# Misoprostol Heals Small Bowel Ulcers in Aspirin Users With Small Bowel Bleeding

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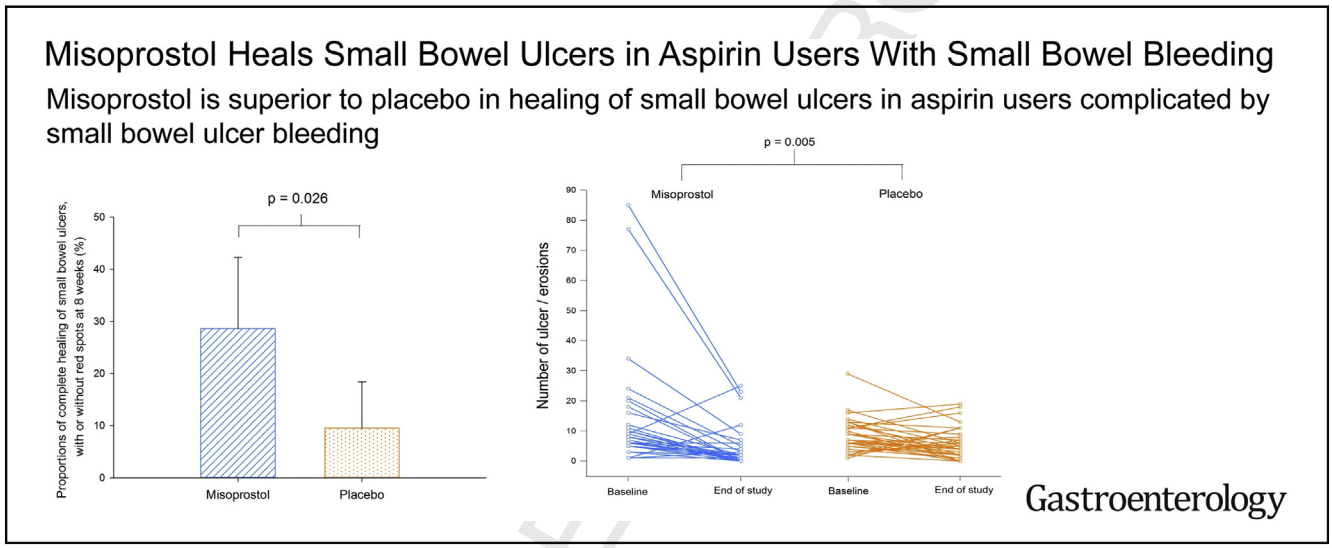


**BACKGROUND & AIMS:** There is no effective treatment for aspirin-induced small bowel ulcer bleeding. We performed a double-blind, randomized, placebo-controlled trial to determine whether misoprostol can heal small bowel ulcers in patients with small bowel bleeding who require continuous aspirin therapy. **METHODS:** We performed a prospective study of 84 aspirin users with small bowel bleeding who required continued aspirin therapy in Hong Kong and Japan. Patients with small bowel ulcers or multiple erosions, detected by capsule endoscopy, were randomly assigned to groups that received either misoprostol (200 $\mu$g, 4 times daily; n = 42) or placebo (n = 42) for 8 weeks. All patients continued taking aspirin (100 mg, once daily). The primary end point was complete ulcer healing at follow-up capsule endoscopy. Secondary end points included changes in hemoglobin level and number of ulcer/erosions from baseline. **RESULTS:** Complete healing of small bowel ulcers was observed in 12 patients in the misoprostol group (28.6%; 95% confidence interval [CI], 14.9%–42.2%) and 4 patients in the placebo group (9.5%; 95% CI, 0.6%–18.4%), for a difference in proportion of 19.0% (95% CI, 2.8%–35.3%; $P = .026$). The misoprostol group had a significantly greater mean increase in hemoglobin than the placebo group (mean difference, 0.70 mg/dL; 95% CI, 0.05–1.36; $P = .035$). The reduction in medium number of ulcers or erosions was significantly greater in the misoprostol group (from 6.5 [range, 1–85] to 2 [range, 0–25]) than in the placebo group (from 7 [range, 1–29] to 4 [range, 0–19] ($P = .005$). **CONCLUSIONS:** In a double-blind, randomized, placebo-controlled trial, we found misoprostol to be superior to placebo in promoting healing of small bowel ulcers among aspirin users complicated by small bowel ulcer bleeding who require continuous aspirin therapy. However, use of misoprostol alone would provide only limited protection against aspirin on the small bowel. ClinicalTrials.gov ID NCT01998776.

*Keywords:* MABLE Study; ASA; Prostaglandin; Anti-Platelet.

*Authors share co-first authorship.

***Abbreviations used in this paper:*** **CI, confidence interval; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.**


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**WHAT YOU NEED TO KNOW**

BACKGROUND AND CONTEXT

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NEW FINDINGS

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LIMITATIONS

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IMPACT

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CLINICAL AT

Bleeding from lower gastrointestinal (GI) tract (bleeding beyond the ligament of Treitz) has become an increasing burden in the last decade. Studies from Spain and the United States have reported a rising trend in lower GI bleeding.[1,2] This temporal change is thought to be associated with escalating use of non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin.[3] Growing evidence suggests aspirin is an important cause of lower GI bleeding.[4,5] A national health database showed that aspirin increases the risk of lower GI bleeding by almost 3-fold.[4] Another prospective study reported that NSAIDs accounted for 40% of all undiagnosed GI blood loss.[6] The prevalence of NSAID use is reported to be as high as 86% in patients with lower GI bleeding.[7] Importantly, lower GI bleeding is associated with a significantly longer hospital stay and higher mortality than upper GI bleeding.[1] As one of the most commonly prescribed drugs worldwide (>58 billion doses ingested each year),[8] aspirin-associated lower GI bleeding has important global health care implications. The burden of this condition is expected to increase with aging populations.[9,10]

The ideal treatment for small bowel ulcers in aspirin users would be withdrawal of aspirin, but this exposes the patient to cardiothrombotic complications. Patients with cardiothrombotic diseases often require lifelong aspirin. We have shown that prolonged discontinuation of aspirin after lower GI bleeding is associated with increased cardiovascular events and death, whereas aspirin continuation increases the risk of recurrent lower GI bleeding.[11] Thus, patients requiring lifelong aspirin are left without a safe option in preventing both GI and cardiothrombotic complications. The decision on whether to resume aspirin after lower GI bleeding remains a management dilemma for clinicians, particularly in the absence of risk-mitigating therapies. It has become an urgent priority to identify a therapy to heal small bowel ulcers in aspirin users.

Currently there is no effective therapy for aspirin-induced small bowel ulcer bleeding. At least 6 small pilot studies have explored various pharmacologic therapies.[12–17] The hope of extracting meaningful conclusions was reduced by either inadequately powered studies,[12–16] using low-risk subjects and subclinical end points,[13,15,17] short study duration,[12,13,15,16] or without an control arm for comparison.[12,14,16] To date, no therapy has ever been tested on clinically important end points (ie, aspirin-induced small bowel ulcers complicated by bleeding).

Randomized trials for the healing of small bowel ulcers in aspirin users complicated by gastrointestinal bleeding are lacking. Our preliminary finding showed that misoprostol could heal subclinical small bowel ulcers in asymptomatic aspirin users.[12] We aimed to test the hypothesis that misoprostol can heal small bowel ulcers in aspirin users complicated by small bowel bleeding.

## Methods

### Study Design and Population

This is a multicentered, industry-independent, double-blind, randomized, placebo-controlled trial conducted at Prince of Wales Hospital of The Chinese University of Hong Kong, and Osaka City University Graduate School of Medicine, Japan. The study was done in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. The local ethics committee approved the study protocol.

We screened aspirin users (≤160 mg/d) presenting with suspected small bowel bleeding as overt bleeding or a significant drop in hemoglobin who required continuous aspirin therapy. Overt bleeding was defined as melena or hematochezia without a source of bleeding from gastroscopy and colonoscopy. A significant drop in hemoglobin was defined as a drop in hemoglobin >2 g/dL without a source of bleeding from gastroscopy and colonoscopy or other non-GI causes of anemia. The exclusion criteria were patients with gastroscopic findings in the stomach accountable for the bleeding episode (eg, esophageal varices, grade C or D erosive esophagitis, vascular malformations, ulcer >2 cm, >5 erosions, or neoplasms); patients with colonoscopic findings accountable for the bleeding episode (eg, diverticular bleeding, angiodysplasia, hemorrhoidal bleeding, or malignant neoplasms); concomitant use of NSAIDs, sucralfate, rebamepide, antibiotics, corticosteroids (prednisolone >7.5 mg daily or equivalent), or iron supplement; contraindications to capsule endoscopy; and pregnancy or women of childbearing age without regular use of contraception.

### Procedure

Aspirin users presenting with suspected small bowel bleeding who were eligible received a baseline capsule endoscopy. Capsule endoscopy was performed using PillCam SB2 (Given Imaging, Ltd, Yoqneam, Israel). Patients were fasted after midnight. Small-bowel preparation consisted of 1 L polyethylene glycol ingested together with capsule. Patient resumed oral diet once confirmation capsule has reached small bowel using real-time viewer. Patency capsule was not routinely used. Baseline capsule endoscopy findings were read