition zone.⁷ In the treatment of acute HAEC, intensive fluid resuscitation to rectify fluid and electrolyte imbalances is critical. In severe conditions, antibiotic treatment is initiated with broad-spectrum intravenous antibiotics. Clostridium difficile coverage must be assured, using a typical regimen consisting of intravenous metronidazole or intravenous vancomycin. Antibiotics can be administered through the stoma or rectum.⁸ Antibiotics are the basis of HAEC therapy owing to the colonization and toxin production of different organisms. Vancomycin is one of the most efficient medicines for eradicating Clostridium difficile infection.⁹ Vancomycin has been shown to be useful in the treatment of HAEC not just intravenously but also orally and rectally. The use of vancomycin for the treatment of HAEC through rectal and oral routes is widely recognized. Other researches assert that the benefit caused by a vancomycin enema is mostly due to the decompression effect that occurs when the medication is supplied by the rectal route. While intravenous (IV) antibiotics are administered, a further dose per rectal is not needed. As mechanical dilatation and fecal stasis may lead to HAEC, decompression of the gut using rectal irrigation should be the basis of conservative therapy for HAEC.¹⁰ Rectal irrigation with normal saline not only facilitates intestinal decompression but also eliminates harmful germs, hence relieving toxin release and symptoms.¹¹ Rectal decompression's significance in the treatment of enterocolitis has been recognized for many years since it not only relieves mechanical obstructions but also eliminates infective organisms such as Clostridium difficile.¹² In pediatric surgical facilities around the globe, vancomycin enema vs. regular saline enema is a common therapeutic choice for children with Hirschsprung's associated enterocolitis. In individuals with Hirschsprung's-associated enterocolitis, there is no randomized controlled trial comparing vancomycin enema

to regular saline enema. In this case, it is impossible to determine which enema method shows better clinical outcome for HAEC in children. We organized this trial because there is a significant need for research comparing vancomycin enema to standard saline enemas in individuals with Hirschsprung's related enterocolitis. The outcomes of this study will help health care practitioners to decide which enema to use.

METHODOLOGY

We conducted a randomized controlled trial from March 2020 to March 2021 after approval from ethical committee of forty patients presented in the pediatric surgical department of Lady Reading hospital Peshawar according to inclusion and exclusion criteria. All the diagnosed pre-operative and post-operative patients of Hirschsprung disease ranging in from 1 month to 14 years meeting the criteria were included in the study and randomly allocated into two groups, while those patients aging more than 14 years, hypersensitive to vancomycin, critically sick on arrival, and those with toxic megacolon in which diverting stoma has to be formed were excluded from study. The patients were randomly allocated in 2 groups by a lottery method with 20 patients in each group: Group A (vancomycin enema) and Group B (normal saline enema). Written informed consent was obtained from guardian's/parents of patients and was explained in detail. A thorough history was obtained, and a comprehensive clinical examination was conducted. Every post-drug administration event was recorded. In case of rapid deterioration of the patient, a diverting stoma was formed and it was considered a failure of therapy. The record of each patient was maintained using a pre-formed Performa. Patients of both groups were resuscitated by fluid resuscitation protocols to correct the fluid and electrolyte imbalance with proper fluid input and urine output monitoring. Rectal irrigation was done as per the respective group. In group A patients for per rectal vancomycin therapy, a solution of vancomycin was prepared at a dose of 20-30mg/kg in crystalloid (according to the weight-20ml/kg). This was repeated after every 8 hours. The method of administration was a retention enema. Normal Saline irrigation per rectally was done in patients with normal saline at 20mL/kg body weight at the interval of 8 hours. However, the volume was varied as per the need of the situation.

The children were assessed for enterocolitis and HAEC scoring was recorded in preformed Performa. Any adverse effects of the enema were also assessed. HAEC scoring was done after taking detailed history, physical examination and investigations. Enterocolitis was considered to be present, if the HAEC score is greater than 10. The patient was discharged when the patient was clinically free of symptoms and the total score was less than 10 for HAEC. Regular follow-up was advised to the attendants

	Score
History	
Diarrhoea with explosive stool	2
Diarrhoea with foul smelling stool	2
Diarrhoea with bloody stool	1
Previous history of enterocolitis	1
Physical Examination	
Explosive discharge of gas and stool on rectal examination	2
Distended abdomen	2
Decreased peripheral perfusion	1
Lethargy	1
Fever	1
Radiology	
Multiple air fluid levels	1
Dilated loops of bowel	1
Saw tooth appearance with irregular mucosal lining	1
Cut off sign in recto-sigmoid with absence of distal air	1
Pneumatosis	1
Laboratory	
Leukocytosis	1
Shift to left	1

Table 1: Showing Hirshsprung Associated Enterocolitis Score (Reference Pediatric surgery textbook Coran)

	Study Group	Mean	Std. Deviation	P value
Age (months)	Vancomycin enema	41.01	28.71799	0.132
	normal saline enema	43.61	34.49462	

Table 2: showing age distribution between the groups

Study Group	Pre Treatment score	Post Treatment score	P value
Vancomycin enema	12.31±1.18	7.73±0.676	0.013
normal saline enema	11.15±1.01	7.61±0.634	0.015

Table 3: showing HAEC scoring pre and post-treatment

in OPD. The collected data was entered and analyzed using SPSS 24.0 (Statistical product and service solution). Mean and standard deviation was calculated for quantitative variables such as age, weight, and days required for remission. Frequency and %ages were calculated for qualitative variables such as success of therapy and need for surgery. For both quantitative and qualitative characteristics, data were presented in tables and graphs. To evaluate the relationship between qualitative variables, the Chi-square test was performed. P-values less than 0.05 were deemed significant.

RESULTS

A Total of 40 patients with HAEC were received in the pediatric surgery department of lady reading hospital Peshawar. Out of 40 patients, there were 31 (80%) male and 9 (20%) female cases.

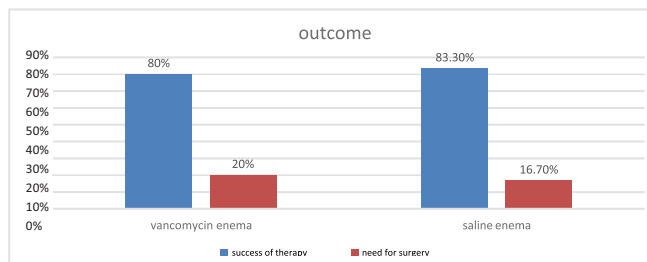


Table 4: showing success of therapy and outcome.

In vancomycin enema group there were 16(82.8%) male and 4(17.2%) female cases while in normal saline enema group there were 15(80%) male and 5(20%) female cases. The gender distribution is statistically same in 2 groups, with a p-value > "0.05". Out of 40 patients, 31 (80%) were pre-operative cases of Hirschsprung disease, whereas only 9 (20%) were post-operative cases after a pull-through procedure. A p-value of 0.001 indicated that there was a significant difference in the study population's Hirschsprung disease status. The mean hospital stay between Vancomycin enema and normal saline enema was 7.91 vs 6.89 days. The p-value (0.031) was statistically significant. At presentation, the mean HAEC score in the Vancomycin enema and normal saline enema was 12.31 and 11.15, respectively. After therapy, HAEC score decreased in both vancomycin and normal saline enema groups as shown in table 3 (7.73 and 7.61 respectively). There was a statistically significant improvement in the HAEC score in both vancomycin and normal saline enema groups after treatment (p-value 0.013 & 0.015) respectively [table 3]. The majority of patients in both groups were successfully treated with rectal washouts and conservative management. Only a total of 7 patients in both groups, symptoms of HAEC didn't settle and needed surgery table [4]. There was no significant (p-value=0.897) difference found as majority of the patients in both groups were treated successfully. Overall, 7.33±2.426 days were required for full remission of HAEC symptoms in the study. There was no significant (p-value= 0.251) difference found between groups in terms of symptom relief.

DISCUSSION

Hirschsprung's disease-associated enterocolitis (HAEC) continues to be the most lethal consequence in individuals with Hirschsprung disease (HD). Antibiotics and intensive fluid resuscitation are the mainstays of therapy. To decompress the gastrointestinal tract, a saline or vancomycin-based rectal enema is used. Numerous papers report oral vancomycin treatment for severe HAEC, but few studies have evaluated the use of vancomycin rectal irrigation. There is no previous research comparing normal saline irrigation with vancomycin irrigation to the best of our knowledge in our local set up. In our

study, males dominated females in the study population, with males accounting for 80% of the population and females accounting for 20%. This is in accordance with the literature, where many researchers have documented the predominance of the male population in the Hirschsprung disease. Demehri et al., in their study, stated that there was a 4:1 ratio between the male and female population.² Similarly, Estevão and colleagues also found male predominance with 75% incidence in the male population.⁸ Patients of Hirschsprung disease usually present in infant age to the 2 years of life. This variation depends upon the time of diagnosis and initiation of conservative therapy. Post operatively, HAEC can occur within 1-2 years of their pull-through procedure.¹ In our study, patients presented at 41 to 43 months. This delayed presentation can be attributed to the delayed diagnosis due to limited number of specialized centers for the pediatric population.⁹ Preoperatively or postoperatively, following diversion or final removal of the aganglionic bowel, patients may develop HAEC. This shows that the etiology is more complex than just the lack or existence of ganglia. In our study, 80% were pre-operative cases whereas only 20% were post-operative cases after a pull-through procedure. Where the post-operative incidence was comparable to the literature but preoperative enterocolitis incidence was way more in our study compared to preoperative enterocolitis (p-value: 0.001). In a research conducted by Guillaume et al., 5.7% of patients were found to have preoperative HAEC⁷ while in our study, 80% of Patients were pre-operative cases of Hirschsprung disease. This can be explained due to the lack of awareness and treatment facilities in underdeveloped countries like Pakistan where hundreds of patients wait for definitive procedures for months.⁹ Rectal irrigation not only helps in bowel decompression but also washes out potentially pathogenic bacteria and therefore toxin release and symptoms can relieve.¹¹ In our study, at presentation, the mean HAEC score in the Vancomycin enema and normal saline enema was 12.3 and 11.5, respectively. After therapy, HAEC decreased in both groups (7.7 and 7.61, respectively). The importance of rectal decompression in the treatment of enterocolitis has been well-known for many years as it not only helps to relieve mechanical obstruction but also washes out infective organisms like *Clostridium difficile*.¹² Marty et al., in their study found that routine postoperative rectal irrigations have significantly decreased (92.5%) the incidence and severity of enterocolitis.¹³ No major complications (like perforation, electrolyte imbalance, hypersensitivity reaction from vancomycin) were noted in the study population. The most frequent problem encountered was irritability and abdominal pain. This was due to the contraction of the gut and spasms of the intestine. Along with that in a few instances, the patient experienced rectal bleeding and anal tears which were managed with

nitroglycerine and lignocaine ointment.² In our study, the Majority of patients in both groups were successfully treated with rectal washouts. Both before and after surgery rectal enema has been found to lower the incidence of HAEC after surgery. According to Marty and Matlak's review, 36% of children in the non-irrigation group experienced postoperative enterocolitis, compared to 8% of participants in the rectal irrigation group.¹³ Similarly, Shelter and colleagues found that intracolonic vancomycin administration treats the HAEC with a success rate of 71%¹⁴, while another study also using per rectal vancomycin showed up to 79% success rates in the treatment of Hirschsprung's associated enterocolitis.¹⁵ Although rectal enema along with antibiotic therapy is a very effective treatment but still some patients need diversion colostomy. In our study, 7 patients needed the diversion colostomy after the failure of conservative therapy. This is consistent with the other research on this topic as demonstrated by the study of Kim et al., which showed a failure rate of 21% with the vancomycin enema¹⁵ while, 7.5% of the patients in Marty et al trial¹³ required diverting colostomies after receiving no benefit from conservative therapy with rectal irrigation.¹³ Sick and late presentation is the major cause of the therapy's failure in HAEC patients. Inadequate volume and errors in the enema administration method are additional potential causes of failure of therapy with rectal enema in HAEC patients.¹⁶ Overall, 7.33 ± 2.426 days were required for full remission of HAEC symptoms in the study. But there was no statically significant difference between the groups in terms of hospital stay. Similarly, there was no significant difference between the groups' difference in terms of the resolution of symptoms (p-value: 0.251). This suggests that the addition of vancomycin in the rectal washouts is an expensive addition to the already effective rectal washouts. Other researchers say that improvement due to vancomycin enema is mainly because of the decompression effect while it is administered through the per rectal route. While IV antibiotics are already given, additional per-rectal antibiotics are unnecessary. Vieten and Spicer, found that Instead of the addition costly antibiotics like vancomycin in rectal enema, decompression of the gut with standardized rectal irrigation should be the mainstay of the conservative treatment of the HAEC.¹⁰ Antibiotics are the mainstay of treatment of HAEC due to colonization and toxin production of various organisms. Vancomycin has been one of the most effective antibiotics to eradicate *Clostridium difficile* infection.⁹ Due to this phenomenon rectal vancomycin administration gain popularity and is being used to treat HAEC in many centers. However, vancomycin is a large hydrophilic molecule, which penetrates poorly across the gastrointestinal mucosa when given parentally.² Our study reports that rectal irrigation with normal saline and vancomycin enema are equally effective, as rectal washouts will washout the organism

adherent to the intestinal mucosa and will also relieve obstruction and stasis.

CONCLUSION

We conclude that rectal washouts with normal saline enema or vancomycin enema along with standard therapy of fluid resuscitation and antibiotic cover are equally effective in treating Hirschsprung-associated enterocolitis as both groups showed resolution of symptoms and shorter hospital stay. However, we didn't find any significant benefit in terms of symptoms resolution from the addition of vancomycin in rectal irrigation in patients of HAEC.

LIMITATION OF STUDY: This is a single-center study with a small sample size due to the short duration of the study. In the future, we recommend multicenter studies with large sample size and longer follow-ups for better protocol recommendations for the treatment of HAEC and benefit from the addition of vancomycin in rectal irrigation in patients of HAEC

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CONFLICT OF INTEREST

Author declared no conflict of interest

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AUTHORS CONTRIBUTIONS

MR: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable.

SG: Conception, Design of the work, Acquisition, Data Analysis, and Drafting, Reviewed, Final approval, Agreement to be accountable.

MSS: Conception, Design of the work, Interpretation of data for the work, and Drafting, Reviewed, Final approval, Agreement to be accountable

NK: Conception, Design of the work, Data collection, and Drafting, Reviewed, Final approval, Agreement to be accountable

KS: Conception, Design of the work, Data analysis, and Drafting, Reviewed, Final approval, Agreement to be accountable

DATA SHARING POLICY

The data that support the findings of this study are available from the corresponding author upon reasonable request.



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