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ORIGINAL ARTICLE

Retrospective Cohort Study

Risk factors and outcomes of peptic ulcer bleed in a Pakistani population: A single-center observational study

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Abstract

BACKGROUND

Peptic ulcer disease (PUD) remains a significant healthcare burden, contributing to morbidity and mortality worldwide. Despite advancements in therapies, its prevalence persists, particularly in regions with widespread nonsteroidal anti-inflammatory drugs (NSAIDs) use and *Helicobacter pylori* infection.

AIM

To comprehensively analyse the risk factors and outcomes of PUD-related upper gastrointestinal (GI) bleeding in Pakistani population.

METHODS

This retrospective cohort study included 142 patients with peptic ulcer bleeding who underwent upper GI endoscopy from January to December 2022. Data on demographics, symptoms, length of stay, mortality, re-bleed, and Forrest classification was collected.

RESULTS

The mean age of patients was 53 years, and the majority was men (68.3%). Hematemesis (82.4%) and epigastric pain (75.4%) were the most common presenting symptoms. Most patients (73.2%) were discharged within five days. The mortality rates at one week and one month were 10.6% and 14.8%, respectively. Re-bleed within 24 h and seven days occurred in 14.1% and 18.3% of patients, respectively.

Most ulcers were Forrest class (FC) III (72.5%). Antiplatelet use was associated with higher mortality at 7 and 30 d, while alternative medications were linked to higher 24-hour re-bleed rates. NSAID use was associated with more FC III ulcers. Re-bleed at 24 h and 7 d was strongly associated with one-week or one-month mortality.

CONCLUSION
Antiplatelet use and rebleeding increase the risk of early mortality in PUD-related upper GI bleeding, while alternative medicines are associated with early rebleeding.

Key Words: Non variceal bleed; Mortality; Re-bleed; Forrest classification; Antiplatelets; Alternative medicines

Core Tip: This Pakistani study flags antiplatelets and alternative meds as risk factors for peptic ulcer bleeding mortality and re-bleed. Considering patient comorbidities and tailoring treatment based on these factors, like avoiding antiplatelets if possible, could improve outcomes in this population. However, larger studies are needed to solidify these findings and personalize treatment further.

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INTRODUCTION

Non-variceal upper gastrointestinal (UGI) bleed is an acute medical emergency and a common cause of hospital admission[1]. Peptic ulcer disease (PUD) related bleeding is one of the major causes of non-variceal UGI bleeding and is a major player in morbidity and mortality[2]. Despite all the advances in Proton pump inhibitor (PPI) therapy, increasing population age along with widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* (*H. pylori*) in our part of the world, PUD has a major share in gastrointestinal (GI) related morbidity and mortality. Its estimated prevalence is around 5%-10%[3]. Infection with *H. pylori* has long been associated with peptic ulcer formation [4]. The increasing population age with ever-increasing use of steroids, NSAIDs, Aspirin, and smoking are other risk factors[5-7]. As expected, the combined use of Corticosteroids along with antiplatelets or anticoagulants increases the risk of bleed from Peptic ulcers even further[8]. Although the Forrest classification is a widely used tool for predicting re-bleed risk in peptic ulcer bleeding (PUB), evidence suggests that comorbid conditions significantly impact outcomes[9, 10]. Re-bleed, length of stay (LOS) and mortality are important outcome parameters to evaluate in cases of PUB. The burden of the disease, along with these outcome parameters, is supposed to have improved with the improvement in endoscopy and overall healthcare facilities. However, despite advances in treatment, PUB remains a significant health burden, and the mortality has remained at 5%-10% over the past three decades[11-14], particularly in regions like Pakistan with high NSAID use and *H. pylori* prevalence[15].

Existing research on PUB outcomes primarily comes from Western populations, potentially overlooking regional factors and specificities. This study aims to fill knowledge gaps by comprehensively analyzing risk factors and outcomes of PUB in a Pakistani population, providing insights relevant to local healthcare practices. This study further delves deeper by investigating the role of comorbidities in re-bleed, mortality, and LOS, as well as the association between re-bleed and mortality.

MATERIALS AND METHODS

This retrospective cohort study was conducted at the Gastroenterology Department of Jinnah Post Graduate Medical Centre, Karachi, from January 2022 to December 2022. A total of 1098 patients were presented to the unit with suspected upper GI bleed (hematemesis or melena). Among them, 142 patients had confirmed peptic ulcer bleed, which were included in the study. Other causes of GI bleed included variceal bleed (702), esophageal cancer (11), gastric malignancies (53), lower GI bleed (155), Mallory Weiss tear (7) and Gastric Antral Vascular Ectasia (28). Patients with other causes of GI bleed and incomplete data were excluded from the study. The detailed demographics were recorded on pre-designed proformas. Any specific medical condition/comorbidity or drugs such as antiplatelets, NSAIDs, Corticosteroids or alternative (herbal/homoeopathic/Hakimi) medications were also extracted from medical records.

The vitals of the patients, along with the presence or absence of shock or tachycardia, were meticulously recorded. The bleeding control pathway was used as a guide for therapy during the hospital stay. Patients were started on intravenous PPIs and were admitted to an appropriate care level after proper triage. Each patient was assessed individually according

to the American Society of Anesthesiology for anaesthesia risk in relation to comorbidity. Endoscopy findings were recorded and documented according to Forrest classification.

All patients who were included in the study underwent endoscopy during the initial 24 h as dictated by the international guidelines[1]. An urgent endoscopy was considered among those patients whose bleed was severe enough to exclude medical management pre-procedure. A peptic ulcer was defined as a breach in the mucosal integrity on endoscopy. Further details of the ulcer, such as its location (gastric or duodenal) and its severity according to the Forrest classification, were recorded through the endoscopy report. The Forrest classification refers to the endoscopic appearance of a peptic ulcer as active spurting (Forrest IA), active oozing (Forrest IB), nonbleeding visible vessel (Forrest IIA), ulcers with adherent clots (Forrest IIB), ulcers with red spots (Forrest IIC) or a clean base (Forrest III). Patients with high-risk ulcers (Forrest 1 and 2) were treated endoscopically with at least dual endoscopic interventional modalities (Sclerotherapy along with hemo-clips).

All patients who received dual endoscopic modality to achieve hemostasis were admitted to the High Dependency Unit post- procedure and were closely monitored for re-bleed. Their vitals and laboratory parameters were recorded according to the bleeding pathway protocol. Target Hemoglobin (Hb) was maintained around 8-9 gm/dL, depending upon their cardiac and volume status.

Any rebleed manifested in the form of Malena, drop in Hb, and/or endoscopic evidence of upper gastrointestinal bleed (UGIB) within 24 h or one week was also recorded. The primary outcomes were LOS, rebleeding in 24 h and one week, and mortality in one week and one month. This study was conducted after approval from the Institutional Review Board of the Jinnah Postgraduate Medical Centre, Karachi.

Statistical analysis

Descriptive statistics were reported as frequency (percentage) for categorical variables and mean ± SD for continuous variables. The association between outcome variables and risk factors was assessed using the chi-square test/Fisher's exact, where appropriate. A P value < 0.05 was considered significant. SPSS 27 was used for statistical analyses.

RESULTS

A total of 142 patients with UGIB secondary to PUD were included in the study. The mean age of the patients was 53 ± 18.5 years, including 97 (68.3%) males and 45 (31.7%) females. The most common presenting symptom was hematemesis and epigastric pain among 117 (82.4%) and 107 (75.4%) patients, respectively. Common comorbid conditions included hypertension (37.3%), diabetes (25.4%) and ischemic heart disease (26.8%; Table 1).

The hospital stay in most patients was ≤ 5 d (n = 104, 73.2%). Fifteen (10.6%) patients died in the first week, while 21 died in one month (14.8%). Re-bleed within 24 h occurred among 20 (14.1%) patients, while 26 (18.3%) patients presented with recurrent bleeding in 7 d.

Those patients who were on antiplatelet drugs, the proportion of 7 d mortality (21.3% *vs* 5.3%, P = 0.007) and 30 d mortality (23.4% *vs* 10.5%, P = 0.042) was high as compared to those who were not on antiplatelet drugs. For those who were on alternative medications, re-bleed in 24 h was high (21.4% *vs* 9.3%, P = 0.042). Smoking, steroids and *H. pylori* did not appear to impact LOS, rebleed, and mortality (Table 2).

On endoscopy, most of the ulcers belonged to Forrest class (FC) III (n = 103, 72.5%), followed by FC II (n = 21, 14.8%) and FC I (n = 18, 12.7%). Patients with FC I showed a higher proportion of re-current bleeding in 7 d (38.9% *vs* 23.8% *vs* 13.6%, P value = 0.034) than those with FC II and FC III (Table 2). However, FC was not found to be significantly associated with any of the risk factors (Table 3).

It was noted that the patients who used NSAIDs had more with FC III (76.1% *vs* 58.6%, P value = 0.037) as compared to those who did not report the use of NSAIDs (Table 4). Re-bleed in 24 h and seven days was found to be statistically significantly associated with mortality in seven days and 30 d (P value < 0.001; Table 5). Table 6 summarises the causes of morality.

DISCUSSION

PUD is a disease entity that includes gastric and duodenal ulcers. For almost two centuries, this disease has continued to be a major causal factor for hospital admissions and a menace in terms of morbidity and mortality. The current study highlighted the risk factors and outcomes of peptic ulcer bleed in a resource-limited developing country.

The risk of PUB varies with the type, dose and duration of anti-platelet agents, along with or without other NSAIDs [16]. In our study, the use of antiplatelet agents was not associated with the severity of the ulcer in terms of the Forrest classification. This is likely because of the low sample size. However, its use led to statistically significant one-week and one-month mortality. This is probably the first study from this part of the world to report this increased mortality (both early and late) due to antiplatelet medications.

The majority of NSAIDs related to peptic ulcers belonged to the Forrest 3 class. The lack of association between NSAID use and higher Forrest-class ulcers could be multifold. First, we did not examine the individual dose, type, and duration of NSAID use. Secondly, the total number of patients on NSAIDs was not significant enough to reach statistical significance. However, Liu *et al*[17], in a similar study, showed similar results: only 17% of the patients had Forrest 1 ulcers.

Table 1 Demographic and clinical characteristics of patients admitted to hospital with upper gastrointestinal bleed (*n* = 142)

Characteristics	*n*	%
Age in years, mean ± SD (min-max)	53.0 ± 18.5	18-90
Gender		
Male	97	68.3
Female	45	31.7
Comorbidity		
Diabetes mellitus	36	25.4
Hypertension	53	37.3
Ischemic heart disease	38	26.8
Asthma	7	4.9
Cerebrovascular accident	14	9.9
Presenting symptoms		
Epigastric pain	107	75.4
Bloating	30	21.1
Hematemesis	117	82.4
Melena	88	62.0
Abdominal pain	19	13.4
Weight loss	12	8.5
Location of ulcer		
Stomach	54	38.0
Duodenum	63	44.4
Stomach and duodenum	25	17.6

Table 2 Association of risk factors and forest classification with outcome variables

Variables	Total, *n* (%)	Hospital stay in days		Mortality in 7 d		Mortality in 30 d		Re-bleed in 24 h		Re-current bleed in 7 d	
		≤ 5 (*n* = 104)	> 5 (*n* = 38)	No (*n* = 127)	Yes (*n* = 15)	No (*n* = 121)	Yes (*n* = 21)	No (*n* = 122)	Yes (*n* = 20)	No (*n* = 116)	Yes (*n* = 26)
Smoking											
Yes	31 (21.8)	24 (77.4)	7 (22.6)	29 (93.5)	2 (6.5)	29 (93.5)	2 (6.5)	27 (87.1)	4 (12.9)	26 (83.9)	5 (16.1)
No	111 (78.2)	80 (72.1)	31 (27.9)	98 (88.3)	13 (11.7)	92 (82.9)	19 (17.1)	95 (85.6)	16 (14.4)	90 (81.1)	21 (18.9)
Steroids											
Yes	8 (5.6)	7 (87.5)	1 (12.5)	7 (87.5)	1 (12.5)	7 (87.5)	1 (12.5)	7 (87.5)	1 (12.5)	7 (87.5)	1 (12.5)
No	134 (94.4)	97 (72.4)	37 (27.6)	120 (89.6)	14 (10.4)	114 (85.1)	20 (14.9)	115 (85.8)	19 (14.2)	109 (81.3)	25 (18.7)
H. pylori											
Yes	26 (18.3)	20 (76.9)	6 (23.1)	24 (92.3)	2 (7.7)	23 (88.5)	3 (11.5)	22 (84.6)	4 (15.4)	20 (76.9)	6 (23.1)
No	116 (81.7)	84 (72.4)	32 (27.6)	103 (88.8)	13 (11.2)	98 (84.5)	18 (15.5)	100 (86.2)	16 (13.8)	96 (82.8)	20 (17.2)
Antiplatele											
Yes	47 (33.1)	34 (72.3)	13 (27.7)	37 (78.7)	10 (21.3)[b]	36 (76.6)	11 (23.4)[a]	37 (78.7)	10 (21.3)	35 (74.5)	12 (25.5)
No	95 (66.9)	70 (73.7)	25 (26.3)	90 (94.7)	5 (5.3)	85 (89.5)	10 (10.5)	85 (89.5)	10 (10.5)	81 (85.3)	14 (14.7)
Alternative medications											

Yes	56 (39.4)	39 (69.6)	17 (30.4)	47 (83.9)	9 (16.1)	44 (78.6)	12 (21.4)	44 (78.6)	12 (21.4)[a]	43 (76.8)	13 (23.2)
No	86 (60.6)	65 (75.6)	21 (24.4)	80 (93.0)	6 (7.0)	77 (89.5)	9 (10.5)	78 (90.7)	8 (9.3)	73 (84.9)	13 (15.1)
Forrest classification											
I	18 (12.7)	10 (55.6)	8 (44.4)	18 (100.0)	0	17 (94.4)	1 (5.6)	13 (72.2)	5 (27.8)	11 (61.1)	7 (38.9)[a]
II	21 (14.8)	14 (66.7)	7 (33.3)	18 (85.7)	3 (14.3)	17 (81.0)	4 (19.0)	17 (81.0)	4 (19.0)	16 (76.2)	5 (23.8)
III	103 (72.5)	80 (77.7)	23 (22.3)	91 (88.3)	12 (11.7)	87 (84.5)	16 (15.5)	92 (89.3)	11 (10.7)	89 (86.4)	14 (13.6)

[a]$P < 0.05$.

[b]$P < 0.01$.

n (%) are reported. *P* value was calculated by Chi-square/Fisher Exact test. *H. pylori*: *Helicobacter pylori*.

The role of *H. Pylori* with PUB is varied and controversial. In a recent study, *H. pylori* infection increased the risk of PUB in patients with NSAIDs, aspirin and non-aspirin antiplatelet agents[18]. However, previous studies have reported more favourable outcomes with *H. pylori*-related PUB. In a survey by Chason *et al*[19], patients with *H. pylori*-related PUB patients had shorter length of hospital stays and lower rebleeding rates. Our data did not show any association of *H. pylori* with LOS, FC, re-bleed or mortality.

The reported mortality related to PUB varies widely from 4%-15% depending on mortality solely due to PUB or all-cause mortality and shows a significant variation depending on age and comorbidity[20,21]. Most of the local studies elaborating on mortality have reported combined mortality of PUB along with oesophagal variceal bleeding. However, one such study reported an even higher mortality (26.7% for non-variceal bleeding)[22]. In the current study, one-week and one-month mortality stood at approximately 11% and 15%, respectively. A similar study from the United Kingdom showed a mortality of around 8%[23]. However, as most (87%) of our patients had low-risk ulcers (Forrest 2b and beyond), this high mortality likely represents all-cause mortality rather than sole ulcer bleed-related mortality. This likely explanation is further supported by the evidence that nearly two-thirds of the mortality occurred in the first-week post-bleed. However, since mortality does not correlate with the Forrest classification of ulcers, it shows that patients died from multiple factors, among which GIB acts as a catalytic agent rather than as the sole cause. The case would have been settled if we had access to details of each mortality.

Among the causal agents' anti-platelets were the only ones leading to statistically significant one-week and one-month mortality. This has been highlighted before by Lanas *et al*[24], that even low-dose aspirin was independently associated with an increased risk of peptic ulcer bleed (OR: 2.4; 95%CI: 1.8–3.3). As seems logical, patients taking antiplatelet medications have concurrent medical conditions such as hypertension and ischemic heart disease, placing them at an additional increased risk of GIB-related mortality.

Our study clearly shows that re-bleed either at 24 h or one week is strongly associated with one-week or one-month mortality. This finding has been documented in multiple other international studies. Branicki *et al*[25] have shown that the mortality was increased by 17 folds in the case of a re-bleed. They also concluded that co-morbidity adds to the mortality in case of peptic ulcer bleed. However, this is the first study from this part of the world covering this aspect of peptic ulcer bleed. As mentioned earlier, this mortality rate is assumed not to be solely attributable to peptic ulcer bleed or re-bleed but a combination of bleed with the comorbid conditions.

Our study shows that alternative (Herbal) medications influence 24-hour or 7-day re-bleed risk. A local research from China in 2016 showed that around 7% of the patients presenting with upper GI bleed used Chinese herbal medicines[26]. The content and composition of these medications are variable and, in most cases, are unknown. At times, they contain a mixture of NSAIDs along with Steroids to treat a variety of medical conditions and musculoskeletal pain. Tomlinson *et al* [27] documented in their study that herbal medicines contaminated with NSAIDs or steroids can lead to an increased risk of peptic ulcer bleed or even perforation. Our study also shows that a sizeable number (40%) of patients were using these alternative medications. This reflects a lack of education and less access to proper healthcare facilities.

The risk of re-bleeding from FC 1 ulcer in our study (39%) is close to the internationally reported risk of around 50% [28]. However, none of the risk factors was associated with the Forrest classification of ulcers. Moreover, the Forrest classification did not correlate with outcome variables like LOS, Re-bleed or Mortality. This could be due to a small number of patients (12.7%) having Forrest 1 type ulcers. Giese *et al*[29] also showed that the Forrest classification did not correlate with these end-point variables as ours. In our study, one week's re-bleed rate from Forrest 3 ulcers (13.6%) is more than the reported initially (0%-10%)[30]. Other factors, such as medications, could have influenced this; however, given the small number of patients, we were unable to perform any multivariate analysis.

In the current study, nearly three-quarters of patients were discharged within five days of admission. This is in line with international data. Schacher *et al*[31], in a study from Switzerland aimed at the length of hospital stay and timing of endoscopy, showed a similar length of hospital stay of around five days, which did not show a statistical difference among patients undergoing early or late endoscopy. A much larger cohort of patients from the United Kingdom that investigated the LOS among a similar group of patients showed a median LOS of around six days[23]. None of the etiological variables or the Forrest classification correlated with LOS. The likely explanation for this high number of early discharges in our study is the low number of patients with high-risk Forrest ulcers (1 and 2a).

In this study, PUD affected patients of all ages. Though subgroup analysis of age groups could not be done due to a low number of patients, this goes hand in hand with the local studies[15].

Table 3 Association of risk factors with Forest classification

Risk factors	Total	Forrest classification		
		I (*n* = 18)	II (*n* = 21)	III (*n* = 103)
Smoking				
Yes	31 (21.8)	2 (11.1)	6 (28.6)	23 (22.3)
No	111 (78.2)	16 (88.9)	15 (71.4)	80 (77.7)
Steroids				
Yes	8 (5.6)	0	1 (4.8)	7 (6.8)
No	134 (94.4)	18 (100.0)	20 (95.2)	96 (93.2)
H. pylori				
Yes	26 (18.3)	5 (27.8)	5 (23.8)	16 (15.5)
No	116 (81.7)	13 (72.2)	16 (76.2)	87 (84.5)
Antiplatelet				
Yes	47 (33.1)	5 (27.8)	7 (33.3)	35 (34.0)
No	95 (66.9)	13 (72.2)	14 (66.7)	68 (66.0)
Hakeemi medications				
Yes	56 (39.4)	5 (27.8)	7 (33.3)	44 (42.7)
No	86 (60.6)	13 (72.2)	14 (66.7)	59 (57.3)

n (%) are reported. *P* value was calculated by Chi-square/Fisher Exact test. *H. pylori*: *Helicobacter pylori*.

Table 4 Correlation of nonsteroidal anti-inflammatory drugs with outcome variables and Forrest classification

Variables	Total	NSAIDs	
		Yes (*n* = 113)	No (*n* = 29)
Hospital stay (d)			
≤ 5	104 (73.2)	80 (70.8)	24 (82.8)
> 5	38 (26.8)	33 (29.2)	5 (17.2)
Mortality in 7 d			
No	127 (89.4)	100 (88.5)	27 (93.1)
Yes	15 (10.6)	13 (11.5)	2 (6.9)
Mortality in 30 d			
No	121 (85.2)	95 (84.1)	26 (89.7)
Yes	21 (14.8)	18 (15.9)	3 (10.3)
Re-bleed in 24 h			
No	122 (85.9)	98 (86.7)	24 (82.8)
Yes	20 (14.1)	15 (13.3)	5 (17.2)
Re-current bleed in 7 d			
No	116 (81.7)	93 (82.3)	23 (79.3)
Yes	26 (18.3)	20 (17.7)	6 (20.7)
Forrest classification			
I	18 (12.7)	10 (8.8)	8 (27.6)[a]
II	21 (14.8)	17 (15.0)	4 (13.8)

III	103 (72.5)	86 (76.1)	17 (58.6)

[a]*P* < 0.05.

n (%) are reported. *P* value was calculated by Chi-square/ Fisher Exact test. NSAID: Nonsteroidal anti-inflammatory drug.

Table 5 Association of re-bleed with mortality

Variables	Total	Mortality in 7 d		Mortality in 30 d	
		No (*n* = 127)	Yes (*n* = 15)	No (*n* = 121)	Yes (*n* = 21)
Re-bleed in 24 h					
No	122 (85.9)	117 (95.9)	5 (4.1)[a]	113 (92.6)	9 (7.4)[a]
Yes	20 (14.1)	10 (50.0)	10 (50.0)	8 (40.0)	12 (60.0)
Re-current bleed in 7 d					
No	116 (81.7)	112 (96.6)	4 (3.4)[a]	111 (95.7)	5 (4.3)[a]
Yes	26 (18.3)	15 (57.7)	11 (42.3)	10 (38.5)	16 (61.5)

[a]*P* < 0.01.

n (%) are reported. *P* value was calculated by Fisher Exact test.

Table 6 Causes of mortality

Cause	*n*	%
Re-bleed in 24 h	10	47.6
Re-current bleed in 7 d	1	4.76
Septic shock	3	14.2
Cardiac event	2	9.52
Pulmonary embolism	1	4.76
Others	4	19.04

While this study breaks new ground in analysing PUB risk factors and outcomes for a Pakistani population, its impact is tempered by some limitations. Its pioneering nature and focus on clinically relevant factors such as antiplatelet use and comorbid conditions offer valuable information for local healthcare providers. However, the small sample size and single-centre design restrict its generalizability and necessitate further research with more extensive, diverse samples. Additionally, the lack of data on specific details of medications hindered a more precise understanding of their influence on outcomes. Moving forward, larger studies and targeted investigations into medication profiles are crucial to solidify the findings and personalise treatment protocols. Ultimately, incorporating this research alongside future studies has the potential to inform tailored clinical practice guidelines for Pakistani PUB patients, leading to significantly improved care.

CONCLUSION

Antiplatelet use and rebleeding increase the risk of early mortality in PUD-related UGIB, while alternative medicines are associated with early rebleeding.

FOOTNOTES

Author contributions: But N designed the research study; Mehak N, Mohiuddin G and Khan G performed the data collection; Mughal S analyzed the data; Usmani MT wrote the manuscript; Qazi-Arisar FA revised the manuscript; But N and Qazi-Arisar FA supervised the research; all authors have read and approved the final manuscript.

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ORIGINAL ARTICLE

Prospective Study

Efficacy and tolerability of chitin-glucan combined with simethicone (GASTRAP® DIRECT) in irritable bowel syndrome: A prospective, open-label, multicenter study

Nathalie Talbodec, Pauline Le Roy, Peggy Fournier, Benoit Lesage, Elodie Lepoutre, François Castex, Jean Michel Godchaux, Lionel Vandeville, Benjamin Bismuth, Xavier Lesage, Pauline Bayart, Michael Genin, Christel Rousseaux, Veronique Maquet, Salvatore Modica, Pierre Desreumaux, Caroline Valibouze

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Abstract

BACKGROUND

Irritable bowel syndrome (IBS), defined according to the Rome IV diagnostic criteria, is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain related to altered bowel habits. First-line recommended treatments are limited to combining drugs targeting predominant symptoms, particularly pain (antispasmodics), constipation (laxatives), and diarrhea (loperamide), yielding only a limited therapeutic gain. GASTRAP® DIRECT is a class IIa medical formulation composed of a combination of chitin-glucan and simethicone indicated for the symptomatic treatment of gas-related gastrointestinal disorders by combining different mechanisms of action.

AIM
To evaluate the efficacy, tolerability, and safety of 4-week GASTRAP® DIRECT treatment in patients with IBS.

METHODS
In this prospective, multicenter, open-label trial, 120 patients with IBS received three sticks of GASTRAP® DIRECT (1.5 g/d of chitin-glucan and 0.75 mg/d of simethicone) per day for 4 weeks. The primary endpoint was the responder rate, defined as the number of patients whose abdominal pain score decreased by ≥ 30% from baseline to week (W) 4. The analysis was performed using the per-protocol set. Cardinal symptoms, impact of global symptoms on daily life, change in stool consistency, and improvement in defecatory disorders were evaluated.

RESULTS
Overall, 100 patients were evaluated. At W4, 67% (95%CI: 57-75) showed improvement in abdominal pain (score: 5.8 ± 2.4 *vs* 2.9 ± 2.0, $P < 0.0001$). Similar improvements were observed for bloating [8.0 ± 1.7 *vs* 4.7 ± 2.9, $P < 0.0001$; 60% (95%CI: 50-70) responders], abdominal distension [7.2 ± 2.1 *vs* 4.4 ± 3.1, $P < 0.0001$; 53% (95%CI: 43-63) responders], and impact of global symptoms on daily life [7.1 ± 2.0 *vs* 4.6 ± 2.9, $P < 0.0001$; 54% (95%CI: 44-64) responders]. Stool consistency improved in most patients (90% and 57% for patients with liquid and hard stools, respectively). Overall, 42% of patients with defecatory disorders reported very much/considerable improvements by W2. No severe adverse event occurred, and tolerability was rated "good" or "very good" by 93% of patients.

CONCLUSION
GASTRAP® DIRECT is safe and well tolerated, alleviating IBS symptoms rapidly in 2 weeks. This open-label study suggests that the combination of chitin-glucan and simethicone could be beneficial in patients with IBS.

Key Words: Chitin-glucan; Irritable bowel syndrome; Abdominal pain; Flatulence; Defecatory disorders; Stool consistency; Natural non-pharmacological treatment

Core Tip: Irritable bowel syndrome is a common functional gastrointestinal disorder characterized by recurrent abdominal pain associated with altered bowel habits. Treatment options are limited and often inadequate, which leads to dissatisfaction among patients receiving standard medical care. Our study showed that 4 weeks of daily treatment with GASTRAP® DIRECT, a class IIa medical formulation containing a combination of chitin-glucan and simethicone, is well tolerated and rapidly effective in reducing abdominal pain, bloating, abdominal distension, and flatulence with an improvement of stool consistency and defecatory disorders.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that is prevalent in 5%-10% of the global population. IBS accounts for 3% of visits to general practitioners and approximately 40% of all gastroenterology outpatient consultations[1]. The high prevalence is associated with annual direct and indirect costs of more than $20 billion per year in the United States (US), corresponding to 3.5 million physician visits annually. IBS is also one of the leading causes of work absenteeism[2,3]. This chronic condition is defined according to Rome IV criteria for symptoms and is characterized by recurrent abdominal pain related to altered bowel habits[4]. Although abdominal pain and gas-related bloating are the two dominant and most troublesome symptoms[5], patients with IBS also have frequent

defecation disorders, for which straining, sensation of incomplete evacuation, and manual maneuvers to facilitate defecation are highly suggested to improve their quality of life[4,6]. Although IBS represents a major burden, the recommended therapeutic strategies (*e.g.*, those from European, American, Canadian, Japanese, and British societies)[7-13] are often inadequate, leading to dissatisfaction for many patients with standard medical care[14,15].

Chitin-glucan is a novel non-digestible dietary compound that is considered a safe food ingredient by the European Food Safety Authority (EFSA)[16]. It is the major component of the cell walls of the mycelium of *Aspergillus niger* fungi and is mainly composed of a branched β-1, 3/1, 6 glucan that is linked to chitin *via* a β-1, 4 linkage. Previous preclinical studies in rodent models[14,15], functional in vitro evaluation using the Simulator of the Human Intestinal Microbial Ecosystem model, and clinical exploration in healthy volunteers[17] showed that oral administration of chitin-glucan at the EFSA-recommended dosage induces a microbial signature of a prebiotic[13]. These studies found that chitin-glucan is slowly fermented in all colon segments without enhancement of gas production or fecal calprotectin concentration[18,19]. Gut microbiota analysis using Illumina sequencing also revealed an increased relative abundance of the butyrate-producing genera *Roseburia spp*. and *Faecalibacterium prausnitzii*, a genus with strong anti-inflammatory properties[18,19].

We recently performed preclinical molecular, cellular, and animal studies to evaluate the roles of chitin-glucan in the main pathophysiological mechanisms responsible for symptom generation in IBS (*e.g.*, visceral analgesia, intestinal inflammation, and barrier function) and developed a computational molecular model of the molecule[20]. The results showed that chitin-glucan rapidly and significantly decreases visceral perception and intestinal inflammation through regulation of master genes for pain, inflammation, and intestinal barrier function. Further, it neutralizes harmful substances in the intestinal lumen, such as microbial pathogenic lipids, auguring the use of chitin-glucan treatment in patients with IBS[20].

Simethicone (dimethylpolysiloxane, $[(CH^3)_2[Si(CH^3)_2O]n]$) is a chemically inert compound in silica gel that is not absorbed by the gastrointestinal tract. It is physiologically inactive and non-toxic when administered orally. An *in vitro* study investigating its antifoaming action suggested that simethicone decreases the surface tension of liquids[21]. In rats, oral administration of simethicone reduced stress-induced colonic permeability and hypersensitivity[22]. In humans, simethicone has been used since the 1960s as a well tolerated medication to improve the quality of gastric and colonic mucosal visualization during endoscopy by preventing bubble formation and gas retention[23,24]. In IBS, simethicone in combination with spasmolytics has shown efficacy in reducing abdominal pain and bloating[25,26]. These results suggest that the combination of simethicone and chitin-glucan may be beneficial in patients with IBS by targeting the mechanisms responsible for symptom generation[27,28], including visceral hypersensitivity, intestinal gas retention, dysbiosis, barrier dysfunction, and inflammation. Further, it may help address the low fiber intake observed in European and US populations[29,30]. GASTRAP® DIRECT is a class IIa medical formulation containing 250 mg of simethicone combined with 500 mg of chitin-glucan per sachet. This study aimed to evaluate the efficacy, tolerability, and safety of 4-week GASTRAP® DIRECT treatment in patients with IBS. Toward this goal, GASTRAP® DIRECT was administered for 4 wk in patients with IBS symptoms.

MATERIALS AND METHODS

This prospective, open-label, multicenter study was conducted between September 2021 and June 2022 in France. The study was approved by the Ethics Committee Sud-Est VI of Clermont-Ferrand (France) (Ref. ID-RCB: 2019-A03202-55) and performed in accordance with the International Conference on Harmonization Good Clinical Practice and the ethical principles of the Declaration of Helsinki. A patient information form and a request by the gastroenterologist for non-opposition to the study were obtained from all participants.

Study population

Patients with IBS were recruited by a trial board of 12 French gastroenterologists organized in one tertiary care setting (P. Desreumaux, Coordinator of the study) corresponding to the Department of Gastroenterology of the University Hospital of Lille (Center 1: Principal investigational center) and four secondary care settings located in northern France (Center 2: P Fournier, B Lesage, and B Bismuth; Center 3: N Talbodec and E Lepoutre; Center 4: P Bayart, X Lesage, and L Vandeville; and Center 5: P Le Roy, F Castex, and JM Godchaux). Female and male patients, aged 18–75 years, were eligible for inclusion if they were diagnosed with IBS according to the Rome IV criteria[4]: The presence of bloating or abdominal pain score of ≥ 2 on a visual analog scale (VAS). Patients were excluded on the basis of the following exclusion criteria: (1) Chronic gastrointestinal conditions other than IBS (*e.g.*, lactose intolerance, celiac disease, inflammatory bowel diseases, and diverticulitis); (2) metabolic disorders affecting intestinal transit function or nutrient absorption (*e.g.*, diabetes or unbalanced thyroid dysfunction); (3) pregnant status; (4) chronic alcoholism; and (5) allergy to GASTRAP® DIRECT components or to fructose. Patients with high risk of secondary bile acid malabsorption were excluded (patients with terminal ileal disease or resection, pelvic radiotherapy, diarrhea occurring after cholecystectomy). Concerning primary bile acid malabsorption, since the accurate diagnosis remains challenging, methods of testing were not performed leading to the possibility that this condition may co-exist in about 30% of our patients with diarrhea-predominant IBS.

All patients agreed to maintain their lifestyle behaviors during the study period. Symptomatic drug treatments acting on intestinal functions, including laxatives, anti-bloating agents, probiotics, prebiotics, symbiotics, antispasmodics, anxiolytics, antidepressants, analgesics, and antibiotics, were authorized if consumed for longer than 1 month before inclusion without dose modification and maintained at a stable dosage for the entire study duration.

Study design

This was a 4-wk multicenter, prospective, observational, open-label study. Three medical visits [visit (V) 1–3] were scheduled at day 0 (V1), day 15 (V2), and at the end of the study on day 28 (V3) (Figure 1). At V1, eligibility according to the inclusion/exclusion criteria was assessed, and study instructions concerning the administration of GASTRAP® DIRECT were provided to eligible patients. Altered bowel habits [abnormal stool frequency and stool consistency as evaluated according to the Bristol stool scale (BSS)], symptoms of defecatory disorders including straining at stool and/or sensation of incomplete evacuation, intensity of IBS cardinal symptoms (abdominal pain, bloating, abdominal distension, and flatulence), and impact of global symptoms on daily life were evaluated at V2 and/or V3. The outcomes of individual IBS cardinal symptoms were evaluated using a three-point questionnaire (0, unchanged; 1, very much relieved; and 2, considerably relieved). Treatment tolerability was evaluated at the end of the study (V3) using the following categories: Bad, good, or very good (Figure 1).

Study product (GASTRAP® DIRECT) and compliance evaluation

The class IIa medical formulation GASTRAP® DIRECT is an oral gluten-free and lactose-free powder with vanilla flavor. Each sachet contains 500 mg of chitin-glucan and 250 mg of simethicone, sorbitol, silicon dioxide, acacia gum, xanthan gum, sucralose, and acesulfame K. GASTRAP® DIRECT is prepared in a 12-stick secondary packaging and is administered orally after meals. The recommended daily dose is up to three sticks per day. Patients initially started with one stick per day in the morning during the first 3 d; then increased to two sticks per day at one in the morning and one in the evening for the following 3 d; and finally to three sticks per day at one in the morning, one at noon, and one in the evening until the end of the 4-wk study (Figure 1). Compliance was determined through the assessment of returned packaging and interviews with the patients during V3.

Endpoints

The primary endpoint was the percentage of responders at V3, defined as patients whose abdominal pain score using the 10-point VAS score was reduced by at least 30% from baseline.

The secondary endpoints were the change in abdominal pain, abdominal bloating, abdominal distension. And impact of global symptoms on daily life evaluated by the 10-point VAS score and a three-point satisfaction questionnaire (0: Unchanged; 1: Very much relief; and 3: Considerable relief). Flatulence, constipation, diarrhea, and defecatory disorders were evaluated by the three-point satisfaction questionnaire. Improvement of stool consistency was evaluated according to the percentage of patients having hard (BSS score, ≤ 2) or liquid (BSS score, ≥ 6) stools at V0 and normal stool consistency (BSS score, ≥ 3 to ≤ 5) at V3. Treatment tolerability was analyzed at V3 using a three-point satisfaction score (0: Bad tolerability; 1: Good tolerability; and 2: Very good tolerability).

Safety variables

Adverse events were recorded by the patients and immediately communicated to the investigator for assessment of severity and causality. Severe and non-severe adverse events were recorded using two different forms.

Statistical analyses

Quantitative variables are described as mean ± standard error of the mean. Categorical variables are expressed as percentage and frequency. Responder rates for IBS symptoms (abdominal pain, bloating, abdominal distension, and impact of global symptoms on daily life) are expressed when appropriate using the standard method (normal distribution) with their 95% two-sided confidence intervals (95%CI) of means. Efficacy analyses were performed for the per-protocol population (intention-to-treat population who completed the study and presented no major protocol deviations). For all score outcomes, intragroup analyses were conducted using the two-tailed paired *t*-test or Wilcoxon signed-rank test (non–parametric test comparing ranks) depending on the distribution of the variable of interest for continuous variables to compare baseline values with the values recorded at V2 or V3. Comparisons between groups were performed using the Student t-test or Mann–Whitney–Wilcoxon test (non-parametric test comparing ranks) depending on the distribution of the variable of interest. All statistical analyses were conducted using StatXact 9 software (Cytel Studio 9, Cambridge, MA, United States). All statistical tests were two-sided at the 5% overall alpha risk level. All CIs were two-sided and presented at the 95% confidence level.

RESULTS

Baseline patient characteristics

Among the 145 screened patients, 120 patients were enrolled at V1. Among them, five patients were further excluded owing to voluntary withdrawal and 15 patients discontinued the trial owing to noncompliance (less than 70% intake of expected treatment administration), no follow-up (n = 14), or constipation (n = 1). A total of 100 patients with IBS (76 females and 34 males) who met the Rome IV criteria were included and homogeneously distributed across all care settings (center 1: n = 15, center 2: n = 23, center 3: n = 23, center 4: n = 14, center 5: n = 25). The participant selection flowchart is shown in Figure 2. Overall, 38% of patients had constipation-predominant IBS, 32% had diarrhea-predominant IBS, and 20% had mixed IBS. Most patients (67%) had normal stool consistency at V1 (liquid stools, 18%; hard stools, 15%). Good compliance was recorded during the 1-month treatment (88% ± 5%). The baseline characteristics of the participants are presented in Table 1.

Table 1 Baseline patient characteristics, *n* (%)

	V1 (*n* = 100)
Female sex	76 (76)
Age (yr), mean ± SD	47 ± 13
IBS type	
Constipation-predominant	37/98 (38)
Diarrhea-predominant	31/98 (32)
Mixed	20/98 (20)
Undefined	10/98 (10)
Stool consistency (BSS score), mean ± SD	4.1 ± 1.1
Hard stool (1–2)	14/93 (15)
Normal stool (3–5)	62/93 (67)
Liquid stool (6–7)	17/93 (18)
Excessive flatulence	91/98 (93)
Defecatory disorders	26/100 (26)

V: Visit; BSS: British stool scale.

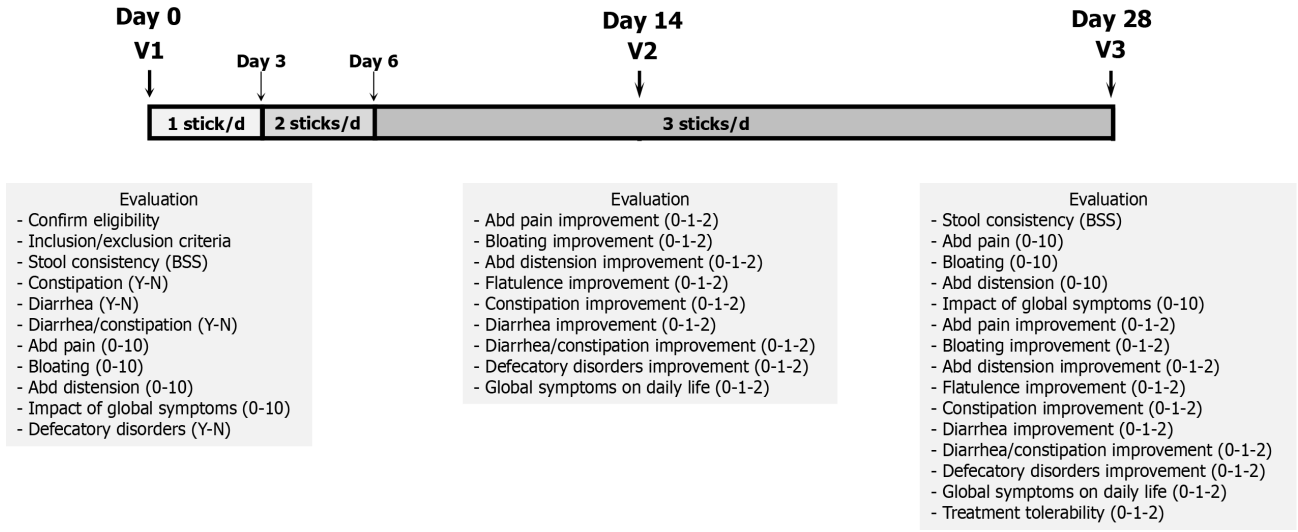

Figure 1 Study design. D: Day; BSS: British stool scale; d: day; V: Visit; Y: Yes; N: No; abd: Abdominal; SGA: Subjective global assessment.

Primary endpoint: Abdominal pain

The responder rate was 67% (64/96, 95%CI: 57-75) (Table 2 and Figure 3). The abdominal pain score was significantly decreased throughout the 4-wk treatment period (5.8 ± 2.4 at V0 *vs* 2.9 ± 2.0 at V3), with a mean reduction of pain intensity of 50% corresponding to a 2.9-point decrease ($P < 0.0001$) (Table 2 and Figure 3). Overall, 66% of the patients reported very much/considerable improvement in abdominal pain score at V3 with a rapid relief of abdominal pain observed from the second week of treatment in 58% of the patients (Table 3).

Secondary endpoints: Bloating, abdominal distension, global symptoms, and flatulence

A significant reduction of bloating (8.0 ± 1.7 at V0 *vs* 4.7 ± 2.9 at V3) and abdominal distension (7.2 ± 2.1 at V0 *vs* 4.4 ± 3.1 at V3) scores were observed after 4 wk of treatment, with a 40% reduction of symptom intensity ($P < 0.0001$) (Table 2, Figures 4A, 4B, 5A and 5B). The responder rates with respect to bloating and abdominal distension were 60% and 53%, respectively (Table 2, Figures 4C and 5C). In total, 67% and 57% of the patients reported very much/considerable improvements in scores on bloating and abdominal distention, respectively, at V3. More than 45% of the patients reported rapid relief for these symptoms starting from the second week of treatment (Table 3). The improvements of cardinal symptoms of IBS were seen with a similar degree of beneficial changes in patients with IBS patients with prevalent constipation (IBS-C), IBS patients with prevalent diarrhea (IBS-D), and IBS patients with mixed symptoms

Table 2 Change in paired scores of irritable bowel syndrome symptoms after week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3)

IBS symptoms	V1, mean ± SEM	V3, mean ± SEM	Responders, Δ > 30%, *n* [% (95%CI)]	Paired decrease, mean ± SE (%)
Abdominal pain (0–10)	5.8 ± 2.4	2.9 ± 2.0[c]	64/96 [67 (57; 75)]	-2.9 ± 0.3 (50)
Bloating (0–10)	8.0 ± 1.7	4.7 ± 2.9[c]	58/96 [60 (50; 70)]	-3.2 ± 0.3 (40)
Abdominal distension (0–10)	7.2 ± 2.1	4.4 ± 3.1[c]	51/96 [53 (43; 63)]	-2.8 ± 0.4 (39)
Impact of global symptoms on daily life	7.1 ± 2.0	4.6 ± 2.9[c]	51/94 [54 (44; 64)]	-2.5 ± 0.3 (35)

[c]$P < 0.001$.

95%CI: Confidence interval of the responder rate (Wilson method); IBS: Irritable bowel syndrome; V: Visit.

Table 3 Symptom relief at weeks 2 and 4 of GASTRAP® DIRECT treatment

Symptom relief	W2 (%)	W4 (%)
Abdominal pain		
Unchanged	42	34
Relief (very much, considerable)	58 (53, 5)	66 (48, 18)
Bloating		
Unchanged	48	33
Relief (very much, considerable)	52 (45, 7)	67 (49, 18)
Abdominal distension		
Unchanged	55	43
Relief (very much, considerable)	45 (33, 12)	57 (40, 17)
Impact of global symptoms on daily life		
Unchanged	37	23
Relief (very much, considerable)	63 (42, 21)	77 (53, 24)
Flatulence		
Unchanged	46	44
Relief (very much, considerable)	54 (44, 10)	56 (41, 15)

W: Week.

(Table 4).

The impact of global symptoms on daily life was significantly decreased by 35% at V3 (4.6 ± 2.9 *vs* 7.1 ± 2.0, $P < 0.0001$) (Table 3 and Figure 6). A total of 63% and 77% of the patients reported very much/considerable relief after 2 and 4 wk of treatment, respectively (Table 3).

Overall, 93% of the patients had excess flatulence at baseline (Table 1). After 4 wk of treatment, 56% reported very much/considerable symptom relief, with improvements starting from V2 in 54% of the patients (Table 3).

Altered bowel habits and symptoms of defecatory disorder

Among the patients with liquid stools at baseline, approximately 90% had normal stool consistency after 4 wk of treatment, with very much/considerable relief of diarrhea observed in 58% of the patients (Table 5 and Figure 7). For patients with hard stools at baseline, 57% had normal stool consistency at V3, and 46% observed a very much/considerable improvement in constipation (Table 5 and Figure 7).

Among the 26% of patients with defecatory disorders (*e.g.*, straining at the stool and/or sensation of incomplete evacuation), 42% showed very much/considerable improvement starting from the second week of treatment (Table 5 and Figure 7).

Safety and tolerability

No serious adverse events were observed. The most frequent symptoms, which accounted for more than 70% of all adverse events, were abdominal pain ($n = 2$), bloating ($n = 2$), constipation ($n = 5$), diarrhea ($n = 1$), and pruritus ($n = 2$).

Table 4 Symptom relief at week 4 of GASTRAP® DIRECT treatment in patients with IBS having prevalent constipation, diarrhea, and mixed irritable bowel syndrome

Symptom relief at W4	IBS-C (%)	IBS-D (%)	IBS-M (%)
Abdominal pain			
Unchanged	42	27	34
Relief (very much, considerable)	58 (50, 8)	73 (46, 27)	66 (48, 18)
Bloating			
Unchanged	42	32	31
Relief (very much, considerable)	58 (46, 12)	68 (41, 27)	69 (53, 16)
Abdominal distension			
Unchanged	46	50	39
Relief (very much, considerable)	54 (39, 15)	50 (36, 14)	61 (39, 21)

W: Weeks; IBS: Irritable bowel syndrome; IBS-C: IBS patients with prevalent constipation; IBS-D: IBS patients with prevalent diarrhea; IBS-M: IBS patients with mixed symptoms.

Table 5 Relief of altered stool pattern at weeks 2 and 4 of GASTRAP® DIRECT treatment

Symptom relief (% *vs* W0)	W2 (%)	W4 (%)
Constipation		
Unchanged	58	54
Relief (very much, considerable)	42 (27, 15)	46 (37, 9)
Diarrhea		
Unchanged	44	42
Relief (very much, considerable)	46 (42, 14)	58 (39, 19)
Defecatory disorders		
Unchanged	56	58
Relief (very much, considerable)	44 (36, 8)	42 (31, 11)

W: Week.

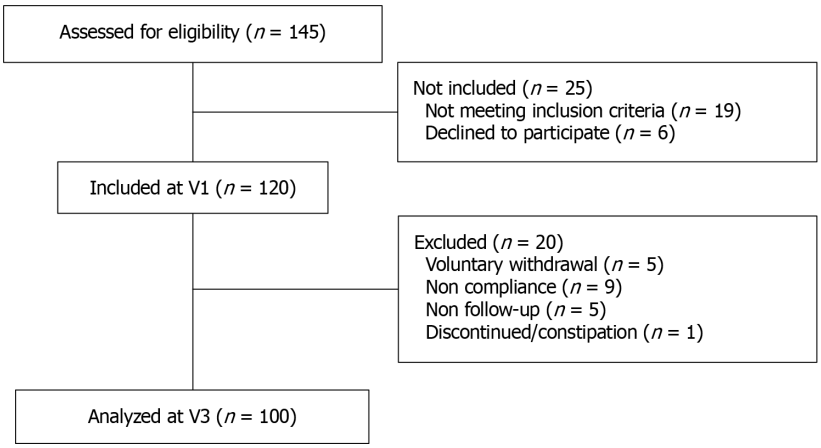

Figure 2 Patient selection flow chart. N: Number; V: Visit.

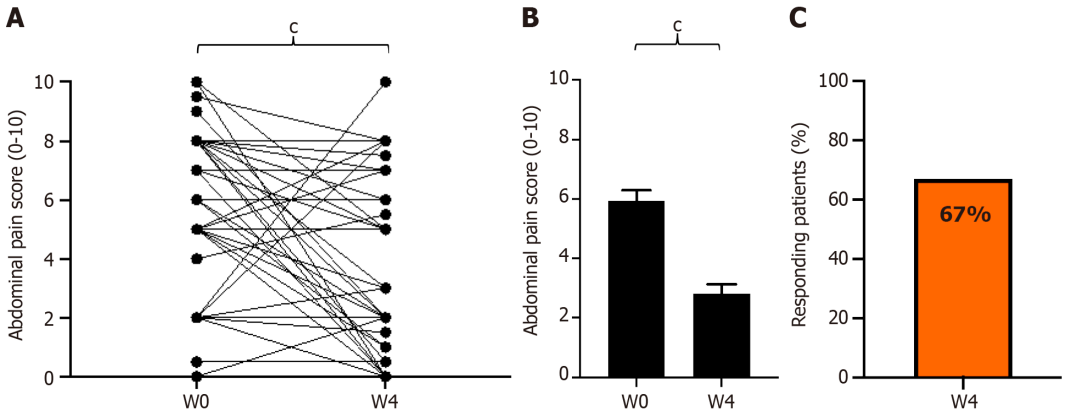

Figure 3 Change in paired abdominal pain scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Paired abdominal pain scores; B: Abdominal pain scores (0–10); C: Patient responders (delta > 30%) with respect to abdominal pain. °*P* < 0.001. W: Weeks.

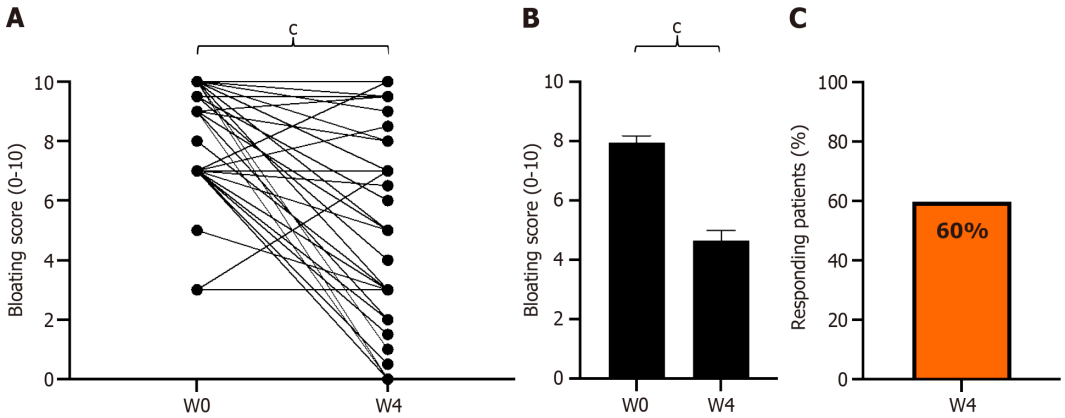

Figure 4 Change in paired bloating scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Change in paired bloating scores; B: Abdominal bloating scores (0–10); C: Patient responders (delta > 30%) with respect to bloating. °*P* < 0.001. W: Weeks.

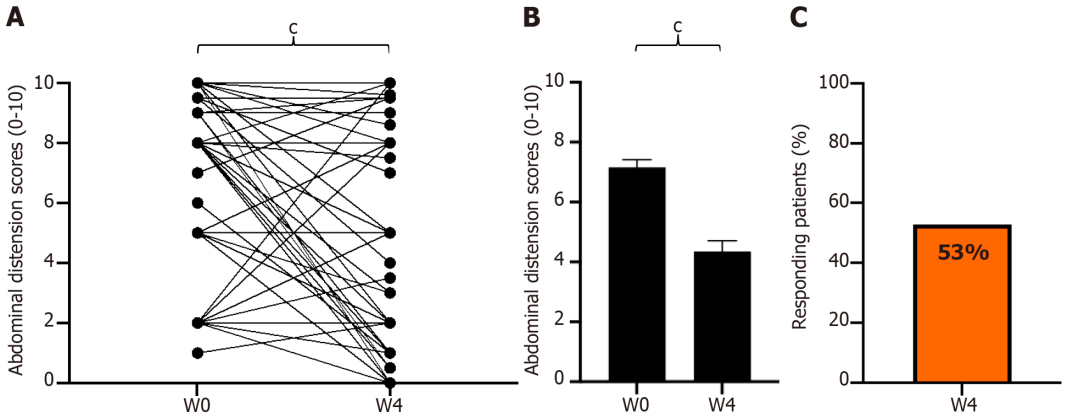

Figure 5 Change in abdominal distension scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Change in paired abdominal distension scores; B: Abdominal distension scores (0–10); C: Patient responders (delta > 30%) with respect to abdominal distension. °*P* < 0.001. W: Weeks.

The relationship with the study product was considered "not excluded" for one patient with constipation who discontinued the treatment. Overall, 93% of the patients at V3 considered that the tolerability of GASTRAP® DIRECT was "good" or "very good" (Figure 8).

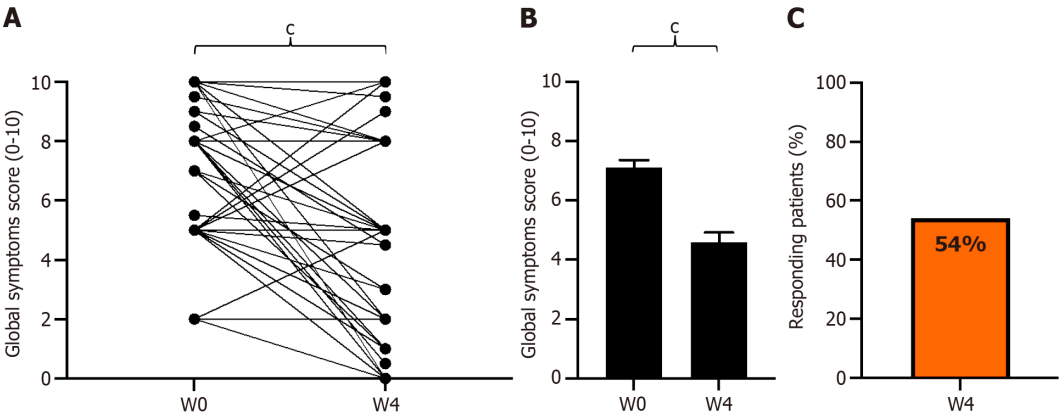

Figure 6 Change in impact of global symptoms on daily life scores from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Paired global symptom scores; B: Global symptom scores (0–10); C: Patient responders (delta > 30%) with respect to global symptoms. $^{c}P < 0.001$. W: Weeks.

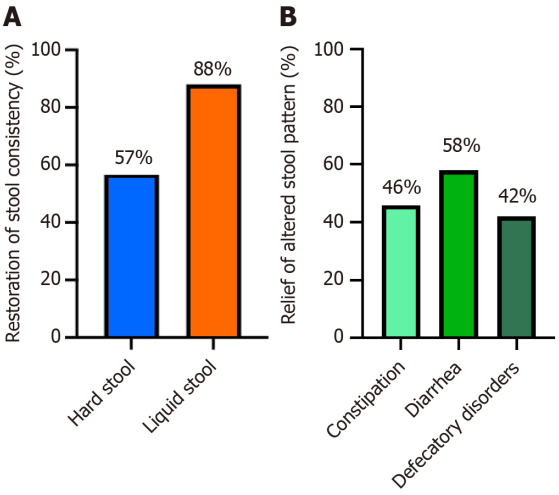

Figure 7 Changes in stool from baseline to week 4 of GASTRAP® DIRECT treatment (visit 1 to visit 3). A: Restoration of stool consistency {hard stool [Bristol stool scale (BSS) score 1–2] to normal; liquid stool (BSS 6–7) to normal}; B: Relief of altered stool pattern.

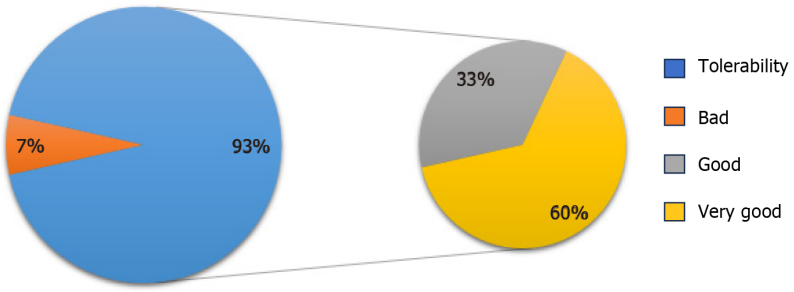

Figure 8 Tolerability of GASTRAP® DIRECT evaluated at week 4.

DISCUSSION

IBS is a heterogeneous disorder with multiple physiopathological mechanisms[27,28]. Exposure to pathogenic organisms, changes in host-microbiota interactions, and disruption of the intestinal barrier can affect the gut–brain axis, triggering locally persistent low inflammation and altering visceral sensitivity[27]. Studies focusing on the basic molecular mechanisms are crucial for improving IBS management and promoting the development of new, specific targeted treatments[27]. In our previous study, we demonstrated that the prebiotic chitin-glucan can rapidly and significantly decrease visceral perception and intestinal inflammation by regulating master genes and binding harmful substances (*e.g.*,

microbial cell walls) in the intestinal lumen[20].

To our best knowledge, the present study is the largest prospective, multicenter open-label trial using chitin-glucan and simethicone in patients with IBS and the first study to be entirely conducted in secondary and tertiary care settings. In a population of IBS patients without benefit from classic first-line therapies, GASTRAP® DIRECT three times a day met the primary outcome with a 50% decreased of abdominal pain score at 1 month compared with baseline resulting in 67% of responders corresponding to patients with a 30% or greater improvement in abdominal pain intensity. GASTRAP® DIRECT also improved the secondary outcomes, showing effectiveness in significantly reducing bloating, abdominal distension, flatulence, and symptoms of defecatory disorders, with an improvement of global symptom-reporting scores considered as important by 77% of patients. No significant adverse events occurred, and 93% of the participants judged the tolerability of the treatment as good or very good.

Our chosen primary outcome of clinically relevant abdominal pain response, defined as ≥ 30% improvement from baseline, follows the Food and Drug Administration (FDA) and European Medicine Agency recommended endpoints[31,32]. Although FDA guidance does not include bloating and abdominal distension as potential exploratory endpoints in clinical trials of IBS, these symptoms are recognized to be troublesome to patients. The 4-week GASTRAP® DIRECT treatment decreased bloating and abdominal distension scores by 40%, with responder rates of 60% and 53% for these symptoms, respectively. Similarly, a comparable improvement in flatulence and the impact of global symptoms on daily life was observed in most patients starting from the second week of treatment. Constipation, diarrhea, and defecatory disorders (*e.g.*, straining of the stool and/or sensation of incomplete evacuation) were also improved. These results are of great clinical interest as they meet the clinically relevance threshold previously proposed[31,32], and they suggest that GASTRAP® DIRECT may be a rapid and effective modality for the management of IBS, regardless of the constipated or diarrheal predominant subtypes.

This study had a number of strengths and some limitations. This prospective, multicenter, observational, open-label study recruited a large number of participants who were objectively diagnosed according to the Rome IV criteria. The patients were recruited from secondary and tertiary care centers, and the population was representative of adults of all ages, with equally represented IBS subtypes. Given that a low baseline symptom score is significantly associated with a higher placebo response rate[33], we included patients with significant abdominal pain (mean VAS pain score: 5.8) and excluded patients with low symptom severity at baseline. Notably, the treatment duration of 4 wk was relatively short, although it is reasonable based on the pharmacology of the compound. Early exploratory studies showed that chitin-glucan is a new-generation prebiotics, which induces rapid antinociception and immediate chelation of harmful microbial products present in the intestinal lumen[20]. Another clinical study aiming to evaluate the efficacy of a 12-wk chitin-glucan treatment for IBS (BK-IBS-2301/NCT number: NCT05780749) is currently ongoing. The placebo effect is an important consideration in clinical trials for IBS treatment, which made it impossible to determine the precise impact of the combination of chitin-glucan and simethicone on IBS symptoms in the present study. The pooled placebo response rate in IBS trials was as high as 37.5%, particularly for clinical studies performed in Europe with a treatment duration of 1–4 wk[34]. Recently, pooled placebo response rates of 34.6% and 40.2% according to the abdominal pain responder definition (≥ 30% improvement) have been reported in patients with IBS-C and IBS-D, respectively[35]. However, the responder rate to abdominal pain was 67% in the current study, exceeding the estimated 35%–40% placebo effect by approximately 30%. In addition, although no formal sample size calculation was performed, using a placebo responder rate of 37.5%, we calculated that a sample size of 100 participants would allow us to show that an observed responder rate of 52% is significantly higher than the reference value (37.5%), considering a power of 80% and a two-sided one-sample proportion test at 0.05 significance level. Thus, the results of this clinical trial are encouraging and could be meaningful in daily practice.

GASTRAP® DIRECT is a class IIa medical with different mechanisms of action involved in its clinical effects as observed in our study. Simethicone is a silicone compound that functions locally as a surfactant and decreases the surface tension of gas bubbles[36]. It acts on the coalescence and dispersion of gas bubbles, facilitating their elimination from the gastrointestinal tract, thus reducing the occurrence and intensity of flatulence and bloating[37]. In contrast, chitin-glucan acts differently, targeting most of the pathophysiological mechanisms associated with IBS. In addition to its prebiotic effect of selectively promoting the growth and activity of beneficial gut bacteria (*e.g.*, *Roseburia spp*. and the *Faecalibacterium prausnitzii*)[18,19], oral administration of chitin-glucan induces visceral analgesic effect, which leads to a rapid and significant inhibition of pain perception. This action is possibly mediated by an increased expression of μ-opioid receptor and cannabinoid receptor 2 on epithelial cells[20]. In mice with colitis, chitin-glucan decreased the intensity of inflammation by 50%, with complete regeneration of the colonic mucosa and restoration of stool consistency through the regulation of major key players driving intestinal inflammation [interleukin (IL)-1, IL-8, and IL-10] and epithelial barrier integrity (mucin-5AC, claudin-2, and zonula occludens-2)[20]. In silico studies have revealed that chitin-glucan exhibits antimicrobial activities by chelating the most active components of Gram-negative and Gram-positive bacteria, as well as the phospholipomannan of yeasts[20].

Rapid action, safety, and tolerability are essential for the development of new IBS therapeutic strategies. The present study observed a significant and rapid improvement of all quantitative and subjective clinical endpoints after 2 wk of GASTRAP® DIRECT administration. GASTRAP® DIRECT showed a high safety profile as evidenced by the absence of serious adverse events and a low number of adverse events. Only one patient developed constipation. The relationship with the study product was considered "not excluded." These data, which should be confirmed in a double-blinded controlled study, may have important implications, particularly for the long-term treatment of IBS with GASTRAP® DIRECT. In addition, the outcomes reflect the results of 10 years of post-market surveillance for this treatment in Europe, with more than 90% of patients reporting that GASTRAP® DIRECT has good or very good tolerability.

CONCLUSION

GASTRAP® DIRECT is a safe and well tolerated non-pharmacological treatment for IBS, providing in this open-label study rapid and significant improvement of cardinal symptoms, including abdominal pain, bloating, flatulence, constipation, diarrhea, and dyschezia, within 2 weeks. Hence, GASTRAP® DIRECT could be a promising natural non-chemotherapeutic solution in the management of patients with IBS. Further double blind randomized controlled study with longer follow-up should be performed in patients with IBS or those with IBS-like symptoms to confirm and extend the use of GASTRAP® DIRECT in patients with intestinal functional disorders.

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FOOTNOTES

Author contributions: Desreumaux P and Valibouze C designed the study; Talbodec N, Le Roy P, Fournier P, Lesage B, Lepoutre E, Castex F, Godchaux JM, Vandeville L, Bismuth B, Lesage X, Bayart P, and Desreumaux P included patients with irritable bowel syndrome; Genin M supervised the statistical analysis; all authors interpreted the data; Valibouze C and Desreumaux P drafted the article; All authors critically reviewed the manuscript and approved the final version for submission. Intestinal Biotech Development supervised study coordination, data collection, and analysis.

Institutional review board statement: This study was approved by the Ethics Committee Sud-Est VI of Clermont-Ferrand (France) (Ref. ID-RCB: 2019-A03202-55) and was performed in accordance with the International Conference on Harmonization of Good Clinical Practice and the ethical principles of the Declaration of Helsinki.

Conflict-of-interest statement: Desreumaux P reports receiving personal fees from Abbvie, Abbott, Amgen, Biocodex, Biofortis, Biogen, Biokuris, Ferring, Fresenius, Janssen, Kitozyme, Lesaffre, MSD, Norgine, Pfizer, Sandoz, Shire, Takeda, Tillotts, and UCB outside the submitted work. Dr. Desreumaux has a patent (WO2009103884) issued. Veronique Maquet is a product development manager at Kitozyme. Salvatore Modica is chief operating officer at Biokuris, a spin-off company of Kitozyme. Christel Rousseaux reports other from Biotech Companies, outside the submitted work. The other authors declare no conflicts of interest.

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