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Assessment of Efficacy, Tolerability and Safety of Sodium Picosulphate (Cremalax®) in Bowel Preparation Needed in Patients Undergoing Gastrointestinal or Ano-Rectal Surgery: A Prospective, Non-Comparative Study

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Abstract

Context: Mechanical bowel preparation (MBP) is a medical process involving evacuation of bowels with the use of laxatives before surgery involving the colon and ano-rectum to cleanse the bowels. MBP is shown to reduces the rates of infectious postoperative complications. Sodium picosulphate is a stimulant laxative commonly used orally for bowel preparation before gastrointestinal (GI)or anorectal surgery. There is scarcity of Indian data on role of sodium picosulphate in bowel preparation needed in patients undergoing gastrointestinal and anorectal surgery. *Aims:* To evaluate the efficacy, tolerability, safety of sodium picosulphate in bowel preparation needed in patients undergoing GI or ano-rectal surgery. *Settings and Design:* Prospective, non-comparative interventional study. *Methods and Material:* 100 patients (55 males and 45 females) between 18 to 65 years of age and posted for GI or ano-Rectal surgery who requires bowel preparation as per PI discretion (elective procedure) and willing to sign the written informed consent form are enrolled in this study. These patients were prescribed 2 tablets of Sodium Picosulphate 10 mg at night before the procedure. The efficacy outcomes were the efficacy of bowel preparation assessed by the surgeon intraoperatively on a 4-point likert scale of 1 = poor (large solid stool), 2 = satisfactory (particulate formed stools), 3 = good (fluid and gas filled), and 4 = excellent (colon/ano-rectum empty and collapsed); clean operative field, difficulty in bowel handling during surgery, and patient satisfaction for bowel evacuation assessed on a scale of 0 = not satisfied at all, 1 = somewhat satisfied, and 2 = completely satisfied. The tolerability and safety was assessed based on the adverse events reported and the symptoms of nausea, vomiting, abdominal pain/cramps, bloating and weakness assessed on a 0-10 visual analogue scale (VAS). *Statistical Analysis Used:* Descriptive statistics are presented for the study outcomes. *Results:* Of the 100 patients enrolled the study (median age of 44.22 years) 54 were males and 45 were females. 44 patients underwent GI surgery while 55 patients underwent anorectal surgery. Efficacy of Bowel preparation (in per-protocol dataset, N=99) as assessed by surgeon intraoperatively was rated as Excellent in 40.41%, Good in 48.48%, Satisfactory in 10.1%, and Poor in 1.01% patients. Operative field as assessed by surgeon during the procedure as "clean" in 98% patients. Difficulty in handling the bowel was reported as "no" in 99% patients. Bowel evacuation satisfaction as assessed by patients was rated as 'Completely satisfied' by 73.74%, 'somewhat satisfied' by 25.25% were and 'not satisfied' by 1.01% patients. Therapy with sodium picosulphate was well tolerated, mild intensity adverse events of weakness, bloating, abdominal cramps, nausea and vomiting were reported by few patients. *Conclusions:* Sodium picosulphate can be considered as a good therapeutic armamentarium to surgeons for its use in bowel preparation needed in patients posted for GI or anorectal surgeries and further studies can be considered to substantiate these findings.

Keywords: Sodium Picosulphate; Mechanical Bowel Preparation; Anorectal Surgery Gastrointestinal Surgery.

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Introduction

Mechanical bowel preparation (MBP) is a medical process involving evacuation of bowels with the use of laxatives before surgery involving the colon and ano-rectum to cleanse the bowels [1]. It is hypothesized that MBP decreases intraluminal faecal mass and decreases bacterial load in the bowel and thus reduces the rates of infectious postoperative complications [2]. MBP also helps for better manipulation of bowel during the surgical procedure. Bowel preparation before elective colorectal surgery can include a variety or combination of interventions like use of an oral laxative solution used to cleanse the bowel of faecal contents (e.g., polyethylene glycol, sodium phosphate, sodium picosulphate, magnesium citrate), or use of evacuation enema [3,4].

Sodium picosulphate is a stimulant laxative commonly used orally for bowel preparation before anorectal or gastrointestinal surgery. It gets activated by the colonic bacteria in the gut and stimulates the nerve endings in the intestinal walls leading to increased peristalsis and bowel evacuation [5]. It is reported to have better tolerability compared to other stimulant laxatives like phenolphthalein, bisacodyl, Karlsbad-salt, and saccharosum + sennosid - B solution [6]. There is scarcity of data on role of sole sodium picosulphate in bowel preparation in patients undergoing GI or Anorectal surgeries especially in Indian clinical settings.

Thus, this prospective, non-comparative study was planned to evaluate the efficacy of bowel preparation with oral sodium picosulphate in patients undergoing GIor Ano-rectal surgery. This study was also planned to assess the tolerability, safety and patient satisfaction of bowel preparation treated with sodium picosulphate.

Materials and Methods

Informed Consent and Ethics

This prospective study was carried out in a surgery centre after obtaining approval of the Institutional Ethics Committee. The study was conducted in accordance with the principles of 'The Declaration of Helsinki' (World Medical Association) and Good Clinical Practice (GCP) Guidelines issued by the ICMR & DCG(I), Govt. of India. Informed written consent was obtained from all patients before starting any study related procedures on the patients. The study is registered in the clinical trials registry of India (CTRI/2016/09/007292).

Study Participants

This was prospective, single-centre, non-comparative, non-randomized, single-arm interventional clinical study. Patients attending the outpatient department (OPD) of the study site with clinical conditions which would require bowel preparationfor any GI or Ano-rectal surgery (as per physician discretion) will be the potential subjects for this study. Patients of either gender between 18 and 65 years of age, those posted for any GI surgery or Ano-Rectal Surgery (elective procedure) and willing to sign the written informed consent form and able to understand and comply with all study requirements were enrolled after obtaining written informed consent.

Patients with known hypersensitivity to study medication or any of the excipients, pregnant and lactating women, and patients undergoing emergency surgical procedures were excluded. Patients with any evidence of structural abnormality of the gastrointestinal tract or diseases/conditions that could affect bowel transit, those with history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions were also not enrolled. Moreover,patients with any cardiac, renal, hepatic, neurological disorders, evidence of cathartic colon or history of laxative abuse, or having any systemic condition which would call for avoidance/non-use of stimulant laxatives were not enrolled.

Study Treatments

All enrolled participants received 2 tablets of Sodium Picosulphate 10 mg (Tab Cremalax Abbott India Ltd) on the night before surgery after light meal. Any other concomitant medication required by the patient was prescribed at the discretion of the investigator and/or the attending clinician in accordance with the routine clinical practice at the study site. Patients were administered routine post-operative antimicrobial therapy at the discretion of the investigator.

Study Outcomes

The primary study outcome was the efficacy of bowel preparation assessed by the surgeon during the intra-operative period (during surgery) based on a 4-point likert scale of *1 = poor (large solid stool), 2 = satisfactory (particulate formed stools), 3 = good (fluid and gas filled), and 4 = excellent (colon/ano-rectum empty and collapsed)*. The secondary efficacy outcomes were clean operative field during surgery, difficulty in

bowel handling during surgery, and patient satisfaction for bowel evacuation assessed in the morning based on the 3-point likert scale of *0 = not satisfied at all, 1 = somewhat satisfied, and 2 = completely satisfied*. The tolerability was assessed based on the symptoms of nausea, vomiting, abdominal pain/ cramps, bloating and weakness assessed on a *0 – 10 visual analogue scale (VAS)* where 0 implies no symptom and 10 implies severe symptom. Clinical safety was assessed based on the adverse events (AE) or serious adverse events (SAE), either spontaneously reported by the patient, or noticed by the clinician will be recorded during the study.

Statistical Analysis

This was a prospective, non-randomized, non-comparative study in which no pre-determined statistical hypothesis is being tested. Although there are no reference studies with sole use of Sodium picosulphate in bowel preparations, there are studies in which Sodium picosulphate has been used in combination with Magnesium citrate in the same indication having sample sizes like 200, 150, 145, 87, 85 and 77 in the same treatment arm [7-12]. Based on the same it was planned to enroll 100 patients in this study.

Continuous variables were summarized with the descriptive statistics n (number of observations), mean, standard deviation, median, minimum and maximum values. A summary of categorical data was done through numbers and percentages. If the data was not available, missing category was presented.

Efficacy analysis was done on the Per-Protocol Set (PPS) which included patients who received at least one dose of study medication and have no major protocol violations. The PPS (n=99) included all patients who satisfied the study criteria and completed the study as per the study protocol. Full Analysis Set (FAS) included all subjects screened and enrolled and received at least one dose of study medication. All safety and tolerability analysis was done on the FAS (n=100).

Only exploratory analysis was done and all testing was done at a 2-sided 5% level of significance. The primary and secondary outcomes were derived also for the different sub-groups based on gender (male and female), age groups (18 – 30 yrs., 31-40 yrs., 41-50 yrs. and 51 – 65 yrs.), BMI categories (normal - <25, overweight - 25 to 30 and obese - >30) and surgery type (GI or anorectal).

Results

Demography and Medical/Surgical History

A total of 100 patients were enrolled in the study out of which 3 patients were above the age limit prescribed in protocol. As per investigator's discretion waiver for age criteria was obtained for 2 subjects (age 66 yrs. and 69 yrs.) and these two subjects were included in the per protocol set (PPS) dataset. One patient aged 82 years was excluded from the PPS dataset due to violation of criteria for age. Thus, 99 subjects comprised the PPS for analysis.

There were 55 males and 45 females with mean age of 44.22 (14.68, 19.0–82.0) and with a mean BMI of 30.08 (5.51, 20.3 – 49.9).36% of the patients were aged 50–65 years, 25% patients were in the 18-30 years, 24% patients were in the 41–50 years and 15% of patients were in the age group of 31-40 years. 56 patients underwent anorectal surgery whereas 44 patients had undergone GI surgery (Table 1). Leading presenting complaints by these patients were anal pain (74%), pain in abdomen (65%), bleeding per rectum (41%), bloating (38%) and loss of appetite

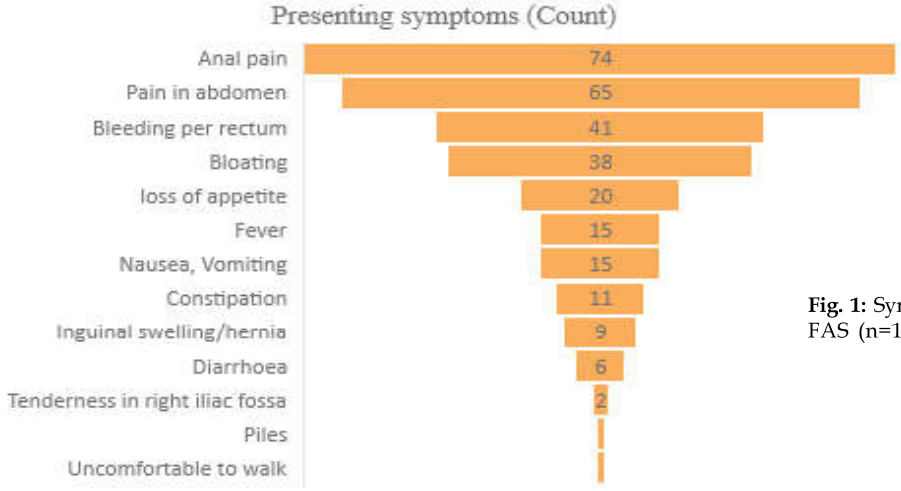

Fig. 1: Symptoms reported by the patients in FAS (n=100)

(20%) (Figure 1).

Efficacy Outcomes

The efficacy outcomes in the FAS and PPS are shown in table-2.Efficacy of Bowel preparation as assessed by surgeon intraoperatively was rated as Excellent in 40.41%, Good in 48.48%, Satisfactory in 10.1%, and Poor in 1.01% patients. Operative field as assessed by surgeon during the procedure as "clean" in 98% patients.

Difficulty in handling the bowel was reported as "no" in 99% patients. Bowel evacuation satisfaction as assessed by patients was rated as 'Completely satisfied' by 73.74%, 'somewhat satisfied' by 25.25% were and 'not satisfied' by 1.01% patients. The efficacy outcomes in the subgroups for gender, BMI categories, age and surgery type (Table 3) were comparable and no significant differences were observed.

Tolerability and Safety

A total of 5 types of adverse events were identified. Theywere nausea (15.0%), vomiting (11.0%), abdominal pain/ cramps (18.0%), bloating (37.0%) and weakness (39.0%). The mean (SD) symptom scores (0–10 scale) for nausea was 0.25 (0.68), vomiting 0.16 (0.48), abdominal pain 0.28 (0.6), bloating is 0.58 (0.85) and weakness 0.75 (1.01). Majority of the eventswere 'mild' in nature and there were no serious adverse events reported. The causality for these adverse events was judged by the investigator andit was observed that majority of the adverse eventswere 'not related' to study medication. All symptoms resolved without specific treatment and all the patients received only the standard post-operative treatment protocol (Table 4).

Table 1: Details of surgical procedures done on the patients

Surgery type	Details of procedure	No.	% (n=100)	% within surgery type
GI Surgery (n=44)	Appendicectomy	22	22.0	50.0
	Exploratory laparotomy	4	4.0	9.1
	Inguinal Hernioplasty	9	9.0	20.5
	Umbilical Hernioplasty	9	9.0	20.5
Anorectal Surgery (n=56)	Anal dilatation with fissure	4	4.0	7.1
	Colonoscopy	6	6.0	10.7
	Excision of Cyst/Polyp	2	2.0	3.6
	Excision of piles	21	21.0	37.5
	Excision of piles with fissurectomy	1	1.0	1.8
	Fissurectomy	3	3.0	5.4
	Fissurectomy with anal dilatation	9	9.0	16.1
	Incision & drainage of abscess	7	7.0	12.5
	Sigmoidoscopy	2	2.0	3.6
	Sigmoidoscopy with anal dilatation	1	1.0	1.8

GI: Gastrointestinal

Table 2: Efficacy outcomes in FAS and PPS

	PPS (N=99)			FAS (N=100)		
	No.	%	95% C.I.	No.	%	95% C.I.
Efficacy of Bowel Preparation as assessed by surgeon						
Poor	1	1.01	-	1	1.0	-
Satisfactory	10	10.10	-	10	10.0	-
Good	48	48.48	-	48	48.0	-
Excellent	40	40.41	-	41	41.0	-
Bowel preparation Good or excellent	88	88.89	79.83 – 93.67	89	89.0	81.17 – 94.38
Clear operative field during surgery	97	97.98	91.44 – 99.38	98.0	98.0	92.96 – 99.76
Difficulty in bowel handling	1	1.02	0.025 – 5.48	1.0	1.0	0.025 – 5.45
Bowel evacuation satisfaction						
Not satisfied	1	1.01	-	1	1.0	-
Somewhat satisfied	25	25.25	-	25	25.0	-
Completely satisfied	73	73.74	64.21 – 82.30	74	74.0	64.27 – 82.26

FAS: Full-analysis set; PPS: Per-protocol set

Table 3: Efficacy outcomes in different surgery types in FAS and PPS

	PPS (N=99)			FAS (N=100)		
	N	No.	%	N	No.	%
Bowel Preparation good or excellent						
Anorectal surgery	*55*	49	89.1	*56*	50	89.3
GI surgery	*44*	39	88.6	*44*	39	88.6
Clear operative field during surgery						
Anorectal surgery	*55*	53	96.4	*56*	54	96.4
GI surgery	*44*	44	100.0	*44*	44	100.0
Difficulty in bowel handling						
Anorectal surgery	*55*	1	1.8	*56*	1	1.8
GI surgery	*44*	0	0.0	*44*	0	0.0
Bowel evacuation complete satisfaction						
Anorectal surgery	*55*	42	76.4	*56*	43	76.8
GI surgery	*44*	31	70.5	*44*	31	70.5

FAS: Full-analysis set; PPS: Per-protocol set; GI: Gastrointestinal

Table 4: Details of adverse events in the patients during study period (FAS)

Sr.	Symptoms	Severity	Seriousness	Relatedness to study medication	Outcome
1	Nausea	13 Mild, 2 Moderate	Not serious	6 related, 9 not related	Resolved without treatment
2	Vomiting	11 Mild	Not serious	3 related, 8 not related	Resolved without treatment
3	Abdominal pain/ cramps	17 Mild, 1 Moderate	Not serious	7 related, 11 not related	Resolved without treatment
4	Bloating	33 Mild, 3 Moderate	Not serious	6 related, 31 not related	Resolved without treatment
5	Weakness	34 Mild, 5 Moderate	Not serious	13 related, 26 not related	Resolved without treatment

FAS: Full-analysis set

Discussion

Use of laxatives before surgery involving the colon and ano-rectum to cleanse the bowels is a common practice [1]. It is hypothesized that use of laxatives for the mechanical bowel preparation (MBP) decreases intraluminal faecal mass and decreases bacterial load in the bowel and that this decrease in faecal load and bacterial contents reduces the rates of infectious postoperative complications. MBP also helps for better manipulation of bowel during the surgical procedure. Some reports also support the use of bowel preparation and systemic pre-operative prophylactic antibiotics together for the prevention of surgical site infections in elective colon and rectal surgery. Moreover, preoperative dietary modification is also considered as an integral components of bowel preparation [2-4].

Bowel preparation before elective colorectal procedures can be done using a variety of agents like oral laxatives like polyethylene glycol (PEG), sodium phosphate, sodium picosulphate, magnesium citrate), or use of evacuation enema. Best results for bowel preparation are obtained using agents which have good compliance, acceptability and tolerability [5,12,13].

Sodium picosulphate is a commonly used oral laxative used for bowel preparation before surgery. Sodiumpicosulphate is a stimulant laxative which gets activated by the colonic bacteria after oral administration. It stimulates the nerve endings in the intestinal walls and stimulates peristalsis thus leading to bowel evacuation. It is commonly used before any surgery on bowels and also during child delivery [15]. It is also reported to be better tolerated and effective for bowel cleansing before surgical procedures involving colon and rectum in adults [14] as well as children [15].

Sodium picosulphate is commonly used in combination with magnesium salts (most commonly citrate) for bowel preparation before surgery and there are many studies which substantiate the efficacy and safety of this combination for the said indication [7-12]. In an observational study conducted in Germany with data for 768 colonoscopies in children, the most frequently reported bowel cleansers were sodium picosulphate (54.2%) and polyethylene-glycol (41.3%) in various combinations. In this study,

the risk of adverse events during preparation was significantly reduced with the use of sodium picosulphate (OR 0.380, P < 0.001). Also, the risk of needing a nasogastric tube to complete clean-out was about greatly reduced when sodium picosulphate was used as against polyethylene-glycol. The authors of this study also pointed out that the regimens have a significant influence on the tolerability and acceptance of the bowel preparation [15]. Similarly, in a patient-blinded study, sodium picosulphate has been reported superior than PEG with respect to compliance, satisfaction, and safety [16]. Few other studies also have reported better flavour, tolerability and convenience of administration with sodium picosulphate containing preparations compared to others containing PEG [8,9,17,18]. In a meta-analysis of 25 RCT's were used to compare the sodium picosulphate/magnesium citrate (SPMC) with polyethylene glycol (PEG) for their efficacy in colonoscopy preparation [19]. Although the efficacy of these two preparations was similar, a higher proportion of patients were likely to complete SPMC preparation (RR 1.08; 95 % CI 1.04-1.13, P < 0.001) and were willing to repeat sodium picosulphate containing regimen (RR 1.44; 95 % CI 1.25-1.67, P < 0.001) and also the total number of adverse events was significantly lower in the SPMC group (RR 0.78; 95 % CI 0.66-0.93, P = 0.004) [19]. In a comparative study, the patients consideredsodium -picosulphate better tolerable compared to other stimulant laxatives like phenolphthalein, bisacodyl, Karlsbad-salt, and saccharosum + sennosid-B solution) based on the questionnaire data [6].

The present study was a prospective, interventional, non-comparative study, where 100 patients (55 male and 45 female) who are posted for GIor Ano-rectal surgerywere included in the study. Patients were administered with 2 tablets of sodiumpicosulphate 10 mg orally on the night before surgery as a protocol for bowel preparation. The primary objective was to study the efficacy of bowel preparation using oral monotherapy with sodium picosulphatein patients undergoing GI/ano-rectal surgery; whereas the secondary objectives were to assess the patient satisfaction, tolerability and safety of bowel preparation using oral sodium Picosulphatein patients undergoing GI/ano-rectal surgery. The study assessments were done during and after surgery. Of the 100 patients 44 underwent GI surgeryand 56 underwent anorectal surgery

The efficacy of bowel preparation was assessed by the surgeon during the surgery on a 4-point likert scale of '1 = Poor (Large solid stool), 2 = Satisfactory (Particulate formed stools), 3 = Good (Fluid and gas filled), and 4 = Excellent (Colon/ano-rectum empty and collapsed)'. The surgeon also assessed whether the operative field was clean during surgery, and whether there was any difficulty in handling of bowels during surgery. The patients rated their assessment for bowel evacuation in the morning after night dose based on the 3-point likert scale of '0 = Not satisfied at all, 1 = Somewhat satisfied, and 2 = Completely satisfied'. Tolerability was assessed based on the adverse events reported by the patients and the symptoms of nausea, vomiting, abdominal pain/ cramps, bloating and weakness assessed on a 0 to 10 visual analogue scale (VAS), where '0' indicates no complaint and '10' indicates severe symptom.

Our results show that monotherapy with sodium picosulphate was rated by surgeon as good to excellent in 88.89% patients, whereas the operative field during surgery was clear in 97.98% patients in per-protocol dataset (n=99). Difficulty in bowel handling was experienced by the surgeon only in one (1.01%) patient in per-protocol dataset. Also, in 73.74% patients the bowel evacuation satisfaction was reported as 'completely satisfied' and in 25.25% patients as 'somewhat satisfied'. Only one patient, the bowel satisfaction was reported as 'not satisfied'. There were no differences observed in all the efficacy outcomes as per gender (males and females), surgery type (anorectal or GI surgery) age groups (18-30 yrs., 31-40 yrs., 41-50 yrs. and >50 yrs.) and BMI categories (normal, overweight and obese). There are not many studies reporting use of monotherapy with sodium picosulphate for bowel preparation and only one randomized controlled study was reported comparing oral sodium phosphate (n=76) with oral sodium picosulphate (n=77) for elective colorectal surgery and colonoscopy [22]. The authors concluded that oral sodium phosphate was well tolerated and superior to oral sodium picosulphate in elective colorectal surgery and colonoscopy. The common adverse events reported by both groups were abdominal pain, nausea, vomiting, embarrassment, fear and fatigue [12].

In our study, the tolerability of monotherapy with sodium picosulphate can be considered as good since 73.74% patients rated the bowel preparation experience as 'completely satisfied'. Few patients had reported nausea, vomiting, abdominal pain, boating and weakness. Majority of the symptoms were of mild in nature and were non-serious and not related to study medication. Better tolerability of preparation containing sodium picosulphate was also demonstrated in earlier published studies [7,8,12].

Our study has several strengths. First, the study

enrolled the significant sample size of 100 patients undergoing GI or Ano-rectal surgery. Second, the efficacy end points were assesses based on validated parameters, used earlier in published literature. There are some limitations of this study as well: first, the non-comparative study design limits any inference drawing since there was no reference standard for comparison; and second, the study was conducted at a single centre, thus the possibility of selection bias. Despite the limitations, this is first of a kind study which demonstrates efficacy of monotherapy with sodium picosulphate for bowel preparation in Indian patients undergoing GI or Ano-rectal surgery and the results of the same are quite encouraging.

Conclusions

Sodium picosulphate can be considered as a good therapeutic armamentarium to surgeons for its use in bowel preparation needed in patients before GI or anorectal surgeries in Indian contextand further randomized controlled studies are needed to substantiate these findings.

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