Misoprostol for small bowel ulcers in patients with obscure bleeding taking aspirin and non-steroidal anti-inflammatory drugs (MASTERS): a randomised, double-blind, placebo-controlled, phase 3 trial

Ali S Taha, Caroline McCloskey, Paula McSkimming, Alex McConnachie

Department of Medicine and Gastroenterology, University Hospital Crosshouse, Kilmarnock, UK (A S Taha PhD, C McCloskey BSc)**; and School of Medicine** (A S Taha) **and Robertson Centre for Biostatistics, Institute of Health and Wellbeing** (P McSkimming BSc, A McConnachie PhD)**,**
University of Glasgow, Glasgow, UK

Correspondence to:
Dr Ali S Taha, Department of
Medicine and Gastroenterology,
University Hospital Crosshouse,
Kilmarnock KA2 0BE, UK
ali.taha1@btinternet.com

Summary

Background The incidence of obscure gastrointestinal bleeding, which originates from the small bowel and is mainly associated with the use of aspirin and non-steroidal anti-infl ammatory drugs (NSAIDs), is rising. We assessed the efficacy and safety of misoprostol for the treatment of small bowel ulcers and erosions in patients taking low-dose aspirin or NSAIDs with obscure gastrointestinal bleeding.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients (aged ≥18 years) with small bowel ulcers who were taking low-dose aspirin, NSAIDs, or both for a minimum of 4 weeks, at University Hospital Crosshouse (Kilmarnock, UK). Eligible patients had evidence of obscure gastrointestinal bleeding (iron deficiency anaemia, a decrease in haemoglobin concentration of ≥20 × 10^3 mg/L, or positive faecal occult blood test) and normal upper endoscopy and colonoscopy. Patients were randomly assigned (1:1) using an interactive voice response system to receive 200 µg oral misoprostol or placebo four times daily for 8 weeks. Patients, investigators, and assessors were masked to treatment allocation. The primary endpoint was the complete healing of small bowel ulcers and erosions, assessed by video capsule endoscopy after 8 weeks of treatment. Primary analysis was by modified intention to treat, which included all randomised patients who received at least one dose of study treatment. Safety was assessed in the same population. The trial is registered with ClinicalTrials.gov, number NCT02202967.

Findings Between Jan 7, 2016, and Oct 11, 2017, we randomly allocated 104 eligible patients: 52 to receive misoprostol and 52 to receive placebo. Two patients allocated to misoprostol were later found to meet one of the exclusion criteria, thus 50 randomly assigned patients in the misoprostol group and 52 patients in the placebo group received at least one dose of study treatment. Complete healing of small bowel ulcers and erosions was noted at week 8 in 27 (54%) of 50 patients in the misoprostol group and nine (17%) of 52 patients in the placebo group (percentage difference 36·7%, 95% CI 19·5–53·9; p=0·0002). Adverse events occurred in 23 (46%) of 50 patients in the misoprostol group and 22 (42%) of 52 patients in the placebo group. The most common adverse events were abdominal pain (ten [20%] in the misoprostol group *vs* 13 [25%] in the placebo group), nausea or vomiting (nine [18%] *vs* seven [13%]), and diarrhoea (11 [22%] vs six [12%]). Four (8%) of 50 patients in the misoprostol group had severe adverse events, compared with none in the placebo group. No serious adverse events were reported.

Interpretation Misoprostol is effective for the treatment of small bowel ulcers and erosions in patients using low-dose aspirin and NSAIDs. Misoprostol might represent a pharmacological treatment option for lesions causing obscure gastrointestinal bleeding that is associated with aspirin and NSAIDs, but its use should be balanced against the risk of side-effects.

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Introduction

Bleeding in the gastrointestinal tract is generally classified according to anatomical location—ie, upper gastrointestinal bleeding (ie, proximal to the ligament of Treitz) or lower gastrointestinal bleeding.[1–3] The incidence of upper gastrointestinal bleeding has been declining since 2007, largely due to the use of proton-pump inhibitors and the eradication of *Helicobacter pylori* infection, and the diagnosis and management of obscure gastrointestinal bleeding, which is distinct from upper and lower gastrointestinal bleeding, has become a focus of research.[3–6] This condition is common in people with iron deficiency anaemia or overt or occult gastrointestinal bleeding, in whom no potential source of bleeding is found on oesophagogastroduodenoscopy or colonoscopy.[3–6] We previously found that the annual incidence of occult or obscure gastrointestinal bleeding among individuals in southwest Scotland increased from 243·1 per 100 000 individuals in 2007, to 292·8 per 100 000 individuals in 2012, and the corresponding incidence of upper gastrointestinal bleeding decreased from 140·1 per 100 000 individuals in 2007, to 88·0 per 100 000 individuals in 2012.[6] These changes were associated with an increase in the number of prescriptions of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, and proton-pump inhibitors between 2007 and 2012.[6] Obscure gastrointestinal bleeding mainly originates from the small bowel, and its incidence has been rising, which might be explained by the widespread use of low-dose aspirin and NSAIDs.[3–6] The diagnosis of small bowel ulcers in patients taking these drugs has been facilitated by the introduction of video capsule endoscopy.[7–9] Small bowel ulcers develop as a result of the suppression of mucosal prostaglandin synthesis by aspirin or NSAIDs,[7–9] and because of the alkaline environment of the small bowel, these ulcers do not respond to acid inhibitors.[7] A pilot study[10] found that small bowel mucosal lesions associated with aspirin use healed following treatment with misoprostol (a prostaglandin analogue) in four of seven patients. Preliminary data[11] have shown that misoprostol was more effective than placebo for the treatment of small bowel ulcers associated with aspirin use. Additionally, a previous retrospective short report[12] of a study including a small number of patients suggested that anaemia improved in 11 patients with NSAID-induced enteropathy given misoprostol compared with ten patients not taking misoprostol. However, these results have not been confirmed in prospective trials or in larger cohorts of patients.[11] Moreover, little is known about the efficacy of misoprostol for the treatment of NSAID-associated or aspirin-associated small bowel ulcers in patients with obscure gastrointestinal bleeding.

The MASTERS study was designed to compare the efficacy and safety of misoprostol for the treatment of small bowel ulcers in patients with obscure gastrointestinal bleeding taking low-dose aspirin or NSAIDs.

Methods

Study design and patients

This randomised, double-blind, placebo-controlled phase 3 trial was done at University Hospital Crosshouse (Kilmarnock, UK). Eligible patients were aged 18 years or older with small bowel ulcers who had been taking low-dose aspirin (75–325 mg per day), NSAIDs, or both for a minimum of 4 weeks. Patients had to have evidence of obscure gastrointestinal bleeding (positive faecal occult blood test within the previous 3 months, iron deficiency anaemia [ferritin <100 µg/L] and a haemoglobin concentration of 70–120 × 10^3 mg/L [women] or 70–130 × 10^3 mg/L [men], or a decrease in haemoglobin concentration of 20 × 10^3 mg/L or more within 3 months of screening). Patients also had to have no evidence of potential or actively bleeding lesions on upper gastrointestinal endoscopy or colonoscopy. Patients were excluded if they had incomplete endoscopy or colonoscopy results, unstable systemic disease at the time of randomisation, upper gastrointestinal lesions (ie, oesophageal varices, oesophageal stricture, oesophageal or gastric neoplasms, pyloric stenosis,

peptic ulcers, or vascular malformations), colonic disorders (neoplasms or adenomatous polyps >5 mm, inflammatory bowel disease, vascular mal formations, or actively bleeding diverticular disease), suspected or confi rmed malignancy, or hypotension (systolic blood pressure <100 mm Hg). Patients who required continuous concomitant therapy with high-dose steroids (>7·5 mg prednisolone daily), cytotoxic drugs, any anticoagulants, or antiplatelet drugs (with the exception of aspirin), high-dose proton-pump inhibitors or H_ receptor antagonists, or magnesiumcontaining antacids) were also excluded, as were women planning pregnancy, pregnant women, and women of childbearing potential not using two contraceptive methods (one of which had to be highly effective). Full exclusion criteria can be found in the appendix (pp 21–23). Individuals taking iron supplements were also excluded; however, for pragmatic reasons, the use of acid inhibitors was permitted and taken note of in the final analysis, because this was considered unlikely to result in healing of small bowel ulcers.[7] The trial was approved by the West of Scotland Research Ethics Committee (reference number 14/WS/1084). All patients provided written informed consent. The study protocol is available in the appendix (pp 7–45)**.**

Randomisation and masking

Patients were enrolled by research staff at University Hospital Crosshouse (Kilmarnock, UK). Randomisation was done at a central randomisation facility based at the Robertson Centre for Biostatistics (Glasgow, UK). Patients were randomly assigned (1:1) to receive misoprostol or placebo using an interactive voice response system. Randomisation was computer generated, using a block size of six without stratification. Patients, investigators, and assessors were masked to study treatment. To ensure masking was maintained, misoprostol and placebo capsules were identical in shape, colour, odour, and taste. The study statisticians were masked to treatment allocations until all analyses programs had been validated and the database had been locked.

Procedures

Patients received oral 200 µg misoprostol (Pfizer, Sandwich, UK) or matching placebo four times daily for 8 weeks. We did clinical assessments, full blood counts, and assessed ferritin concentrations in patients at baseline, and 4 and 8 weeks after randomisation. Patients also had video capsule endoscopy at baseline and after 8 weeks of treatment. Capsule endoscopy was done using the OMOM System (Jinshan Science and Technology, Chongqing, China). Patients attended for the procedure after an overnight fast. To prepare the small bowel, patients were given two sachets of Picolax (Ferring Pharmaceuticals, West Drayton, UK) on the day before the procedure. The small bowel mucosal findings were reported as previously described.[9] Mucosal breaks (ie, ulcers or erosions) were defined as discrete lesions with central pallor and surrounding hyperaemia and loss of villi.[9] Ulcers were arbitrarily defi ned as mucosal breaks measuring at least one-eighth of the cross-sectional view of the small bowel mucosa or extending between two adjacent folds. Smaller breaks were defined as erosions. These definitions were used because the depth of lesions is often difficult to assess as a result of the angle of the capsule endoscopy image.[9] Baseline and post-treatment capsule endoscopy findings were assessed by two adjudicators who were blinded to treatment allocation and had standardised their descriptions before the study. Any discrepancies were resolved by consensus.

Outcomes

The primary endpoint was the complete healing of small bowel ulcers or erosions, as assessed by video capsule endoscopy after 8 weeks of treatment. The secondary endpoints were change in the number of small bowel mucosal erosions, and change in blood haemoglobin concentration after 4 and 8 weeks of treatment. Prespecified per-protocol analyses were

done for the primary and safety endpoints. Subgroup analysis of haemoglobin concentrations at 4 weeks and 8 weeks was done in patients with and without anaemia at baseline. Post-hoc exploratory endpoints were complete healing of small bowel mucosal ulcers and erosions, change in the number of small bowel mucosal ulcers, and complete case analysis of complete healing of small bowel mucosal ulcers and erosions, change in the number of small bowel mucosal ulcers, and change in the number of small bowel mucosal erosions, assessed at 8 weeks. Adverse events and safety were assessed using patient diaries, face-to-face interviews, and clinical and laboratory assessments done at each visit.

Statistical analysis

In the OMNIUM trial,[13] in which patients were assigned to receive misoprostol at a similar dose and for a similar duration as in our protocol, including those who did not complete treatment, approximately 70% of NSAID-induced gastric and duodenal ulcers were successfully healed. On the basis of these results, we assumed a similar response rate in the misoprostol group in the treatment phase of this study. For the placebo group we assumed that 30% of patients would respond to treatment (including any patients misclassified as having completely healed lesions because lesions were missed). We assumed that an additional 20% of patients in each group would not have a satisfactory video capsule endoscopy 8 weeks after treatment. For the primary analysis, this implies treatment success rates of 56% (70% × 80%) for the misoprostol group and 24% (30% × 80%) for the placebo group. Thus, a sample size of 104 (52 per group) was calculated to provide 90% power with a two-tailed significance level of 5%.

Up to 71% of chronic NSAID users have erosive changes in the small bowel mucosa.[8] The prevalence of such lesions in patients taking low-dose aspirin is unknown, but we assumed that at least 40% of patients taking NSAIDs or aspirin in this study would have small bowel erosions or ulceration on initial video capsule endoscopy, and thus would be eligible for the treatment phase. We therefore aimed to screen 260 patients taking low-dose aspirin, NSAIDs, or both. Categorical data are presented as frequencies and percentages, and continuous data are presented as median and IQR. Randomised groups were compared using Fisher's exact test for binary outcomes, and continuous outcomes were compared using the Wilcoxon-Mann-Whitney test. Estimated treatment differences are reported as the absolute percentage difference (healing outcomes), the rate ratio (number of mucosal erosions and ulcers), or the mean difference (haemoglobin concentrations), with 95% CIs. Rate ratios were estimated using negative binomial regression models, and mean differences in haemoglobin were estimated using linear regression models, adjusted for baseline haemoglobin concentrations. Primary analyses were by modified intention to treat, with primary outcome data analysed for all patients who were randomly assigned and received at least one dose of study treatment. The safety analysis was done for the same group. Patients who did not have video capsule endoscopy 8 weeks after treatment, or those with inadequate images, were assumed not to have completely healed lesions. For the secondary analyses of the numbers of mucosal ulcers and erosions, patients without final video capsule endoscopy data were assumed to have the same findings at follow-up as recorded at their baseline examination. Therefore, intention-to-treat analyses of primary and secondary endpoints used a last value-carried-forward method of imputation of baseline measurements to impute missing values. All other analyses used complete data only (ie, all patients with data for the 8 week video capsule endoscopy were included). Primary and secondary analyses were repeated in the per-protocol population, which included all patients who took more than 75% of study drug capsules, did not miss more than 7 consecutive days of treatment with study drug, and had the final endoscopic examination. For the secondary outcomes of the number of mucosal erosions and haemoglobin concentrations at 8 weeks, and post-hoc analysis of number of mucosal ulcers, multivariable regression analyses were done adjusting for the following baseline factors: age, sex, use of aspirin, NSAIDs, proton-pump inhibitors, and statins, number of mucosal erosions, number of mucosal ulcers, and haemoglobin concentration. All statistical analyses were done using SAS software (version 9.4). This trial is registered with ClinicalTrials.gov, number NCT02202967.

Role of the funding source

The sponsor reviewed the protocol and regularly monitored the trial. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between Jan 7, 2016, and Oct 11, 2017, 232 patients were screened, of whom 104 were randomly assigned (1:1) to receive misoprostol (n=52) or placebo (n=52; figure). Two patients assigned to the misoprostol group were excluded because their blood pressure at screening was lower than permitted by the protocol, and thus 50 patients in the misoprostol group and 52 patients in the placebo group received the study drug and were included in the modified intention-to-treat analysis set. Baseline characteristics, including the number and types of comorbidity, were similar across the two treatment groups (table 1). 35 (70%) of 50 patients in the misoprostol group and 34 (65%) of 52 patients in the placebo group were taking low-dose aspirin for cardiovascular protection, and 22 (44%) and 20 (38%) patients were taking non-selective NSAIDs for osteoarthritis. Seven (14%) of 50 patients in the misoprostol group and two (4%) of 52 patients in the placebo group were taking both aspirin and NSAIDs. The types of NSAIDs used are shown in table 1. None of the randomised patients had obscure overt gastrointestinal bleeding. 12 patients did not complete the study because they were unwilling to continue (ten [20%] of 50 patients in the misoprostol group, two [4%] of 52 patients in the placebo group), four of whom withdrew their consent (three in the misoprostol group, one in the placebo group; figure). 27 (54%) of 50 patients in the misoprostol group and nine (17%) of 52 patients in the placebo group had completely healed ulcers and erosions at 8 weeks (percentage difference 36·7%, 95% CI 19·5–53·9; p=0·0002; table 2). Similar results were obtained when complete healing of ulcers and erosion were assessed separately (table 2). The median number of mucosal ulcers decreased between baseline and after 8 weeks of treatment in the misoprostol group, and increased during the same period in the placebo group (p<0·0001; table 2). Similarly, the median number of mucosal erosions decreased between baseline and after 8 weeks of treatment in the misoprostol group, and increased during the same period in the placebo group (p<0·0001). No significant differences in haemoglobin concentration were identified between baseline and 4 weeks after treatment, or between baseline and 8 weeks after treatment in either group (table 2). Subgroup analysis revealed no significant differences in haemoglobin concentrations at 4 weeks and 8 weeks of treatment in patients with and without anaemia at baseline (appendix p 4). Per-protocol analysis indicated that a higher proportion of patients in the misoprostol group had completely healed lesions than in the modified intention-to-treat analysis, and the number of patients with completely healed lesions was higher in the misoprostol group than the placebo group (appendix pp 2, 3).

Treatment compliance did not differ significantly between the two groups: 38 (76%) of 50 patients in the misoprostol group and 47 (90%) of 52 patients in the placebo group took more than 75% of study drug capsules (p=0·065). The median time patients did not adhere to treatment for was 14 days (IQR 4–28) in the misoprostol group and 15 days (13·5–16·5) in the placebo group (p=0·93). One patient in the misoprostol group and three patients in the placebo group missed more than 7 consecutive days of treatment and were excluded from per-protocol analysis. 23 (46%) of 50 patients in the misoprostol group reported adverse events compared with 22 (42%) of 52 patients in the placebo group (table 3). Abdominal pain represented 14 (22%) of 65 events in the misoprostol group versus 14 (25%) of 57 events in the

placebo group, diarrhoea represented 13 (20%) events versus eight (14%) events, nausea or vomiting represented 13 (20%) events versus 11 (19%) events, and bloating, constipation, and reflux symptoms represented 25 (39%) events versus 24 (42%) events (table 3). Severe adverse events occurred in four (8%) of 50 patients in the misoprostol group (nausea and vomiting and bloating [n=1], nausea or vomiting [n=1], bloating [n=2]); p=0·017 *vs* placebo, Fisher's exact test).

No serious adverse events were reported in either treatment group. Multivariable regression analysis of the number of mucosal ulcers or erosions showed that the treatment effect persisted after adjustment for a range of baseline covariates (both p<0·0001), but not haemoglobin concentration (p=0·44; appendix pp 5, 6). Patients taking aspirin at baseline had fewer mucosal erosions after 8 weeks of treatment than patients not taking aspirin at baseline (rate ratio [RR] 0·31, 95% CI 0·11–0·90, p=0·030), and those taking statins had more mucosal ulcers after 8 weeks of treatment than at baseline (RR 1·62, 1·05–2·49, p=0·028). None of the other baseline characteristics analysed (except for baseline measures of the outcome being modelled) was associated with study outcomes.

Discussion

We have shown that misoprostol is effective for the treatment of mucosal ulcers and erosions of the small bowel in patients with obscure gastrointestinal bleeding taking low-dose aspirin or NSAIDs. Low-dose aspirin and NSAIDs are widely used for their respective anti-thrombotic and anti-inflammatory activities. These drugs are known to have damaging side-effects on the upper gastrointestinal tract (ie, oesophagus, stomach, and duodenum), where acid inhibition, particularly with proton-pump inhibitors, is known to be effective for the treatment of ulcers. As a result of effective acid-inhibiting drugs, the incidence of upper gastrointestinal bleeding has decreased.[1–3,6] By contrast, diagnosis of ulcers and erosions of the small bowel among individuals taking aspirin and NSAIDs has increased; these patients have few treatment options because prostaglandin production (rather than excess acid) is the primary driver of ulcer pathogenesis in the alkaline environment of the small bowel.[3–11,14,15] Since aspirin and NSAIDs are known to cause ulcers by suppressing mucosal prostaglandin synthesis,[3–11] we chose to include patients taking these drugs in our study. These factors highlight the importance of identifying a drug that can be used to heal small bowel ulcers in patients who take aspirin and NSAIDs. The preparations of aspirin and NSAID used in this study were non-enteric coated and no comparison with enteric coated compounds was done.

Our intention-to-treat analyses of primary and secondary endpoints used a last-value-carried-forward method of imputation of baseline measurements to impute missing values, and thus included patients who had discontinued study treatment. Since the disease was progressive in patients in the placebo group, this imputation method, in combination with a higher number of discontinued patients in the misoprostol group, could have biased the results toward the null for these endpoints. However, the per-protocol analysis showed a small increase in the number of ulcers and erosions in the placebo group compared with a marked decrease in the misoprostol group. Imputation of missing data as no change would therefore decrease the between-group difference, thus we feel that the intention-to-treat analysis as specified is a conservative approach.

Distinguishing between small bowel ulcers and erosions identified by capsule endoscopy can be difficult, which represents a limitation of our study.[8,9] To overcome this limitation, the images were examined by two assessors who standardised their interpretation, and any discrepancies were resolved by consensus. Moreover, we showed that misoprostol was effective in healing both ulcers and erosions, regardless of their classification, when analysed separately and in combination.

Our study has a number of additional limitations. The study was done at a single centre, most patients were white, and no women of childbearing age were included. Furthermore, less than half of patients taking either misoprostol or placebo had iron deficiency anaemia at baseline and patients with severe or unstable systemic

diseases were excluded. These factors might limit the generalisability of our findings and warrant further investigation. To the best of our knowledge, this is the largest study to date investigating the efficacy of misoprostol in this setting. Our findings are consistent with the results of an open-label pilot study[10] and double-blind study[11] investigating misoprostol in individuals using low-dose aspirin. In those studies, the number of patients with completely healed lesions was lower than that in our study, possibly because of the difference in ethnicities of the included populations (individuals from southeast Asia *vs* individuals from western Europe). However, similar to our study, haemoglobin concentrations were not found to increase as a result of small bowel ulcer and erosion healing,[11] which might indicate that small bowel lesions were not the cause of gastrointestinal bleeding manifesting as iron deficiency anaemia or decreased haemoglobin concentrations. However, we believe that the strict inclusion and exclusion criteria used, coupled with the absence of potential sources of blood loss on upper endoscopy and colonoscopy, indicate that obscure gastrointestinal bleeding was most likely to be caused by small bowel lesions in this study and previous studies.[2–11] Patients taking iron supplements, which are frequently given to treat obscure gastrointestinal bleeding,[6] were excluded from this study and previous studies.[11] Therefore, the intake of misoprostol for longer than 8 weeks or combined with iron supplements might result in higher haemoglobin concentrations than observed,[11] but this needs to be confirmed.

Our study included patients with abdominal symptoms and positive faecal occult blood tests, but normal haemoglobin concentrations, which might have made it difficult to identify any increases in haemoglobin concentrations after 8 weeks of treatment, and might be considered a limitation of our study. However, these findings should not diminish the clinical importance of the findings of this study. We also believe that the identification of small bowel ulcers is clinically significant in patients with abdominal complaints and positive faecal occult blood tests who are taking aspirin or NSAIDs. Clinicians might find it difficult to reassure these patients about their small bowel ulcers and occult bleeding solely on the basis of normal endoscopy and colonoscopy results. Patients taking aspirin or NSAIDs who have similar ulcers in the stomach or duodenum are normally prescribed acid inhibitors or misoprostol, regardless of the presence or absence of symptoms, because of the risk of serious complications, such as bleeding. Small bowel ulcers can also lead to bleeding (hence the concept of obscure gastrointestinal bleeding[3–6]) and thus the patient's desire to receive treatment would be understandable.

In this study, we included patients taking proton-pump inhibitors who had small bowel ulcers at baseline. Previous literature[3,6] has suggested that proton-pump inhibitors might aggravate the damaging effects of aspirin or NSAIDs on the small bowel mucosa. Multivariate regression analysis showed that the intake of these drugs did not influence the outcomes in our trial, but this result cannot be considered conclusive in view of the small sample size.

Consistent with the results of our study, a previous trial[13] reported that misoprostol is associated with nausea, vomiting, diarrhoea, and abdominal pain. The overall incidence of these adverse events was similar between the two treatment groups, but more patients in the misoprostol group reported severe symptoms than did patients in the placebo group. Notably, severe adverse events, which can be subjective, should not be confused with serious side-effects, which can lead to hospital treatment, disability, or death. No serious side-effects were noted in our study, and since none of the female patients were of childbearing age, there was no risk of abortion in the misoprostol group. The proportion of patients with adverse events in the placebo group (42%) and the misoprostol group (46%) was relatively high. Although some of these events were considered treatment-related, ulcerative small bowel disease itself is associated with many of the same side-effects as those our patients were prompted to record in their study diaries.

We used the maximum recommended dose of misoprostol to maximise the number of patients with completely healed ulcers, thus it is possible that lower doses might still have efficacy and might be better tolerated, but this needs to be confirmed. Despite the adverse events, compliance to study treatment was not significantly different between the two groups. However, misoprostol should not be taken by women of childbearing age unless they use reliable contraceptive

methods because the drug can cause abortion.

In conclusion, we have shown that misoprostol is more effective than placebo for the treatment of small bowel ulcers and erosions in patients using low-dose aspirin and NSAIDs who have obscure gastrointestinal bleeding. Thus, treatment with misoprostol would enable these patients to continue treatment with these drugs for their intended indications. However, the use of misoprostol must be balanced against the risk of side-effects. Also, it is difficult to anticipate the effectiveness of misoprostol in a population of patients with obscure gastrointestinal bleeding and transfusion-dependent anaemia. Efficacy and safety data for a population with more severe disease would be needed before the widespread use of misoprostol could be recommended.

Contributors

AST, CM, and AM contributed to writing the study protocol. PM did the statistical analysis under the guidance of AM. All authors contributed to writing the article.

Declaration of interests

PM and AM report that their institution received funding from National Health Service Ayrshire and Arran to cover salaries and costs of the statistical analysis. AST and CM declare no competing interests.

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Research in context

Evidence before this study

We searched PubMed from inception to Feb 2, 2018, for studies of any type published in English, regardless of date, using the search term “misoprostol for small bowel ulcers”. We found two publications that matched the search term. A previous preclinical trial found that gastroprotectant drugs prevented the exacerbation of enteric damage induced by non-steroidal anti-inflammatory drugs (NSAIDs) in rats. An open-label pilot study in human beings showed that erosive lesions of the small bowel in individuals taking enteric-coated aspirin healed in four of seven patients given misoprostol. Little is known about the efficacy of misoprostol for the treatment of small bowel ulcers associated with NSAIDs or aspirin in patients with obscure gastrointestinal bleeding. In view of the rising incidence of obscure gastrointestinal bleeding caused by aspirin and NSAIDs, which is now known to originate from the small bowel, misoprostol has received attention as a potential treatment for this condition.

Added value of this study

To the best of our knowledge, this is the largest study to date investigating the efficacy of misoprostol in patients taking NSAIDs or aspirin with obscure gastrointestinal bleeding. Our results show that misoprostol is more eff ective than placebo for the complete healing of small bowel ulcers in these patients after 8 weeks of treatment. No significant differences in haemoglobin concentrations were found between baseline and after 8 weeks of treatment in either group. Notably, the incidence of adverse events was relatively high in the misoprostol group.

Implications of all the available evidence

The results of this randomised trial indicate that misoprostol might represent a treatment option for patients with small bowel ulcers, which could be taken concurrently with NSAIDs or aspirin. However, misoprostol use can be associated with abdominal pain, nausea or vomiting, or diarrhoea in some patients. Future studies investigating the association between the treatment of small bowel ulcers and changes in haemoglobin concentrations in patients treated for longer than 8 weeks, or in patients taking iron supplements, are warranted. We caution against giving misoprostol to women of childbearing age without the use of reliable contraceptive measures.

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CONSORT 2010 Flow Diagram

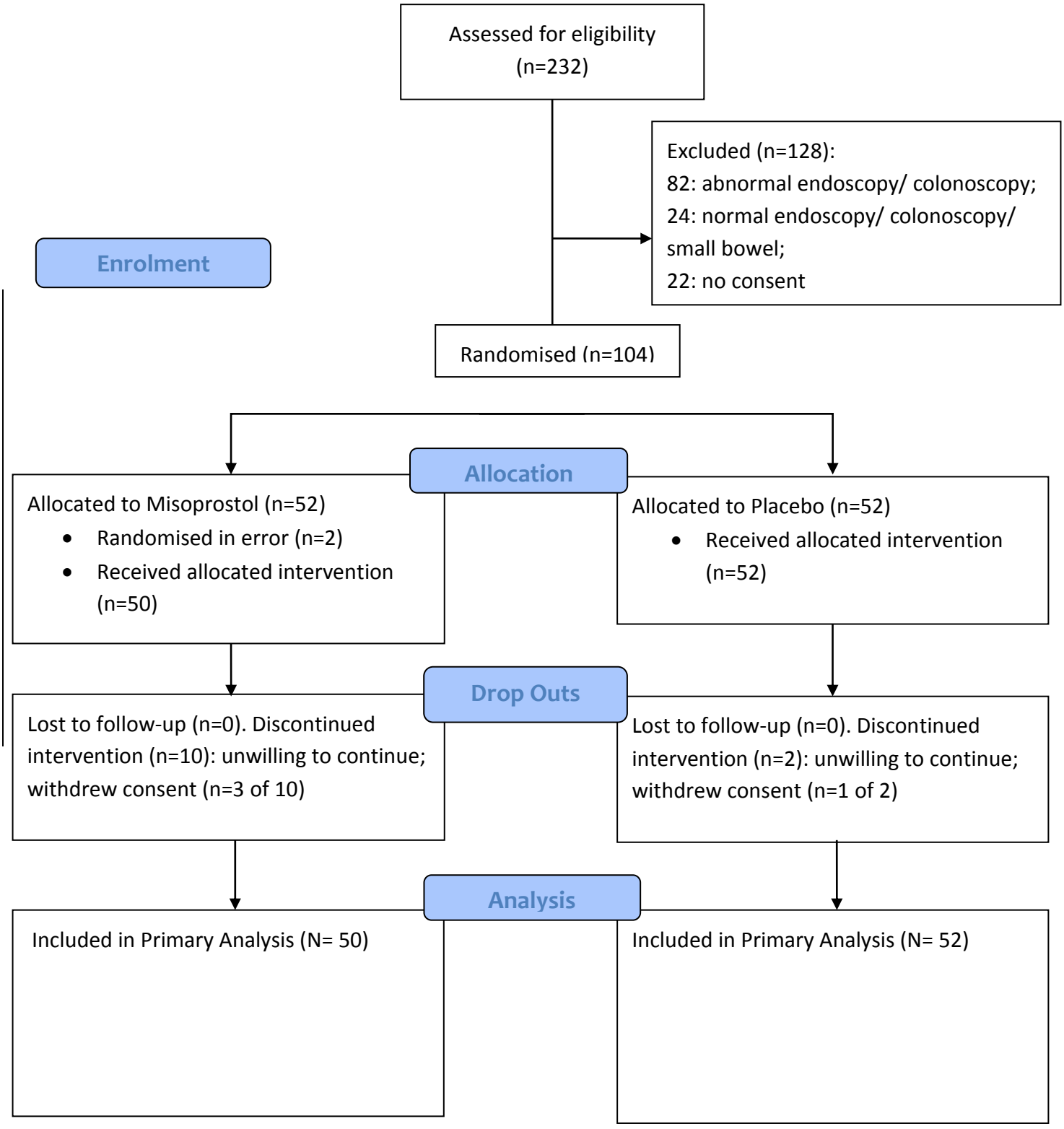

Table 1. Baseline characteristics. Data reported as number (%) or median [IQR].

Variable	Misoprostol N=50	Placebo N=52
Age (years) at randomisation	68 [58, 71]	63 [57, 71]
Gender		
Male	30 (60%)	24 (46.2%)
Female	20 (40%)	28 (53.8%)
Ethnicity		
White	50 (100%)	50 (96.2%)
Mixed/ multiple ethnic groups	0 (0%)	1 (1.9%)
Black/ African/ Caribbean	0 (0%)	1 (1.9%)
Woman of child bearing age	0 (0%)	0 (0%)
Iron deficiency anaemia	18 (36%)	22 (42.3%)
Drop in haemoglobin > $20x10^3$ mg/L within 3 months of screening	1 (2%)	3 (5.8%)
Positive faecal occult blood	31 (62%)	27 (52%)
Other comorbid conditions	48 (96%)	50 (96.2%)
Drug intake:		
Proton-Pump Inhibitors	34 (68%)	33 (63.5%)
NSAIDs	22 (44%)	20 (38.5%)
Aspirin	35 (70%)	34 (65.4%)
Both NSAIDs and Aspirin	7 (14%)	2 (3.8%)
Types of NSAIDs Taken:		
Dicolfenac	2 (1.0%)	1 (0.5%)
Etodolac	3 (1.5%)	0 (0.0%)
Ibuprofen	1 (0.5%)	3 (1.4%)
Meloxicam	2 (1.0%)	6 (2.9%)
Nabumetone	1 (0.5%)	0 (0.0%)
Naproxen	14 (7.0%)	10 (4.8%)

Table 2: Primary* and secondary outcomes, intention-to-treat analysis. Data reported as number (%) or median [IQR]. Treatment effect estimate reported as absolute percentage difference (PD), rate ratio (RR), or mean difference (MD) (Misoprostol – Placebo). P-values from Fisher's Exact Tests, or Wilcoxon-Mann-Whitney tests**

Outcome	Misoprostol N=50	Placebo N=52	Treatment Effect Estimate		(95% CI)	p-value
Full healing of mucosal ulcers and erosions*						
	27 (54%)	9 (17.3%)	PD	36.7%	(19.5%, 53.9%)	0.0002
Full healing of mucosal ulcers*						
	34 (68%)	9 (17.3%)	PD	50.7%	(34.2%, 67.2%)	<0.0001
Number of mucosal ulcers**						
Baseline	3 [2, 4]	2 [2, 4]				
8 weeks	0 [0, 1]	3 [1.5, 4]	RR	0.22	(0.13, 0.35)	<0.0001
Change	-2 [-4, -1]	0.5 [-1, 1]				<0.0001
Full healing of mucosal erosions*						
	28 (56%)	11 (21.2%)	PD	34.8%	(17.2%, 52.5%)	0.0005
Number of mucosal erosions**						
Baseline	4 [3, 6]	4 [3, 6]				
8 weeks	0 [0, 3]	5 [2, 6.5]	RR	0.36	(0.23, 0.56)	<0.0001
Change at 8 weeks	-3 [-4, 0]	1 [-2, 2]				<0.0001
Haemoglobin**						
Baseline	N=49 136 [117, 145]	N=52 133 [122, 146.5]				
4 weeks	N=42 133 [119, 147]	N=50 132 [120, 147]	MD	-0.14	(-3.90, 3.62)	0.95
Change at 4 weeks	-5 [-7, 1]	-4.5 [-9, 2]				0.80
8 weeks	N=39 136 [121, 145]	N=50 136 [121, 145]	MD	1.20	(-1.84, 4.24)	0.82
Change at 8 weeks	0 [-3, 4]	-3 [-5, 4]				0.18

Note: subjects without final video capsule endoscopy data are assumed to have the same number of mucosal ulcers and erosions as at baseline, and are counted as not healed, in these analyses (web appendix page1 for complete case analysis and page 2 for per-protocol analysis results). The haemoglobin analysis uses complete data only and was derived from normal linear regression.

Table 3: Adverse Events. Data reported as number (%).

	Misoprostol N=50		Placebo N=52	
Number of Adverse Events	65		57	
Patients with at least one Adverse Event	23 (46%)		22 (42%)	
Number of Serious Adverse Events	0		0	
Patients with at least one Serious Adverse Event	0 (0%)		0 (0%)	
Adverse Event Type	**N Events**	**Patients**	**N Events**	**Patients**
Abdominal Pain	14	10 (20%)	14	13 (25%)
Diarrhoea	13	11 (22%)	8	6 (12%)
Nausea/vomiting	13	9 (18%)	11	7 (14%)
Other:	25	13 (26%)	24	15 (29%)
Bloating	7	3 (6%)	6	4 (8%)
Constipation	1	1 (2%)	2	2 (4%)
Difficulty Swallowing	3	2 (4%)	1	1 (2%)
Heartburn	10	7 (14%)	14	12 (23%)
Regurgitation	4	3 (6%)	1	1 (2%)
Adverse Event Severity*				
Mild	34	16 (32%)	40	17(33%)
Moderate	25	16 (32%)	16	10 (19%)
Severe	6	4 (8%)	0	0 (0%)

***** p=0.017 vs. placebo, Fisher's Exact Test for Number of Events. Number of patients for each severity level Fisher's Exact tests p-values are not significant