Original research

Prevention of rebleeding after primary haemostasis using haemostatic powder in non-variceal upper gastrointestinal bleeding: a multicentre randomised controlled trial

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ABSTRACT

Background Non-variceal upper gastrointestinal bleeding (NVUGIB) remains a major cause of morbidity and mortality. Rebleeding rates following endoscopic treatment can reach up to 25% within 72 hours in patients with high-risk lesions.

Objective To evaluate the efficacy of a haemostatic powder (Nexpowder) in reducing rebleeding rates after conventional endoscopic treatment in patients with NVUGIB.

Design This was a prospective, multicentre, randomised controlled trial involving patients with acute NVUGIB from high-risk lesions who achieved initial endoscopic haemostasis. Participants were randomised 1:1 to receive either the haemostatic powder or no further therapy (control group). The primary outcome was the rebleeding rate within 72 hours post-treatment. Secondary outcomes included the 30-day rebleeding rate and the safety profile.

Results A total of 341 patients (72.1% male; mean age 64.8 years) were included, with 173 in the powder group and 168 in the control group. Baseline characteristics were similar between groups. Ulcer bleeding was the predominant aetiology (n=317), with Forrest type I bleeding observed in two-thirds of cases. The 72-hour rebleeding rate was significantly lower in the powder group (2.9%, 95% CI 0.9 to 6.6%) compared with the control group (11.3%, 95% CI 6.9 to 17.1%; p =0.005). A significant reduction was also observed in the 30-day cumulative rebleeding rate (7.0% vs 18.8%), with similar findings in the ulcer subgroup for the 3-day rebleeding rate (3.0% vs 12.0%; p =0.004). No adverse events related to the powder application were reported.

Conclusion The application of Nexpowder following endoscopic haemostasis significantly reduced both early (3 days) and late (30 days) rebleeding rates in patients with NVUGIB, particularly in cases of ulcer-related bleeding.

Trial registration number NCT04124588.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite advancements in endoscopic haemostasis and pharmacologic therapies, rebleeding after conventional endoscopic intervention for non-variceal upper gastrointestinal bleeding (NVUGIB) remains associated with high mortality rates and prolonged hospital stays. To date, the only established method for reducing rebleeding following endoscopic treatment in NVUGIB has been the administration of proton pump inhibitors.

WHAT THIS STUDY ADDS

⇒ The application of Nexpowder significantly reduced the rebleeding rate following conventional endoscopic haemostasis in NVUGIB, without any procedure-related complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study is the first since the introduction of proton pump inhibitor therapy to demonstrate that an additional endoscopic preventive intervention—specifically, the application of a mucoadhesive hemostatic powder—can further reduce the risk of rebleeding following initial endoscopic haemostasis.

INTRODUCTION

Non-variceal upper gastrointestinal bleeding (NVUGIB) is a major cause of emergency department visits and hospitalisations, contributing significantly to morbidity and mortality.[1] Despite a decline in incidence, NVUGIB still accounts for over 200 000 hospital admissions annually in the USA,[2] with a 30-day readmission rate of 14%.[3] Rebleeding after conventional endoscopic therapy remains a major clinical challenge, occurring in 14%–25% of cases,[3–5] and up to 29.5% in high-risk lesions (Forrest Ia, Ib, IIa), even with proton pump inhibitor (PPI) therapy.[6] Rebleeding is associated with increased mortality, prolonged hospitalisation and the need for additional interventions.[2 3 7] Although PPI therapy and *Helicobacter pylori* eradication are recommended post-treatment, no intervention has yet reliably reduced the risk of rebleeding.[8]

Conventional endotherapy methods include injection therapy, thermal coagulation and clipping, with outcomes influenced by lesion characteristics, available equipment and operator skill.[9–12] These methods can also cause mucosal injury and complications. Topical haemostatic agents (eg, Hemospray, EndoClot, PuraStat) offer ease of use and are effective for immediate haemostasis, but they have not demonstrated efficacy in preventing delayed rebleeding.[13–17] Nexpowder (NEXTBIOMEDICAL, Korea) is a novel mucoadhesive powder that forms a strong gel barrier on contact with moisture, providing both mechanical haemostasis and mucosal protection.[18] Its delivery system uses low-pressure room air, minimising the risk of barotrauma and perforation, with no adverse events reported in preclinical or clinical studies.[18–21]

This study aimed to evaluate the safety and efficacy of Nexpowder when applied after conventional endoscopic measures to reduce rebleeding rates in patients with acute NVUGIB due to high-risk lesions.

METHODS

Study design

This prospective, multicentre, single-blind (participant-blinded), randomised controlled trial evaluated the efficacy and safety of Nexpowder in patients who achieved initial haemostasis following conventional endoscopic therapy. A total of 348 patients were targeted for enrolment across three institutions in South Korea, accounting for an anticipated 10% dropout rate. The study protocol was approved by the institutional review boards of all participating centres and registered at ClinicalTrials.gov (NCT04124588).

Patients and randomisation

Between November 2018 and November 2021, patients presenting with signs of NVUGIB—including haematemesis, melena or haemodynamic instability—were screened at the participating institutions. Informed consent was obtained prior to any endoscopic procedures. Eligible patients were aged 19 years or older and had achieved successful haemostasis through conventional endotherapy for Forrest Ia, Ib, IIa or IIb lesions. For Forrest IIb lesions, inclusion required that the adherent clot be easily removed with gentle irrigation, revealing an underlying lesion classified as Forrest IIa or higher. Patients were excluded if conventional therapy failed to achieve haemostasis, if informed consent was not obtained before the procedure or if the patient was pregnant or lactating. A total of 348 patients met the inclusion criteria (figure 1).

Following successful endotherapy, patients were sequentially assigned a study registration number and randomised in a 1:1 ratio to either the adjuvant Nexpowder group or the control group (no further intervention) using a block randomisation method. Allocation was based on a pre-generated randomisation table, with sealed opaque envelopes managed independently at each site. This was a single-blind study: operators could not be blinded due to the nature of the procedure, but participants were blinded to their treatment allocation.

Study treatment

Prior to enrolment and randomisation, patients suspected of UGIB underwent endoscopy to confirm the presence of a high-risk lesion. On identification, appropriate conventional endotherapy was performed, including haemostatic clipping, thermal coagulation or injection with diluted epinephrine. In accordance with the 2021 American College of Gastroenterology guidelines, epinephrine injection was always followed by an additional modality, either clipping or thermal therapy.[22] Due to Korea's insurance structure and the established efficacy of thermal methods, two primary techniques—argon plasma coagulation (APC) and coagulation forceps—were predominantly used. Haemostasis was defined as the absence of active bleeding for 5 min following endotherapy. If haemostasis could not be

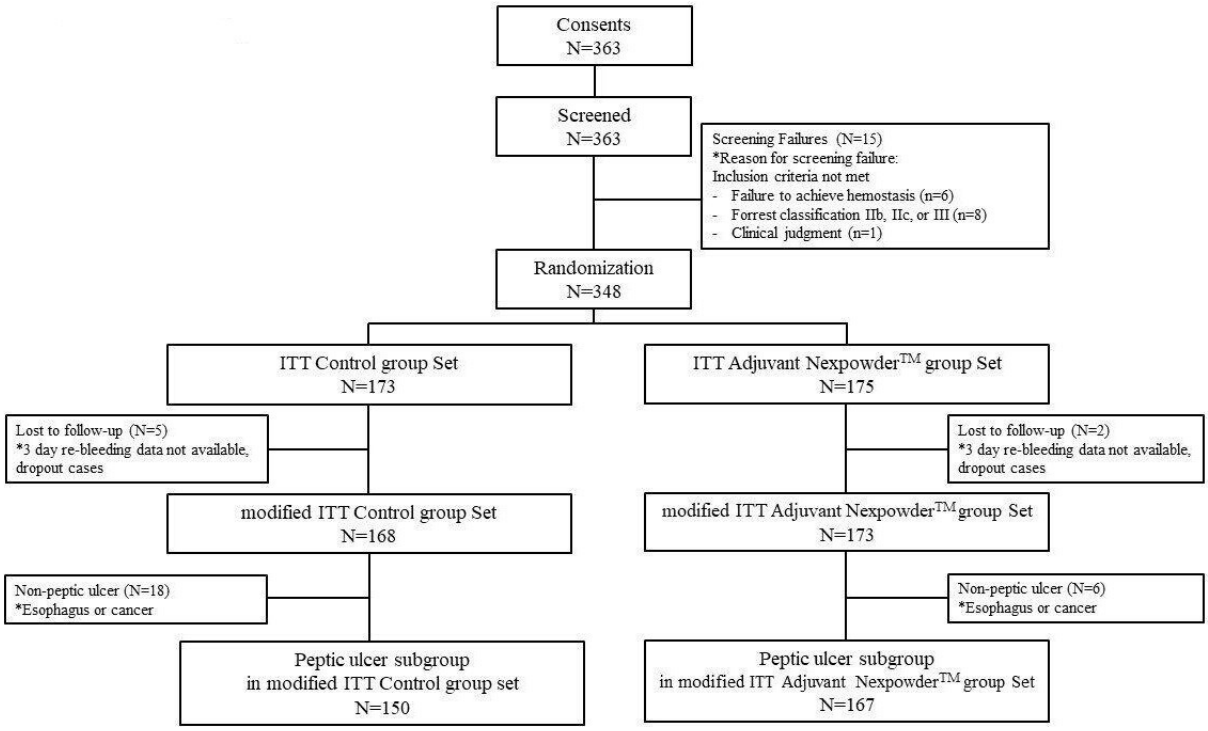

Figure 1 Patient selection flowchart of the study. ITT, intention-to-treat.

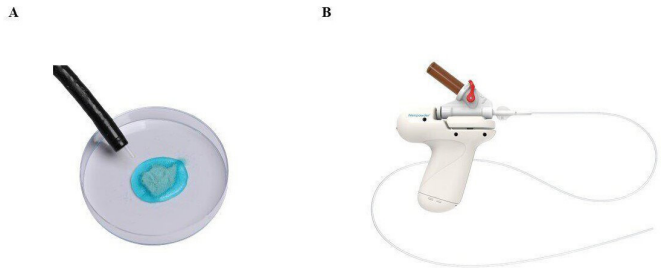

Figure 2 (A) Nexpowder and (B) powder delivery devices.

achieved with endotherapy alone, patients were treated with Nexpowder, surgery, or arterial embolisation and were subsequently excluded from the study.

In the adjuvant Nexpowder group, 3 g (one vial) of Nexpowder (figure 2A,B) was applied to the lesion. A second 3 g dose was administered if the initial quantity was deemed insufficient to fully cover the bleeding site. Following haemostasis, both groups received intravenous pantoprazole, consisting of an 80 mg bolus followed by continuous infusion at 8 mg/h for 72 hours.

Outcomes and follow-up

The primary outcome was the rate of rebleeding within 72 hours after the initial endoscopy. Secondary outcomes included the rate of rebleeding within 30 days and the safety profile of Nexpowder.

Patients were monitored during the 3-day hospitalisation period. If clinical signs of rebleeding emerged, a blinded investigator or clinical research coordinator reviewed vital signs and clinical data to assess for the following predefined rebleeding criteria:

1. Melena following normalisation of bowel movements
2. Haematochezia after normalised bowel movements or bloody stool following melena
3. New-onset tachycardia (heart rate ≥110 bpm) or hypotension (systolic blood pressure ≤90 mm Hg) after ≥1 hour of haemodynamic stability, without an alternative cause (eg, sepsis, shock, medication effect)
4. Haemoglobin drop ≥2 g/dL after stabilisation (compared with <0.5 g/dL in stable patients).
5. Persistent tachycardia or hypotension for >8 hours post-endoscopy.
6. Haemoglobin decrease >3 g/dL within 24 hours in the presence of ongoing melena or haematochesia.
7. Haematemesis, or any of the above signs, occurring ≥6 hours after endoscopy (to exclude procedural failure).

If any of these criteria were met within 72 hours, a second-look endoscopy was performed. In cases of confirmed rebleeding, additional conventional endoscopic therapy was administered at the discretion of the endoscopist.

All patients were followed for 30 days postrandomisation. Follow-up was conducted either through outpatient visits or telephone contact. Serious adverse events were reported within 7 days to the Korean Ministry of Food and Drug Safety, in accordance with national medical device safety reporting guidelines.

Statistical analysis

Sample size estimation was based on reference rebleeding rates derived from previous studies.[6 23–27] It was assumed that the rebleeding rate would be 18% in the control group and 7.5% in the adjuvant Nexpowder group. The alpha level was set at 5% and the study power at 80%. A 10% dropout rate was also factored into the calculation.

Clinical characteristics of study participants were expressed as medians (ranges) or means±SD for continuous variables and as numbers (percentages) for categorical variables. Statistical significance between groups for categorical variables was assessed using Pearson's $\chi 2$ test or Fisher's exact test, as appropriate. Differences in continuous variables were evaluated using the independent two-sample t-test. Two-tailed P values <0.05 were considered statistically significant. Statistical analyses were performed using R software V.4.3.1 (CRAN, USA).

RESULTS

Study recruitment and follow-up

Between November 2018 and November 2021, 363 patients presenting with NVUGIB underwent screening via endoscopy. Fifteen patients were excluded for the following reasons: failure to achieve haemostasis (n=6), ineligible Forrest classification (n=8) or clinician judgement due to absence of active bleeding (n=1). Thus, 348 patients were randomised.

Seven patients (two from the adjuvant Nexpowder group and five from the control group) were lost to follow-up and excluded from the intention-to-treat (ITT) analysis due to missing 3-day rebleeding data required for the primary outcome. The modified ITT (mITT) population included 341 patients: 173 in the adjuvant Nexpowder group and 168 in the control group (figure 1).

For the ulcer subgroup analysis, which focused on high-risk peptic ulcer bleeding, patients with bleeding from oesophageal lesions or tumours were excluded—specifically, 16 patients with oesophageal bleeding (12 in the control group, 4 in the powder group) and eight with tumour-related bleeding (six in the control group, 2 in the powder group). As a result, 167 patients in the adjuvant Nexpowder group and 150 in the control group were included in the final mITT analysis for peptic ulcer bleeding.

Baseline characteristics

The baseline and clinical characteristics of the control and adjuvant Nexpowder groups in the ulcer subgroup are summarised in table 1. No significant differences were observed between the groups regarding sex distribution (female: 26.7% vs 30.5%, p=0.524), age (64.7 ± 14.1 vs 64.7 ± 13.8 years, p=0.997) or initial vital signs, including systolic and diastolic blood pressure. Similarly, no significant difference was found in the Glasgow-Blatchford bleeding score (GBS: 10.7 (95% CI 9.8 to 11.0) vs 10.3 (95% CI 10.1 to 11.3), p=0.473). The use of anticoagulant or anti-platelet medications (p=0.829) and the distribution of comorbidities were also comparable between the two groups. Baseline characteristics for the overall study population are presented in online supplemental table S1.

Bleeding characteristics of study treatments

There were no significant differences between the two groups regarding bleeding characteristics (table 2 and online supplemental table S2), including Forrest classification (p=0.924), initial cause of bleeding (p=0.478) and bleeding site (p=0.595).

A range of endotherapy modalities was applied to achieve initial haemostasis, with one to four techniques used as needed. Thermal haemostasis—comprising APC and monopolar coagulation forceps—was the most commonly used method (control vs adjuvant Nexpowder: 96.0% vs 92.2%, p=0.364). Haemostatic clips (16.0% vs 13.2%, p=0.580) and epinephrine injection prior to thermal or mechanical therapy (10.7% vs 7.8%, p=0.376) were employed less frequently.

Table 1 Baseline and clinical characteristics of study subjects (in mITT group: ulcer subgroup)

	Control group (n=150)	Adj. Nexpowder group (n=167)	*P* value‡
Sex (female, n, %)	40 (26.7)	51 (30.5)	0.524
Age (year)*	64.7±14.1	64.7±13.8	0.997
SBP (mm Hg)	123.2±19.7	122.7±18.9	0.816
DBP (mm Hg)	72.8±12.1	71.7±11.3	0.406
GBS Score††	10.7 (10.4±0.6)	10.3 (10.7±0.6)	0.473
Anti-thrombotic (n, %)			0.829
Aspirin	26 (17.3)	26 (15.6)	0.786
Clopidogrel	18 (12.0)	24 (14.4)	0.648
Cilostazol	5 (3.3)	3 (1.8)	0.608
Warfarin	1 (0.7)	6 (3.6)	0.165
Ribaroxaban	4 (2.7)	0 (0.0)	0.105
Heparin	3 (2.0)	0 (0.0)	0.209
Ticlopidine	3 (2.0)	0 (0.0)	0.209
Edoxaban	0 (0.0)	1 (0.6)	1.000
Mesoglycan	0 (0.0)	1 (0.6)	1.000
Ticagrelor	1 (0.7)	0 (0.0)	0.957
Beraprost	1 (0.7)	0 (0.0)	0.957
Comorbidities (n, %)			
Stroke	17 (11.3)	12 (7.2)	0.278
Cancer	8 (5.3)	11 (6.6)	0.816
Cardiovascular disease	12 (8.0)	16 (9.6)	0.766
Liver disease	4 (2.7)	5 (3.0)	1.000
Renal disease	17 (11.3)	13 (7.8)	0.376

*Mean, SD.
†Mean (95% CI).
‡*P* values were calculated using the *t*-test or $\chi 2$ test.
DBP, diastolic blood pressure; GBS, Glasgow-Blatchford bleeding score; mITT, modified intention-to-treat; SBP, systolic blood pressure.

Table 2 Bleeding characteristics of study subjects in the ulcer subgroup

	Control group (n=150)	Adj. Nexpowder group (n=167)	P value*
Forrest classification (n, %)			0.924
Forrest Ia	18 (12.0)	23 (13.8)	–
Forrest Ib	79 (52.7)	86 (51.5)	–
Forrest IIa	52 (34.7)	56 (33.5)	–
Forrest IIb	1 (0.7)	2 (1.2)	–
Initial bleeding cause (n, %)			0.478
Gastric ulcer	106 (70.7)	125 (74.9)	–
Duodenal ulcer	44 (29.3)	42 (25.1)	–
Initial bleeding site (n, %)			0.595
Body	57 (38.0)	72 (43.1)	–
Antrum	49 (32.7)	53 (31.7)	–
Duodenum	44 (29.3)	42 (25.1)	–
Haemostatic methods (n, %)			0.181
Thermal	144 (96.0)	154 (92.2)	0.364
Argon plasma coagulation	84 (56.0)	86 (51.5)	0.490
Coagulation forceps	70 (46.7)	82 (49.1)	0.748
Haemostatic clips	24 (16.0)	22 (13.2)	0.580
Injection of diluted epinephrine	16 (10.7)	13 (7.8)	0.376
No. of used haemostatic methods (n, %)			0.181
1	109 (72.7)	133 (79.6)	–
2	37 (24.7)	30 (18.0)	–
3	2 (1.3)	4 (2.4)	–
4	2 (1.3)	0 (0.0)	–

**P* values were calculated using the $\chi 2$ test.

Monotherapy was the most common endotherapy approach, used in over 70% of cases in both groups. Two patients in the control group received a combination of four modalities. Overall, no significant differences were observed between the groups regarding the choice or combination of endotherapy methods.

Primary outcome

Rebleeding within 72 hours

The overall 72-hour rebleeding rate in the full study population was 7.3% (24/341). In the adjuvant Nexpowder group, rebleeding occurred in 2.9% of patients (5/173) compared with 11.3% (19/168) in the control group—a statistically significant difference (p=0.005) (figure 3 and online supplemental table S3).

In the ulcer subgroup (patients with peptic ulcer bleeding), the 72-hour rebleeding rate was also 7.3% (23/317). Among these patients, the adjuvant Nexpowder group had a rebleeding rate of 3.0% (5/167), significantly lower than the 12.0% (18/150) observed in the control group (p=0.004) (table 3 and figure 3).

Of the 23 patients who experienced rebleeding in the ulcer subgroup, three exhibited no stigmata of bleeding on repeat endoscopy and did not require further haemostatic treatment. In 16 patients, endoscopic haemostasis was successfully achieved using thermal monotherapy, combination therapy or Nexpowder monotherapy, with successful haemostasis in all cases.

One patient in the control group developed haematemesis 6 hours after the initial endoscopy. Follow-up endoscopy revealed active bleeding with perforation, necessitating surgical intervention (table 3, online supplemental table S4). In the remaining three patients, repeat endoscopy was not performed due to clinical deterioration, contraindications related to comorbidities, or refusal of further intervention.

Secondary outcomes: 30-day rebleeding and safety outcomes

Analysis of delayed rebleeding within 30 days after initial endoscopic haemostasis in patients with peptic ulcer bleeding showed

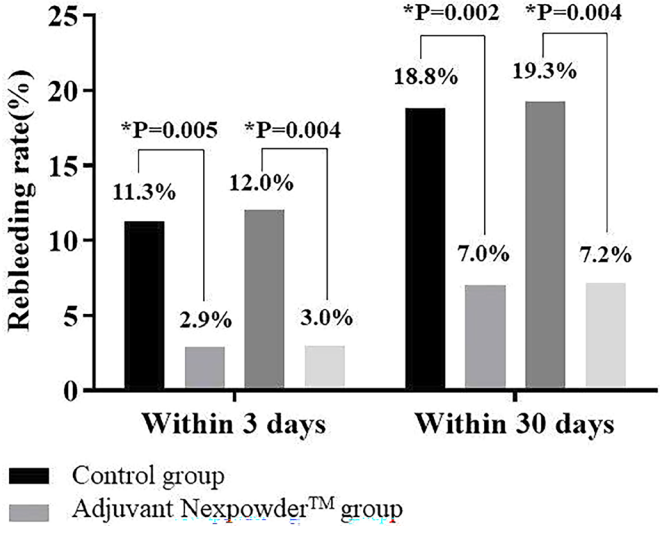

Figure 3 Cumulative rebleeding rates within 3 days and within 30 days.

Table 3 The rebleeding rate and the lists of adverse events in the ulcer subgroup

Variables	Control group (n=150)	Adj. Nexpowder group (n=167)	P value
Cumulative re-bleeding (n, %)*			
Within 72 hours	18 (12.0)	5 (3.0)	0.004
Within 30 days (0 days~30 days)	29 (19.3)	12 (7.2)	0.004
Treatment methods for subjects with rebleeding within 72 hours† (n, %)	(n=18)	(n=5)	
Additional treatment	14 (77.8)	3 (60.0)	0.576
No additional treatment	4 (22.2)	2 (40.0)	0.576
Other (surgery)	1 (5.6)	0 (0.0)	1.000
Adverse event (n, %)*			
Perforation	1 (0.7)	0 (0.0)	0.957
Anaemia (red blood cell transfusion)	1 (0.7)	0 (0.0)	0.957
Obstruction	0 (0.0)	0 (0.0)	N/A
Embolism	0 (0.0)	0 (0.0)	N/A
Coronary artery bypass graft procedure for coronary artery disease	0 (0.0)	0 (0.0)	N/A
Chest infection/pneumonia	0 (0.0)	0 (0.0)	N/A
Allergy	0 (0.0)	0 (0.0)	N/A

*P values were calculated using the $\chi 2$ test and Yates correction.
† P values were calculated using the $\chi 2$ test and Fiser's exact test.

a significantly lower rebleeding rate in the adjuvant Nexpowder group. Specifically, rebleeding occurred in 7.2% of patients (12/167) in the powder group compared with 19.3% (29/150) in the control group (p=0.004) (table 3, figure 3).

This trend was consistent in the full study population (n=341), with a rebleeding rate of 7.0% (12/173) in the powder group versus 18.8% (31/168) in the control group, also showing a statistically significant difference (p=0.002) (figure 3, online supplemental table S3).

Safety outcomes were assessed through in-person outpatient visits or telephone contact 30 days postprocedure (table 3). No device-related adverse events—such as embolism, obstruction, allergic reaction or perforation—were observed in the adjuvant Nexpowder group. A total of eight serious adverse events were reported, all attributed to patients' underlying medical conditions. Two deaths occurred in each group, due to causes unrelated to the endoscopic procedure (multiorgan failure and cardiac arrest).

Multivariate risk factor analysis for 72-hour rebleeding

Risk factors for rebleeding within 72 hours were analysed across all subjects. Variables assessed included sex, age, GBS, Forrest classification, cause and location of bleeding, and the number of haemostatic methods used. None of these factors were significantly associated with rebleeding (tables 1 and 2, online supplemental tables S1 and S2). However, the use of Nexpowder was significantly associated with a reduced risk of rebleeding (p=0.004).

DISCUSSION

Despite the introduction of PPI therapy more than 20 years ago, progress in reducing the risk of rebleeding after conventional endoscopic therapy for NVUGIB has been limited. This prospective, randomised, multicentre study evaluated the safety and efficacy of Nexpowder as an adjunctive endoscopic intervention to prevent rebleeding in patients with NVUGIB and high-risk lesions.

To the best of our knowledge, this is the first study since the introduction of PPI therapy to demonstrate a substantial and statistically significant reduction in rebleeding rates following endoscopic treatment. In the ulcer subgroup, the application of Nexpowder significantly reduced the 72-hour rebleeding rate (3.0% (5/167) vs 12.0% (18/150), p=0.004), with no device-related serious adverse events observed. Furthermore, multivariable analysis confirmed that neither the type nor number of haemostatic methods influenced rebleeding risk—only the use of Nexpowder was associated with reduced rebleeding (p=0.004).

It should be noted that bipolar coagulation, a preferred thermal haemostasis technique, was not used due to unavailability in Korea. However, previous studies and guidelines have shown no significant differences in outcomes between thermal modalities such as bipolar, monopolar, and APC.[8 28]

Timely endoscopic intervention—ideally within 24 hours—is recommended to reduce rebleeding and mortality.[6 29] High-dose PPI therapy has also been shown to lower rebleeding risk following endoscopic treatment.[25 30] Current standard of care for NVUGIB with high-risk lesions includes conventional endoscopic therapy followed by intravenous PPI therapy.[31] However, aside from PPI use, few advances in endoscopic techniques have meaningfully reduced rebleeding rates, and second-look endoscopy has not consistently demonstrated benefit.[32]

Our findings demonstrate that adjunctive application of Nexpowder after conventional endoscopic therapy and PPI administration significantly lowers rebleeding rates at both 72 hours and 30 days. Rebleeding is associated with increased mortality, prolonged hospital stays, readmissions and higher healthcare costs,[2 3 7] making these results highly encouraging.

In this trial, the choice of initial haemostasis method was left to the discretion of the endoscopist. The lower use of haemostatic clips compared with thermal therapy may reflect technical challenges, such as difficult lesion locations or fibrotic ulcer bases. Prior studies have shown that while successful clip application is superior to injection therapy alone, it is comparable to thermal therapy in achieving haemostasis, with no significant differences in mortality or rebleeding.[33 34] As initial haemostasis was achieved in all cases and treatment distribution was similar between groups, the lower use of clips is unlikely to have affected the observed benefit of Nexpowder.

Topical haemostatic powders have gained popularity due to ease of use and rapid haemostatic effects. Previous studies have shown their efficacy in achieving initial haemostasis and reducing short-term rebleeding rates to approximately 15%–20%.[21 35 36]

However, when compared with conventional endoscopic therapy, topical powders have not demonstrated significant reductions in rebleeding, particularly in active spurting bleeds (Forrest Ia), where they are less effective than in oozing lesions (Forrest Ib).[36]

Unlike previous studies assessing powders as monotherapy, our study evaluated Nexpowder as an adjunct to conventional endoscopic therapy. This combined approach resulted in a significant reduction in rebleeding rates.[37 38] Nexpowder forms a highly adhesive hydrogel on contact with moisture, providing mechanical coverage and protection of the ulcer base. This property may explain the sustained reduction in rebleeding. However, given that topical agents differ in composition and mechanism, our findings should not be generalised to all powders. Further comparative studies, including head-to-head trials between different haemostatic agents, are needed.

Despite the strength of a randomised design, this study has several limitations. First, the observed rebleeding rates were lower than expected (3.0% vs 12.0%), limiting the power of risk factor analysis. Additionally, the number of rebleeding events was small, and the fragility index was identified as 5. This low fragility index suggests that a few events could shift results from statistically significant to non-significant. Although low fragility indices have been noted in other randomised trials,[39] and the number of lost follow-ups did not exceed the fragility index, this limitation must be considered when interpreting the robustness of the results.

Second, the study was conducted exclusively in Korea in an Asian population, where the high prevalence of *H. pylori* may influence 30-day rebleeding rates. To enhance generalisability, multinational studies involving more diverse populations are warranted.

CONCLUSION

This multicentre randomised trial demonstrated that adjunctive application of Nexpowder after successful conventional endoscopic therapy significantly reduces the risk of rebleeding at both 72 hours and 30 days in patients with NVUGIB, without procedure-related complications. Supported by prior evidence, it is likely that Nexpowder protects the ulcer base during the critical 72-hour post-haemostasis period. This study represents an important advance, being the first since the introduction of PPI therapy to show that an additional endoscopic intervention can further reduce rebleeding risk after initial endoscopic haemostasis.

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Contributors SJH is the guarantor. JS, BC, JTH, KSK, EL, JHM, J-WC, DKP, YJK, KAK, JHK, SJH and KOK made substantial contributions to the conception and design of the study, acquisition of data, analysis and interpretation of data and drafted/revised the manuscript for important intellectual content. K-SS contributed to the selection of statistical analysis methods and overall statistical description. SJH and KOK were co-corresponding authors and were responsible for the conception and design of the study; the acquisition, analysis, and interpretation of the data; and drafting of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants. The study protocol received approval from the institutional review board of our institution (GDIRB2018-381, INHAUH 2018-08-028, SCHBC 2018-09-007). As a prospective study, patient consent was obtained for data collection or analysis, in accordance with the approvals granted by each institutional review board. All methods were carried out in accordance with relevant guidelines and regulations. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer-reviewed.

Data availability statement Data are available upon reasonable request. The datasets used and analysed during the current study are not publicly available to maintain patient privacy. However, they can be obtained from the corresponding author upon reasonable request.

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