ORIGINAL ARTICLE

A pilot study on the efficacy of Picolax given as a four-week course for the treatment of refractory constipation

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Objectives Although Picolax (sodium picosulphate and magnesium citrate) has been widely documented for use in bowel preparation, there is limited literature on its efficacy in the treatment of constipation. Refractory constipation is a more difficult situation with limited treatment options available. The primary objective of this study was to investigate the efficacy of Picolax in the treatment of refractory constipation.

Design Prospective single-centre cohort study.

Setting The Gastroenterology and Hepatology Centre of a major private hospital in Hong Kong.

Patients Patients aged 18 years or more with chronic constipation refractory to tegaserod or polyethylene glycol and attending the centre in the period of July 2009 to June 2010.

Results A total of 20 patients completed this 6-week single-centre study, with a 2-week baseline assessment and 4-week treatment period. Complete data sets were available for analysis from 17 of these patients. The mean (standard deviation) age of the cohort was 50 (9) years, of which 94% were female. Treatment consisted of half-a-sachet of Picolax taken orally on alternate days, 3 times a week. Patients were required to fill in daily and weekly diary entries of their bowel habit. The mean (standard deviation) number of weekly complete spontaneous bowel movements increased from 0.5 (0.9) to 2.4 (2.6) times per week (P=0.02) after initiation of the treatment, which was a clinically and statistically significant difference; with a mean change of +1.9 (95% confidence interval, 0.3 to 3.4) per week. As a secondary endpoint, 11 patients recorded the use of rescue medication before and after the 4-week treatment. The ratio of patients who took rescue medication decreased significantly from 73% (n=8) to 0% (n=0) [P=0.008]. The mean reduction in the frequency of resorting to rescue medication was 2.6 times (95% confidence interval, -4.2 to -1.1) per week.

Conclusions Picolax improved the number of complete spontaneous bowel movements and significantly reduced resorting to rescue medication. This formulation could therefore be considered as a treatment option in patients with chronic constipation who are refractory to conventional treatment regimens.

Key words
Constipation; Laxatives; Picolines; Polyethylene glycols; Treatment outcome

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New knowledge added by this study

- Picolax (sodium picosulphate and magnesium citrate) improves the weekly complete spontaneous bowel movement rate in patients with chronic constipation refractory to conventional treatment.
- The proportion of patients resorting to rescue medications decreased after the treatment with Picolax.

Implications for clinical practice or policy

- Despite Picolax's sole licensed indication being bowel preparation, it also appears to be effective in treating chronic constipation.

Introduction

Chronic constipation is a common disorder that affects up to about 20% of the population depending on demographic factors, and the sampling methods and definitions used.[1] A

recent survey in Hong Kong showed a prevalence of 14% according to the Rome criteria.[2,3] In the US, 2.5 million annual physician visits are attributable to this problem.[4]

In addition to the distressing physical symptoms, refractory chronic constipation is associated with anxiety, depression, and social dysfunction,[2] which has a considerable impact on quality of life. For most patients with chronic constipation, the situation could be relieved by combining dietary planning, fibre supplementation, increased fluid intake, increased physical exercise, and conventional laxatives. The latter include polyethylene glycol (PEG) and/or prokinetics such as tegaserod, but the extent of relief they afford is usually partial.[5,6] Alternative medications may be considered as the next step.[7] Theoretically, a combination of different laxatives with complementary actions may improve the efficacy while the adverse effect of increased doses of a single agent can be avoided.[8]

Picolax (Ferring Pharmaceuticals Ltd., Berkshire UK) consists of a stimulant laxative (sodium picosulphate) and an osmotic laxative (magnesium citrate) used for bowel cleansing prior to X-ray examinations, endoscopy, or surgery.[6] Notwithstanding this being its sole licensed indication, anecdotal reports support its efficacy in chronic constipation. In our pilot study, we observed the efficacy of sodium picosulphate in refractory chronic constipation patients to be 75% (unpublished data).

In the Chinese population, there is limited literature on the efficacy of Picolax in the treatment of refractory constipation, as well as insufficient data available on constipation per se. The objectives of this study therefore were to investigate the efficacy of Picolax in the treatment of refractory constipation by assessing its impact on the number of complete spontaneous bowel motions (CSBMs) per week and the use of rescue medications, as well as to monitor side-effects.

連續四週服用Picolax治療難治性便秘的效用：先導性研究

目的 Picolax含匹可硫酸鈉和檸檬酸鎂，一向被廣泛應用於清理腸道。可是文獻中很少報導有關Picolax治療便秘的效用。難治性便秘是一個更難處理的疾病，治療選擇亦有限。本研究的主要目的是探討Picolax治療難治性便秘的效用。

設計 前瞻性單一中心定群研究。

安排 香港一間大型私家醫院的腸胃肝臟科中心。

患者 2009年7月至2010年6月期間到上述中心應診的18歲或以上已服用替加色羅（tegaserod）或聚乙二醇（polyethylene glycol, PEG）後便秘沒有反應或改善的慢性便秘患者。

結果 20位病人完成了共六個星期的單一中心研究，當中包括兩星期沒有藥物治療的基線期及四星期的藥物治療。最終17位填寫完整的資料紀錄，他們的平均年齡為50歲，標準差9歲；94%為女性。他們的治療為每星期服用Picolax三次，即隔天口服半包藥粉。病人需要填寫日記及週記以記錄其排便習慣。經過四週的治療後，完全自發性腸臟蠕動由原來平均（標準差）每週0.5（0.9）次增加至2.4（2.6）次（P=0.02），達統計顯著性。完全自發性腸臟蠕動平均每週次數的改變為+1.9次（95%置信區間：0.3至3.4）。在次要療效指標上，11名病人記錄了治療前及經過四週治療後使用額外瀉劑的情況。需要使用額外瀉劑的病人由治療前的73%（8名）減至治療後的0%（0名）〔P=0.008〕。每週使用額外瀉劑的次數減少2.6次（95%置信區間：-4.2至-1.1）。

結論 Picolax可以有效增加完全自發性腸臟蠕動的次數，並減少病人額外使用瀉劑的需要。當傳統治療無效時，Picolax可以是治療慢性便秘的一個安全和有效的選擇。

Methods

This was a 6-week prospective study involving a single centre, which entailed a 2-week baseline assessment and a 4-week treatment period. The study protocol was approved by the Institutional Review Board of Hong Kong Sanatorium and Hospital, a major private hospital in Hong Kong.

A patient with refractory constipation is arbitrarily defined as a subject who does not respond to tegaserod (6 mg x 2 daily) or PEG (1 sachet x 2 daily). Patients previously recruited for constipation studies at Queen Mary Hospital, a government hospital in Hong Kong, who did not respond to tegaserod or PEG, and attended the Gastroenterology and Hepatology Centre of the Hong Kong Sanatorium and Hospital in the period of July 2009 to June 2010 were invited to participate.

To be eligible, subjects had to be aged 18 years or above, and have a history of constipation for 12 months or more. Bowel movement was considered to be spontaneous if it was not preceded by use of any other laxative or enema in the preceding 24 hours. Constipation was defined as having less than three spontaneous bowel movements per week that resulted in a feeling of complete evacuation, and one of the following occurring for at least 25% of defaecations: lumpy and/or hard stools, straining, or the sensation of incomplete evacuation.

Exclusion criteria were: a history of laxative abuse, non-functional intestinal or colonic disease, malignancy, and significant systemic disease, or an

active surgical or medical condition that interfered with the pharmacokinetics of the study medication. Subjects whose chronic constipation was clinically suspected to be due to bowel or gynaecological surgery, neurological disorders, systemic sclerosis, amyloidosis, scleroderma or myotonic dystrophy were also excluded. Similarly, fertile women who were pregnant or breast feeding, or not already practising a medically approved method of contraception at least 1 month before and after, and during the study were deemed ineligible. All subjects had to have had an endoscopic or radiological evaluation to exclude malignancy, inflammatory bowel disease, or other structural disease within the preceding 5 years. Written informed consent was signed by each patient before any treatment and data collection.

At baseline, subjects stopped taking any concomitant medications known to affect the bowel habit, with sustained abstinence throughout their participation in the study. A general physical examination was conducted and blood tests were carried out at baseline and regularly thereafter. Subjects were advised against changing their diet or lifestyle.

Over the 4-week treatment period, subjects were asked to take half a sachet of Picolax orally 3 times a week on Monday, Wednesday, and Friday. They were also supplied with bisacodyl 5 mg tablets to be used as rescue medication only if preceded by at least 96 hours of no bowel movement. If there was no bowel opening after the maximum daily dose of 15 mg bisacodyl had been taken, patients were to contact the investigator before increasing the dose or resorting to alternative therapy. In case of diarrhoea, patients were to contact the investigator and could interrupt the study medication at the investigator's discretion, but were instructed to resume within 48 hours of resolution.

Treatment efficacy was assessed with daily and weekly proforma-type diary entries beginning at baseline and continuing throughout their participation in the study. The primary endpoint was the number of CSBM (as already defined) during the 4-week treatment period. The time and the feeling of complete evacuation of stool was to be recorded if any bowel movement was experienced. As a secondary endpoint, the time and dosage of the rescue medication (bisacodyl) taken was also to be recorded if taken. The quality of bowel movements was also evaluated, which included a record of (i) stool quality, using the 7-point Bristol Stool Form Scale (1=hard lumps, 7=watery); and (ii) straining at stool.

For all recruits, hospital visits were scheduled at weeks 2 and 4. Evaluation for the safety of the medication entailed collecting data on vital signs, laboratory evaluation, bisacodyl tablets dispensed, diary collection and verification, any adverse effects, and patient comments. The duration and severity of reported adverse effects were recorded. Besides the voluntary report, blood samples were collected for a panel of tests including liver enzymes, serum total protein, albumin, globulin, blood urea nitrogen, creatinine and serum electrolytes (K^+, Cl^-, Na^+) before and after Picolax treatment.

Statistical analysis

Descriptive data were used for quantitative variables, and frequency counts and percentages used for qualitative variables. The paired *t* test was used to determine treatment effects on the numbers of CSBMs and occasions of rescue drug usage. The McNemar test with binomial distribution was used to analyse effects on the use of rescue medication after treatment. As appropriate, 95% confidence intervals (CIs) were calculated.

Results

A total of 31 subjects were recruited in this study, of whom 25 received Picolax, four were excluded upon screening and two were lost to follow-up (Fig 1). Of these 25 patients, two failed to complete the study, two withdrew due to diarrhoea, and one due to bloating. Thus, 20 subjects completed the study, 17 (85%) of whom provided complete data entries for analysis (Fig 1). Their demographic data are shown in Table 1.

Their constipation history and symptoms at screening, mean number of years of constipation, mean number of bowel movements per week, and patient characteristics according to the Rome criteria are summarised in Table 2.

Primary efficacy endpoint

The mean (standard deviation) number of weekly CSBMs increased from 0.5 (0.9) to 2.4 (2.6) times per week after the treatment with Picolax (P=0.02) in the 17 patients with complete data available for analysis. The change in the numbers of weekly CSBMs of individual study subjects is shown in Figure 2. A general increase in CSBM was observed, whereas no change and a decrease in CSBMs was evident in four and two subjects, respectively. The increase in weekly CSBMs was statistically significant, the mean increase being 1.9 (95% CI, 0.3-3.4) times/week (Fig 2).

Secondary endpoints

No concomitant laxatives were allowed throughout the study other than bisacodyl as a rescue medication as described already. In all, 11 patients completed

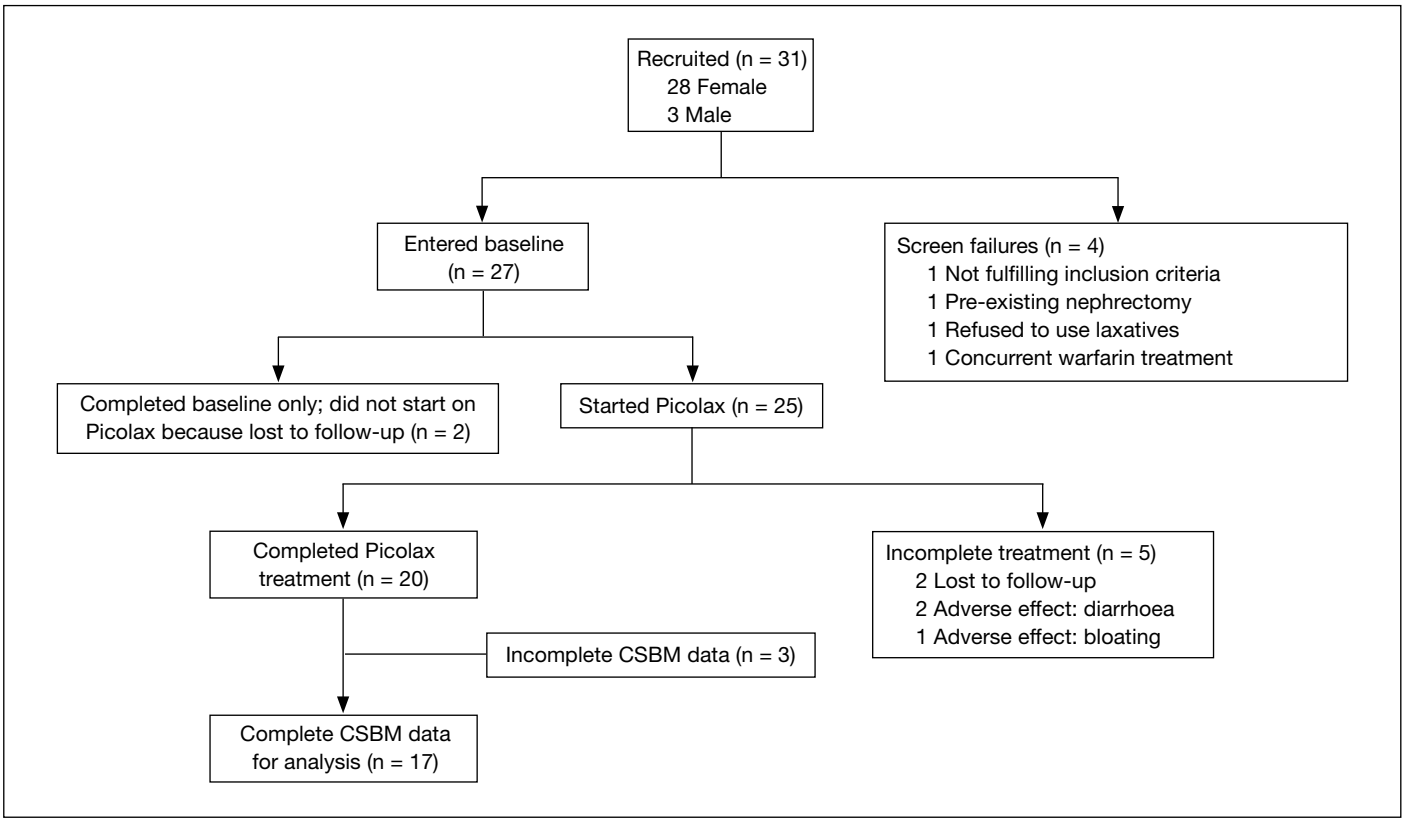

FIG 1. Disposition of participants
CSBM denotes complete spontaneous bowel motions

TABLE 1. Demographic data of the recruited patients (n=17)

Demographics	Data*
Sex (F/M)	16/1†
Age (years)	50 ± 9 (31-62)
Weight (kg)	55 ± 11 (43-86)
Height (cm)	158 ± 7 (147-170)

* Data are shown as mean ± standard deviation (range), unless otherwise specified
† No. of patients are shown

TABLE 2. Constipation history and symptoms at screening (n=17)

History/symptom	Data*
Mean duration of constipation (years)	23 ± 14 (3-45)
Median No. of bowel movements/week†	1 (0-7‡)
Rome criteria	
Incomplete evacuation	13 (76)
Outlet obstruction	10 (59)
Stool lumpy/hard	11 (65)
Straining	14 (82)
Digital evacuation	2 (12)

* Data are shown as mean ± standard deviation (range), median (range), or No. (%) of patients
† Inclusive of bowel movement resulting in feeling of complete and incomplete evacuation
‡ Bowel movement not resulted in complete evacuation

the record on the time and dosage of any rescue medication used. The proportion of these patients who took rescue medication was 73% (8/11) pre-treatment and 0% (0/11) post-treatment (P=0.008). The change in the number of weekly rescue medications these individuals used is shown in Figure 3. The mean reduction in the frequency of rescue medication use was 2.6 (95% CI, -4.2 to -1.1) times/week.

Among the 17 patients with complete data available for analysis, four (n=3 to n=7) achieved stool of Bristol Stool Form Type 4 (smooth and soft, sausage/snake-like) and for patients not having to strain increased by 4 (n=3 to n=7) after completion of treatment in the stated period. The sensation of complete evacuation improved in 11 patients (n=4 to n=15). The data showed a tendency of improved quality of bowel movement. This difference, however, did not attain statistical significance.

Safety assessments

During the two hospital visits scheduled at weeks 2 and 4, two of the 17 patients who completed the study reported diarrhoea; the others reported no adverse effects. No significant changes were observed in the results of laboratory tests carried out in the course of this study.

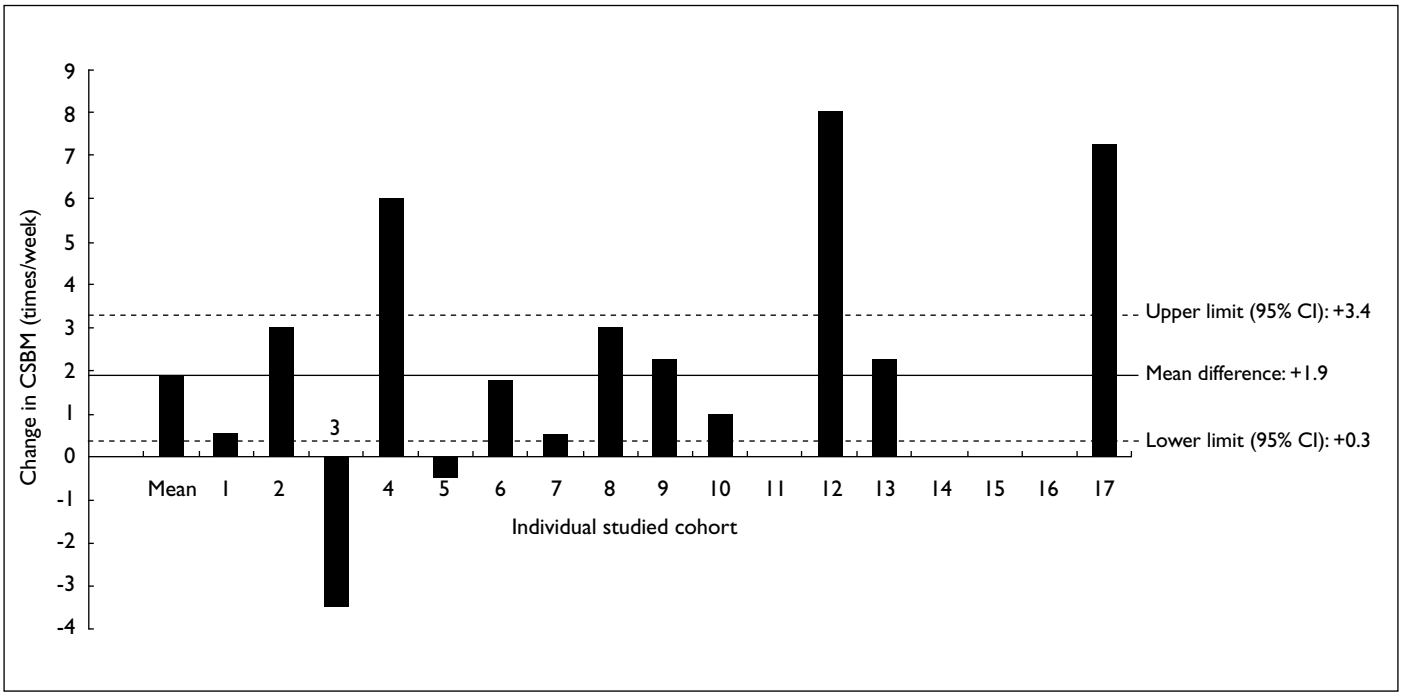

FIG 2. Change in complete spontaneous bowel movements (CSBMs) [times/week] during the 4 weeks of Picolax treatment and the mean difference for the entire cohort (n=17)

A positive value of Y-axis indicates an increase in CSBMs and a negative value indicates a reduction. The upper and lower limits were calculated with 95% confidence intervals (CIs)

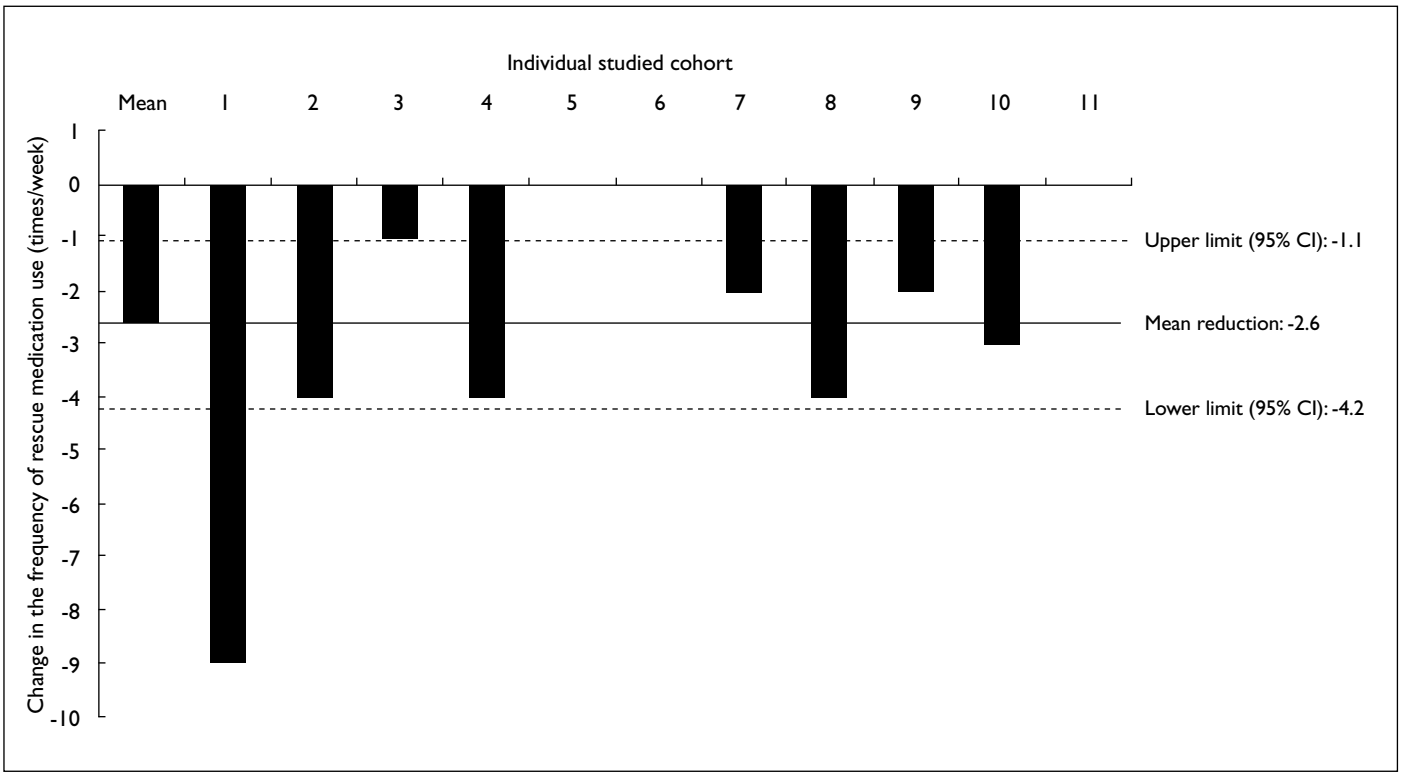

FIG 3. Change in the rescue medication use (times/week) during the 4 weeks of Picolax treatment of individuals who kept a complete record on the time and dosage of rescue medication used (n=11)

A positive value of Y-axis indicates an increase in the frequency of rescue medication use and a negative value indicates a reduction. The upper and lower limits were calculated with 95% confidence intervals (CIs)

Discussion

The efficacy of Picolax treatment for constipation has been demonstrated in our study, with significant improvement in the number of CSBMs and having to resort to rescue medication use. Although the relatively small sample size may have masked the true clinical benefit, our findings suggest promising normalisation of bowel movement patterns in patients who were refractory to other constipation treatments (tegaserod and PEG). There was a strong trend indicating that Picolax promotes and resumes bowel regularity in patients with refractory chronic constipation. This was supported by the observation of improved stool form, impact on straining at stool, and the feeling of complete evacuation. Presumably, due to the small sample size, no statistical significance was attained for many of the differences observed.

In the current study, patients who did not respond to the initial therapy of tegaserod and PEG were considered as having refractory constipation. Picolax may be a desirable alternative over the use of multiple laxatives for these types of patients, since it is a unique dual-action purgative. Sodium picosulphate is one of its constituents that acts as a stimulant laxative, and magnesium citrate (its other constituent) acts as an osmotic laxative. It is indicated for bowel cleansing prior to X-ray examination, endoscopy, or surgery.[9] In a number of large randomised control trials in bowel cleansing, Picolax was shown to be better tolerated than PEG and Fleet Phospho-soda, with significantly fewer side-effects and was preferred by patients.[10-16]

While PEG has now been used for treating chronic constipation, Picolax may also have similar potential, after adjusting for dose. In addition to being better tolerated and preferred by patients, it was also shown to be significantly superior to PEG in terms of the quality of bowel cleansing reported in an intention-to-treat analysis.[17] Picolax was reported to be superior to PEG in patients older than 45 years, while there was no significant difference observed in younger patients.[18] For tegaserod (another treatment option for chronic constipation), the US Food and Drug Administration has therefore recommended its use in patients younger than 55 years without any history of cardiovascular problems or risk factors.[19]

As per the company's product insert, the dosage of Picolax for bowel cleansing is 1 sachet on the day prior to the hospital procedure and another sachet on the day of the procedure.[20] The dosage used for the current study was half-a-sachet every alternate day. The current regimen, however, may need to be optimised, as two out of five patients who dropped out of our study did so due to diarrhoea. This suggests that the dosage used in the current regimen may be too high for some patients with good clinical responses. Further investigations are necessary to explore optimum dosing in different patient sub-sets. Arguably, with dosage adjustment, these two patients could have responded to the treatment without side-effects. Moreover, dosage adjustment might be easier if the drug was available in liquid form.[6]

During the two hospital visits, the 17 patients who completed the study were asked if they had experienced any adverse effects during the treatment, to which two reported diarrhoea, while the other 15 patients had none. Moreover all physical examination and laboratory test findings yielded no significant changes. Overall, Picolax treatment was well-tolerated. The 4-week exposure to the medications should have been adequate to detect any important changes in electrolyte balance and/or other serious sequelae. Patients with chronic constipation are nevertheless likely to require regular therapeutic measures over a long period of time.[21] Further investigations to look out for long-term safety during the use of Picolax for chronic constipation may be prudent.

One limitation of this study was that it was conducted at a single-centre and may not be representative for the Chinese population. Moreover, the bowel quality was evaluated by self-reporting, which is subjective. Also, as already mentioned, the dosage has yet to be optimised to allow for better treatment outcomes. Thus, additional randomised controlled trials are needed to determine the optimum dosage, efficacy, and safety of Picolax in patients with chronic constipation.

Conclusions

For the treatment of patients with chronic constipation and refractory to tegaserod and PEG, Picolax appears to improve bowel function, normalise the frequency of CSBMs, and is well-tolerated over 4-week treatment periods.

Declaration

No conflicts of interest were declared by the authors.

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