A Randomized Double-Blind, Placebo-Controlled, Cross-Over Study Using Baclofen in the Treatment of Rumination Syndrome

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OBJECTIVES: **Both rumination syndrome and supra-gastric belching (SGB) have limited treatment options. We demonstrated (open-label) that baclofen reduces pressure flow events in these patients. We aimed to study the effect of baclofen in a placebo-controlled, double-blind, cross-over study in patients with clinically suspected rumination and/or SGB.**

METHODS: **Twenty tertiary-care patients (mean age 42 years (range 18–61), 13f) with clinically suspected rumination and/or SGB were randomized to receive baclofen (10 mg, t.i.d) or placebo for 2 weeks with cross-over to the alternative intervention after a 1 week wash-out period. At the end of each treatment period, patients underwent a solid-state high-resolution impedance manometry measurement, during which they registered symptoms. Patients received a solid meal and recordings continued for 1 h. They scored overall treatment evaluation (OTE) on a −3 to +3 scale.**

RESULTS: **Both the number of regurgitation event markers and rumination episodes were significantly decreased after baclofen (6 (0–19) vs. 4 (0–14), *P*=0.04; 13 (8–22) vs. 8 (3–11), *P*=0.004). The number of SGB episodes was similar in both groups. Lower esophageal sphincter (LES) pressure was significantly higher and the number of transient LES relaxations was significantly lower after baclofen (17.8 (12.7–22.7) vs. 13.1 (7.2–16.9) mm Hg, *P*=0.0002; 4(1–8) vs. 7(3–12), *P*=0.17). The number of reflux events decreased in the baclofen condition (4 (1–9) vs. 3 (0–6), *P*=0.03). Straining episodes were similar in both arms, but the rumination/straining ratio was significantly lower in the baclofen arm (0.06 (0–0.32) vs. 0.33 (0–0.51), *P*=0.0012). OTE was superior after baclofen compared to placebo (*P*=0.03).**

CONCLUSIONS: **Baclofen is an effective treatment option for patients with rumination syndrome, probably through its effect on LES pressure.**

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INTRODUCTION

Rumination is the repetitive, effortless regurgitation of recently ingested food into the mouth followed by rechewing and/or re-swallowing or expulsion of the food bolus (1). It is not preceded by retching and patients most often do not experience heartburn, abdominal pain, or nausea (2). Rumination syndrome was historically thought to be limited to children and mentally disabled people, but is now recognized to frequently occur in adults with normal cognitive function as well (3,4). Rumination is the result of a voluntary, yet unintentional contraction of the abdominal muscles, which increases intra-gastric pressure (IGP, strain), so it can overcome lower esophageal sphincter (LES) pressure and drive gastric contents into the esophagus, pharynx, and mouth (5–7). Rumination is often misdiagnosed when only taking into consideration the clinical symptoms, as patients typically present with regurgitation suggesting gastro-esophageal reflux disease and/or vomiting suggesting a very severe form of gastroparesis or another vomiting disorder (8). Using high-resolution impedance manometry (HRiM) it is possible to detect rumination and to discriminate from reflux. Recently, Kessing *et al.* (6) proposed HRiM

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criteria for rumination defined as regurgitation into the proximal esophagus while associated with a rise in IGP >30 mm Hg.

Supra-gastric belching occurs when air is sucked into the esophagus by a decreasing intra-thoracic pressure (1). The air is immediately expelled, as the LES remains closed (9,10). In case of supra-gastric belching, upper esophageal sphincter relaxation precedes the onset of the anterograde flow of air, while during gastric belching, upper esophageal sphincter relaxation occurs after the onset of the retrograde airflow (1). Supra-gastric belching typically stops when patients are talking, sleeping, and often even when distracted.

Both rumination syndrome and supra-gastric belching are highly bothersome and significantly impair quality of life, however, treatment options are limited (8,11–15). Besides lifestyles changes and proton pump inhibitor therapy, behavioral modification is one of the few options. Diaphragmatic breathing exercises with biofeedback to compete with the urge to ruminate have been suggested (16–19). Although this was effective in more than half of the patients, there is only one placebo-controlled trial for rumination: Barba *et al.* (20) showed a decrease in the number of rumination episodes in the biofeedback group, but not in the placebo group. Second, due to a lack of skilled personnel, this therapeutic approach is often difficult to achieve. Third, not all patients are willing to undergo behavioral therapy. An intervention by a speech pathologist has been suggested in patients with supra-gastric belching. The focus lies on avoiding glottis closure and regaining control of diaphragmatic breathing to prevent episodes of supra-gastric belching (10). In case series, this technique was successful in 55% of patients. However, this therapy is also complex, requires highly trained therapists, is unlikely to be widely available, and requires acceptance by the patients. Therefore, there is an unmet need for other therapeutic options in both rumination syndrome and supra-gastric belching.

Baclofen, a gamma-aminobutyric acid agonist, is able to reduce the number of transient LES relaxations (TLESRs) and increase LES pressure. It reduces reflux events irrespective of their acidity and has been successfully used in the treatment of gastro-esophageal reflux disease (21–25). Patients with rumination syndrome are able to exceed the barrier pressure provided by the LES and crural diaphragm by temporarily increasing the IGP, and could therefore benefit from the increase in LES pressure provided by baclofen. A previous open-label study by our group showed that baclofen decreased the number of flow events and the number of symptoms during a meal manometry in patients with rumination syndrome and supra-gastric belching (26). In this study, we wanted to explore whether baclofen can be used in the treatment of patients with rumination syndrome and/or supra-gastric belching in a randomized, double-blind, placebo-controlled manner.

METHODS

Patients

We included patients attending the outpatient clinic at the University Hospital Gasthuisberg (Leuven, Belgium) with a clinical suspicion of rumination syndrome and/or supra-gastric belching, according to Rome IV criteria (1). Patients with rumination syndrome typically present with persistent or recurrent regurgitation of recently ingested food into the mouth, not preceded by retching or nausea (1). Repetitive bothersome belching is the main symptom of patients with supra-gastric belching (1). We deliberately based the inclusion of patients on clinical suspicion of rumination and supra-gastric belching, rather than on manometric diagnosis because availability of HRiM with prolonged recording after a standardized meal is limited and because many patients display both types of events when studied with HRiM (5). All patients underwent empirical treatment with proton pump inhibitors without full resolution of their symptoms. None of the patients underwent any form of behavioral therapy before inclusion in the study. Exclusion criteria were as follows: >75 years; a history of thoracic or upper abdominal surgery; and prior treatment with baclofen. The study was approved by the ethics committee of the University Hospital (S53446) and was registered at ClinicalTrials.gov (NCT03113396). All patients gave written informed consent before inclusion in the study.

On the basis of a previous study from our group, we used G*Power to calculate the sample size. With an 80% power, with alfa set to 0.05 and an effect size of 0.585 (based on the difference in the regurgitation marker between placebo and baclofen in the paper of Blondeau *et al.* (26)), we needed to include 20 subjects in the study.

A randomization scheme was generated independent from the researchers, by the pharmaceutical services of the University Hospital (using www.randomization.com).

Study protocol

After inclusion in the study, patients were randomized into baclofen or placebo t.i.d. for 2 weeks after which they underwent a stationary HRiM recording (**Figure 1**). After an overnight fast, a single solid-state catheter containing 36 pressure channels and 16 impedance channels (Unisensor AG, Attikon, Switzerland) was positioned in the esophagus and proximal stomach. Pressure and impedance signals were recorded on a personal computer system (Medical Measurement System, Enschede, The Netherlands). After placement of the catheter, patients remained in a semi-recumbent position for the entire study period. A series of 10 wet swallows (5 ml saline) were performed to study esophageal peristalsis, after which a baseline recording for 30 min was performed. Thereafter, patients received a 1,000 kcal test meal (meat loaf, mashed potatoes, and apple sauce) after which recordings were continued for another 60 min. Patients were instructed to carefully record symptoms of regurgitation and/or belching during the entire study period using the respective event markers. After a 1-week wash-out period, patients were crossed over to the alternative treatment, and after 2 weeks of treatment, a similar HRiM recording was performed. Patients were instructed to take the study medication before the start of the recording.

Medication consisted of identically looking capsules of baclofen (5 mg) or placebo. Patients were instructed to take one capsule t.i.d. during the first week, which was increased to two capsules (10 mg baclofen) t.i.d. in the second week. Adverse events were recorded throughout the entire study.

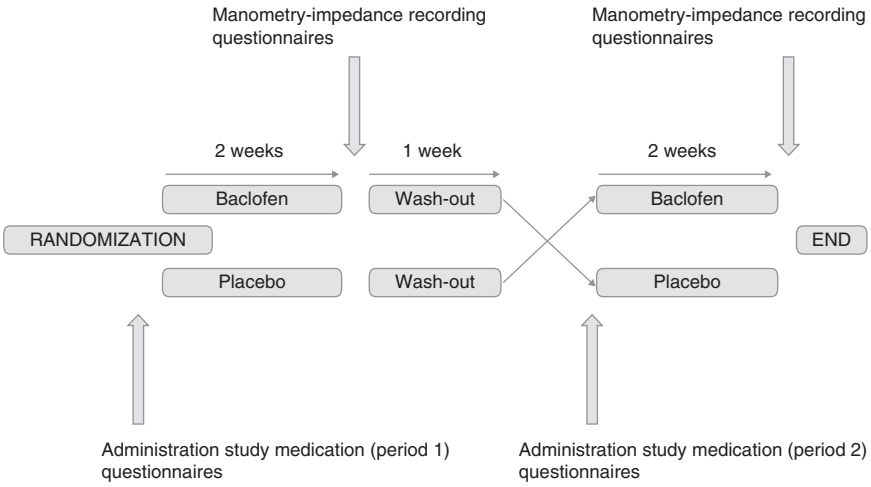

Figure 1. Overview of the study.

During the study, patients were asked to fill out a questionnaire concerning "overall treatment evaluation" (OTE). At the end of each treatment period, we asked patients how they perceived their complaints compared to the pre-treatment period (−3 became totally unbearable, −2 became much worse, −1 became slightly worse, 0 did not change, +1 became slightly better, +2 became much better, and +3 totally resolved) (27).

Analysis of symptom markers

We counted the number of times patients indicated regurgitation or belching during the entire study period using the designated event marker.

Analysis of flow events

All HRiM tracings were analyzed blindly by one investigator (A.P.). Meal periods were excluded for analysis. The different flow events were classified as reflux, rumination, supra-gastric belching, and gastric belching.

Gastro-esophageal reflux was defined as an orally progressing drop in impedance of at least 50% compared to baseline starting in the most distal channel and propagating retrogradely to at least the next more proximal impedance channel (28). Rumination was defined as a reflux episode associated with an abrupt rise in IGP (strain) (5,6). Rumination episodes were subdivided into primary rumination (IGP rise precedes the retrograde bolus flow), secondary rumination (increase in IGP after the onset of a reflux event), and supra-gastric belch associated rumination (a supra-gastric belch precedes a rumination episode) (6). Supra-gastric belching was defined as a rapid increase in impedance (3,000 Ω/s) progressing in an aboral manner followed by an immediate expulsion (impedance values returning to baseline in a retrograde way) (29). Gastric belching was identified as a rapid increase in impedance in at least two consecutive impedance channels progressing in a retrograde manner (28,29).

Analysis of LES pressure, transient LES relaxations, and esophageal peristalsis

We measured basal LES pressure at end expiration relative to IGP and calculated LES pressure as the average of 1 min periods every 15 min, provided the measurement was stable and no swallow or TLESR occurred. TLESRs were identified using established criteria: (i) absence of pharyngeal swallowing 4 s before to 2 s after the onset of esophago-gastric junction relaxation; (ii) relaxation rate of ≥1 mm Hg/s; (iii) time from onset of relaxation to complete relaxation of ≤10 s; and (iv) nadir pressure of ≤2 mm Hg. LES relaxations lasting longer than 10 s were also classified as TLESR, irrespective of the timing of the onset of swallowing (30). Esophageal body contractions were classified using the criteria adopted by the Chicago classification for HRM (31).

Statistical analysis

Data are presented as median with interquartile range, unless stated otherwise. Analyses were performed using GraphPad Prism 7.0 (La Jolla, CA).

The primary symptom outcome variables were the number of symptoms of regurgitation, assessed as an event marker pushed by the patients during the HRiM measurement and the OTE. The number of flow events, the number of symptoms, LES pressure, and the number of TLESRs were compared between baclofen and placebo treatment using a paired *t*-test or Wilcoxon matched signed rank test in case of non-parametric distribution. When analyzing the different flow events, only patients demonstrating the examined flow events where taken into consideration. A P value <0.05 was considered significant.

RESULTS

Conduct of the study

We enrolled 21 patients with a mean age of 42 years (range 18–61); the majority was female (13 females/8 males; **Figure 2**).

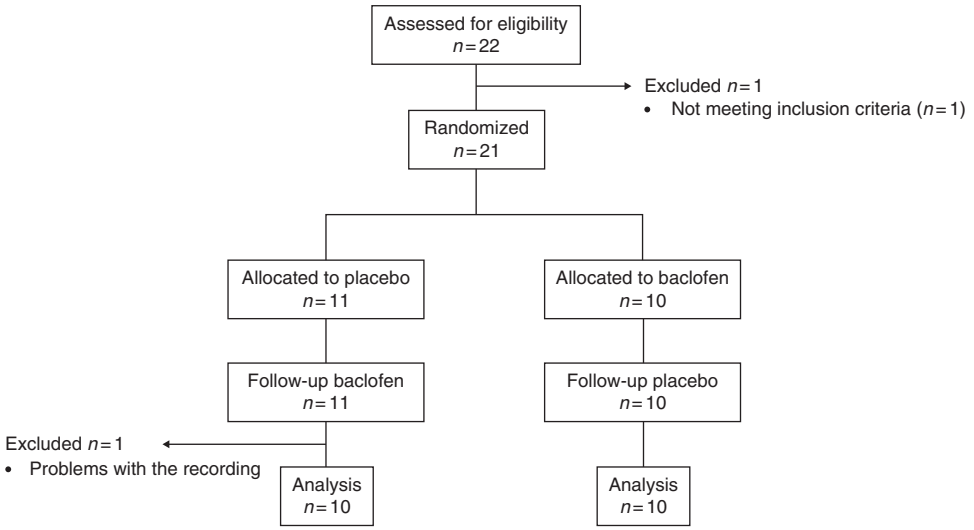

Figure 2. Consort trial flow diagram.

All patients presented with complaints of postprandial regurgitation and/or belching, suggesting rumination syndrome or supragastric belching. Regurgitation was found to be the predominant symptom in 16 patients, whereas 5 patients presented with belching as their predominant symptom.

All patients followed the treatment protocol as planned without any dropouts. One patient had to be excluded from the analysis due to recording errors. During the baclofen treatment period, three patients experienced sleepiness, two patients had some complaints of dizziness, and two patients had acral paresthesia. However, these mild side effects disappeared after a maximum of 2 days and none of the patients had to end the study prematurely. No side effects were reported in the placebo condition.

Symptom markers

In total, the median number of times patients marked an event in the placebo condition was 17 (4–75) compared to 13 (7–54) in the baclofen condition (P=0.72). The majority of symptoms were recorded in the postprandial period, both in the placebo as well as in the baclofen condition (89% and 92%, respectively). In general, the vast majority of events marked by the patients corresponded to a flow event, identified by HRiM, both in the baclofen as well as in the placebo condition (98 (94–100)% vs. 98 (88–100)%, P=0.17). There were no differences in the number of events marked by the patients in the preprandial period between both treatment arms. The median number of times that the patients used the "belching" marker during the postprandial period was similar in placebo and baclofen condition (2 (0–30) vs. 5 (0–28), P=0.35). However, the median number of times that the "regurgitation" marker was pushed was significantly lower in the baclofen condition compared to the placebo condition (4 (0–14) vs. 6 (0–19), P=0.04; **Figure 3**).

Flow events

We recorded a total of 1,307 flow events in the placebo condition and 891 in the baclofen condition (**Figure 4**). The median total

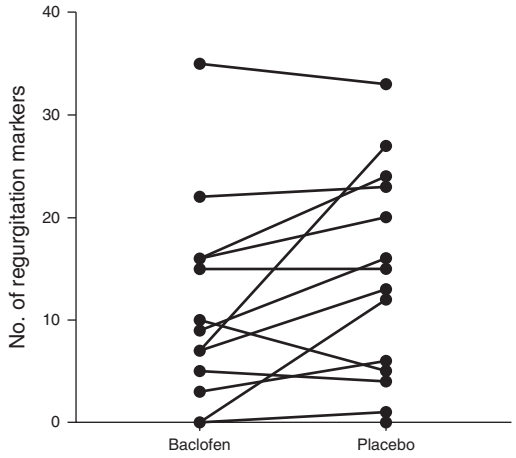

Figure 3. The median number of times patients used the "regurgitation" marker was significantly lower in the baclofen condition compared to the placebo condition (4 (0–14) vs. 6 (0–19), P=0.04).

number of flow events per patient was lower after baclofen treatment compared to placebo (15 (8–45) vs. 20 (13–86), P=0.02). Dividing the patients according to their manometry/impedance profile during placebo, we found that 4/20 had only reflux episodes, 4/20 presented with solely rumination syndrome, 3/20 had supra-gastric belching, and 9/20 had episodes of both rumination and supra-gastric belching. The number of supra-gastric belches was similar between placebo and baclofen (38 (1–127) vs. 22 (2–126), P=0.72). Episodes of rumination were significantly lower in the baclofen treatment arm compared to the placebo arm (8 (3–11) vs. 13 (8–22), P=0.004; **Figure 5**). Distributions were similar in placebo and baclofen condition when dividing rumination episodes into primary, secondary, and supra-gastric belch-associated rumination (placebo: 113/202 (56%), 25/202 (12%), and 64/202 (32%); baclofen: 70/107 (66%), 8/107 (7%), and 29/107

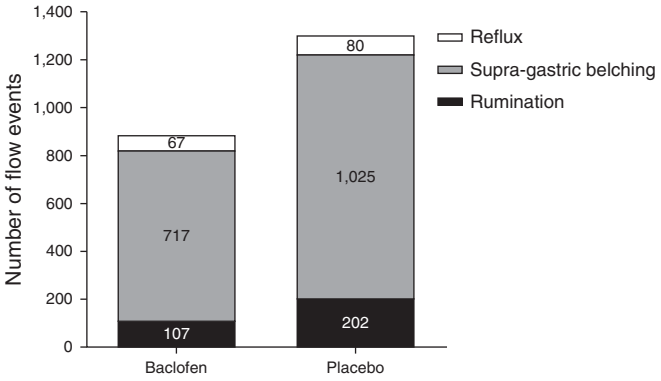

Figure 4. A total of 1,307 flow events was detected in the placebo condition and 891 in the baclofen condition.

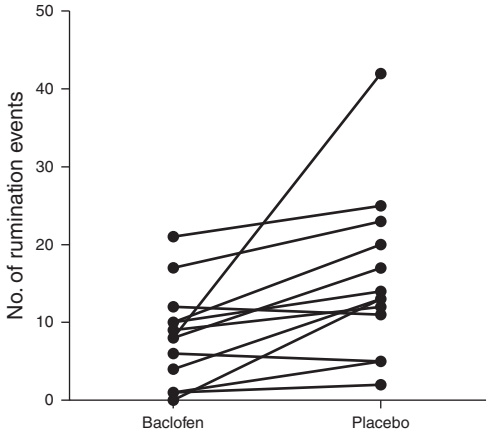

Figure 5. The number of rumination episodes was significantly lower in the baclofen treatment arm compared to the placebo arm (8 (3–11) vs. 13 (8–22), *P*=0.004).

(27%), respectively). The number of reflux episodes was significantly lower after baclofen treatment compared to placebo treatment (3 (0–6) vs. 4 (1–9), *P*=0.03).

LES pressure, transient LES relaxations, and esophageal peristalsis

As expected, LES pressure decreased significantly after the meal period, both in the placebo as well as in the baclofen arm (placebo 22.00 (18.25–25.90) vs. 13.06 (7.16–16.91) mm Hg, *P*<0.0001; baclofen 22.00 (20.00–30.88) vs. 17.79 (12.72–22.68) mm Hg, *P*=0.0003).

However, postprandial LES pressure was significantly higher in the baclofen treatment arm compared to the placebo treatment arm (17.79 (12.72–22.68) vs. 13.06 (7.16–16.91) mm Hg, *P*=0.0002; **Figure 6**). We found a borderline negative correlation between postprandial LES pressure and the number of rumination episodes in the baclofen condition (*P*=0.056, *r*=−0.54).

The number of postprandial TLESRs was significantly lower after baclofen compared to placebo (4 (1–8) vs. 7 (3–12), *P*=0.017).

We could detect straining episodes in all patients, and their number did not differ between placebo and baclofen condition (33 (22–71) vs. 30 (22–49), *P*=0.4). However, the ratio rumination/straining was significantly lower after baclofen treatment compared to placebo treatment (0.16 (0.06–0.35) vs. 0.43 (0.33–0.54), *P*=0.0012; **Figure 7**).

The integrated relaxation pressure was significantly higher in the baclofen treatment arm compared to the placebo arm (13 (7–16) vs. 6 (5–13) mm Hg, *P*=0.0031). No differences were found in distal latency or distal contractile integral between both treatment arms (data not shown). Four patients were diagnosed with ineffective esophageal motility in the placebo arm, while only one patient had ineffective esophageal motility and one presented with absent peristalsis in the baclofen arm.

Questionnaires

Patients reported significantly better OTE ratings after treatment with baclofen compared to placebo (mean score 1 (0–2) vs. 0 (−1–1), *P*=0.03). On baclofen treatment, 63% of patients improved while this was only the case in 26% of patients on placebo treatment (*P*<0.0001; **Figure 8**).

DISCUSSION

Both rumination syndrome and supra-gastric belching are highly bothersome with a major negative impact on quality of life (8,11,12). Treatment options are limited and patients often feel misunderstood. Baclofen is able to increase LES pressure and might be helpful in the treatment of rumination syndrome/supra-gastric belching based on open-label observations (27). In this double-blind, placebo-controlled, cross-over study, we examined the effect of baclofen on symptoms and flow events in patients with clinical suspicion of rumination and/or supra-gastric belching.

We showed that (i) regurgitation was significantly less registered by the patients in the baclofen arm compared to the placebo arm, with no differences in relation to the perception of belching; (ii) the number of flow events was significantly lower after baclofen compared to placebo, which was due to a significant reduction in the number of rumination episodes; (iii) LES pressure was significantly higher and the number of TLESRs was significantly lower after baclofen compared to placebo, the number of straining episodes was similar in both conditions, however, (iv) the ratio rumination/straining was significantly lower after baclofen compared to placebo; and (v) OTE was better in patients in the baclofen arm compared to the placebo arm.

The primary symptom outcome variable was the number of symptoms of regurgitation, assessed as events marked by the patients during the HRiM monitoring. The number of regurgitation symptoms was significantly lower after baclofen compared to placebo, which was in line with the previous open-label study performed in our hospital (27). There was no difference in the number of symptoms of belching during the measurement after baclofen treatment and placebo.

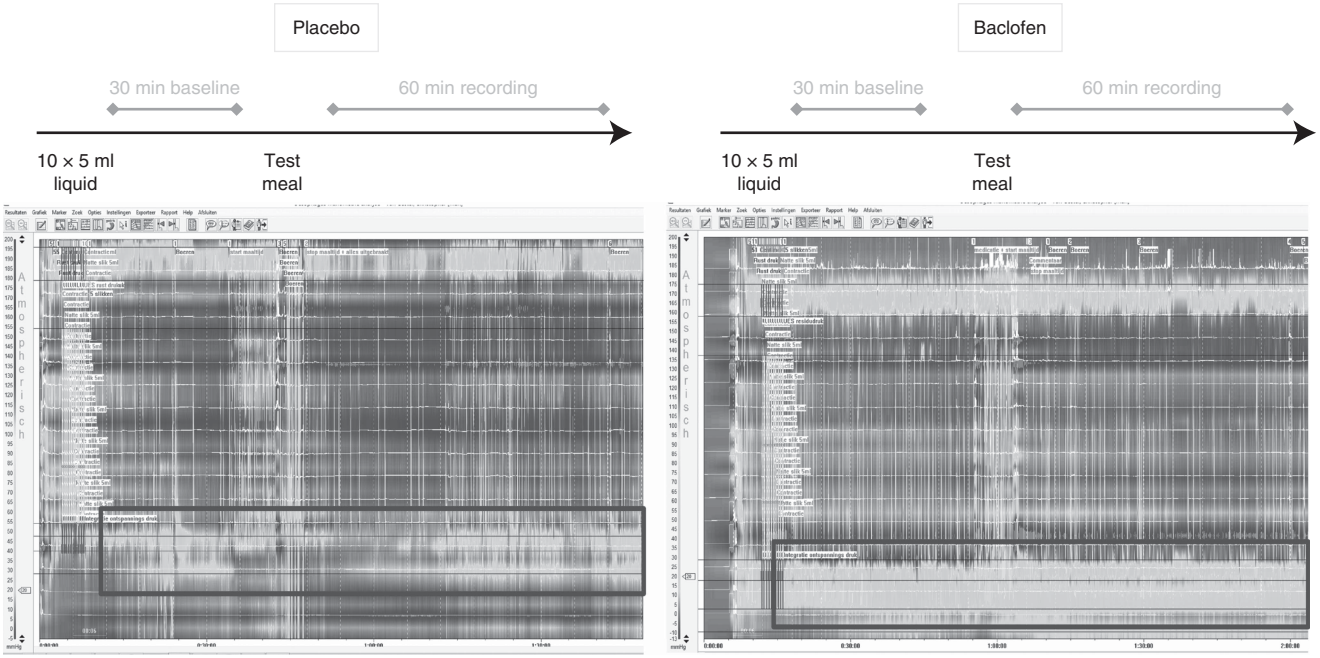

Figure 6. Postprandial lower esophageal sphincter (LES) pressure was significantly higher in the baclofen treatment arm compared to the placebo treatment arm, throughout the entire HRM monitoring.

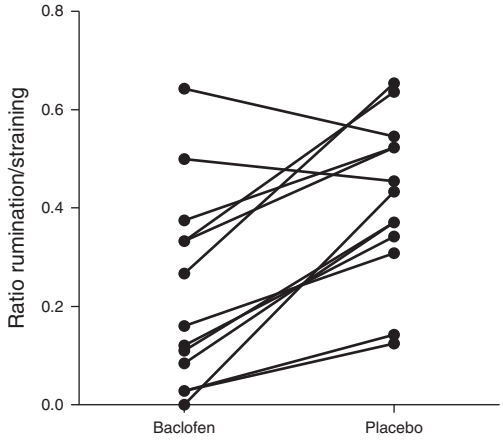

Figure 7. The ratio rumination/straining was significantly lower after baclofen treatment compared to placebo treatment (0.16 (0.06–0.35) vs. 0.43 (0.33–0.54), *P*=0.0012).

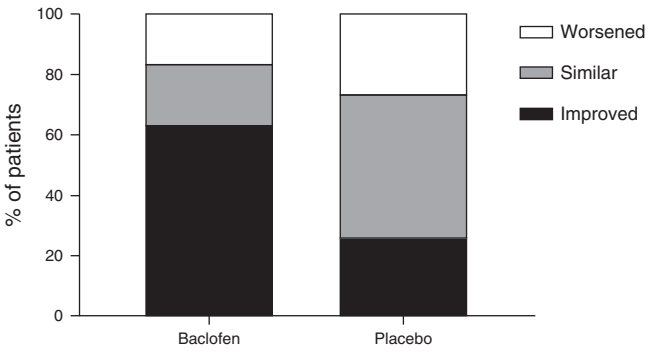

Figure 8. On baclofen treatment, 63% of patients improved while this was only the case in 26% of patients on placebo treatment (*P*<0.0001).

We also documented a decrease in rumination episodes. The total number of flow events, measured during the HRiM monitoring, was significantly lower after baclofen compared to placebo, and this was due to a significant reduction in the number of rumination episodes. Under normal conditions, the LES and the crural diaphragm constitute a high-pressure zone between the stomach and the esophagus, preventing gastric contents to enter the esophagus. In order for rumination to occur, patient's abdominal muscles contractions have to overcome this high-pressure zone. In this study, we found that the number of straining episodes was similar in the baclofen and placebo arm, but the ratio rumination/straining was significantly lower after baclofen treatment. Most likely, the rise in IGP after straining is less frequently sufficient to overcome the increased LES pressure generated by baclofen, which prevents rumination-induced reflux of gastric contents. This is supported by the borderline negative correlation between postprandial LES pressure and the number of rumination episodes. Second, the decrease in the number of TLESRs observed in the baclofen arm might also contribute to a decrease in the number of secondary rumination episodes.

It remains uncertain why patients with rumination syndrome strain. Both psychological factors as well as an attempt to alleviate dyspeptic symptoms with belching, leading to rumination, have been suggested (2,16,32). Thumshirm *et al.* (33) showed that patients with rumination syndrome were characterized by an

increased gastric sensitivity to mechanical distention in the proximal stomach and an impaired accommodation in a subset. These patients might be highly sensitive for a subtle gastric distention, and to relieve some dyspeptic symptoms, they may respond with voluntary straining. Under normal circumstances, an increased abdominal pressure leads to an increase in LES pressure and a tonic contraction of the crural diaphragm, as a mechanism to prevent gastric contents from flowing into the esophagus. In patients with rumination syndrome however, this protective effect might be lost (32). In addition, it has been demonstrated that baclofen can affect primary vagal afferents, reducing mechanosensitivity of the proximal stomach after gastric distention (34,35).

Baclofen treatment did not reduce the number of supra-gastric belching episodes. It seems that neither increasing postprandial LES pressure nor decreasing the number of postprandial TLESRs, as observed with baclofen, has a significant effect on supra-gastric belching. The latter is not really surprising, as it has been previously shown that there is no evidence of LES relaxation during supra-gastric belching (29).

In line with previous studies, we found less TLESRs and a small decrease in the total number of reflux episodes during baclofen treatment (24).

OTE was significantly better after baclofen treatment compared to placebo. This is in line with the reduction in rumination episodes and in symptoms of regurgitation during the HRiM measurements.

The current study has some limitations. First of all, the sample size was limited. In total, 22 patients were assessed for eligibility, of which 20 were analyzed. We recruited both patients with a clinical suspicion of rumination syndrome and/or supra-gastric belching, because both syndromes are associated with contraction of the abdominal muscles, and many patients display both types of events when studied with HRiM (1,5,36). This approach is close to clinical practice and, as expected based on previous data (5), this resulted in a heterogeneous group of patients including four who did not have any episode of rumination or supra-gastric belching during the measurements. As a large group of patients had both episodes of rumination and supra-gastric belching, subdividing patients into different groups was complicated. We therefore focused on analyzing events per patient, instead of differentiating them into little subgroups. Because of the small sample size, we cannot completely rule out a type II error. Second, it is not clear what the long-term outcome of baclofen treatment in these patients is. Therefore, further studies are warranted. Until then, baclofen is preferably used as a bridge to behavioral therapy, or as alternative option in those not responding to behavioral therapy.

In conclusion, we demonstrated that baclofen reduces rumination events and symptoms of regurgitation, and increases overall well-being in patients with rumination. This was partially due to a significant increase in postprandial LES pressure and a reduction in the number of postprandial TLESRs. Baclofen did not affect supra-gastric belching or symptoms of supra-gastric belching.

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CONFLICT OF INTEREST

Guarantor of the article: Jan Tack, MD, PhD.

Specific author contributions: A.P.: acquisition of data; analysis and interpretation of data; drafting of the manuscript; and approval of the final manuscript. C.B.: acquisition of data and approval of the final manuscript. B.V.H.: acquisition of data and approval of the final manuscript. N.R.: critical revision of the manuscript for important intellectual content and approval of the final manuscript. T.V.: critical revision of the manuscript for important intellectual content and approval of the final manuscript. J.T.: study concept and design; critical revision of the manuscript for important intellectual content; and approval of the final manuscript.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Rumination syndrome and supra-gastric belching are highly bothersome and impair quality of life.
- ✓ Availability and patient's consent to behavioral therapy is often problematic.
- ✓ Baclofen is able to reduce the number of transient lower esophageal sphincter relaxations (TLESRs) and increase the LES pressure.

WHAT IS NEW HERE?

- ✓ Baclofen reduces the number of regurgitation markers pushed by the patients and the number of rumination episodes.
- ✓ Patients strain equally after baclofen or placebo, but the ratio rumination/straining is lower after baclofen.
- ✓ Baclofen improved overall treatment evaluation in patients with rumination syndrome.

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