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ORIGINAL CONTRIBUTIONS

Does Bismuth Subgallate Affect Smell and Stool Character? A Randomized Double-Blinded Placebo-Controlled Trial of Bismuth Subgallate on Loop Duodenal Switch Patients with Complaints of Smelly Stools and Diarrhea

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Abstract

Background Loop duodenal switch (LDS) can result in fat and starch malabsorption. In a small percentage of patients, a relevant qualitative and quantitative change in stools happens usually characterized by steatorrhea-like diarrhea. Bismuth subgallate (BS) has been marketed as a way to eliminate the odor associated with flatulence and bowel movements. The objective of this study is to see the efficacy and effect of BS on the quality of life (QOL) in patients undergoing LDS.

Methods A prospective, randomized, double-blinded, placebo-controlled, crossover study was designed. Thirty-six patients who reported flatus and/or stool odor changes and have completed at least 6 months post-LDS were included. Patients participated in two treatment periods, each lasting for 1 week, separated by 1-week washout. Patients received 200 mg BS, 2 capsules per meal, or placebo for 1 week each. The Gastrointestinal Quality of Life Index (GIQLI) questionnaire was used to compare the QOL before the initiation of the therapy and after each treatment completion.

Results Of 36 patients, 5 patients were lost to follow-up and 2 were withdrawn from the study. And 29 patients were included for final analysis. GIQLI scores obtained with BS treatment completion were significantly higher both overall ($P = 0.007$) and in the digestive domain ($P < 0.001$) than those obtained before the treatment. GIQLI scores obtained from the other domains were also higher compared to the pre-treatment as well as placebo treatment but not statistically significant.

Conclusion In our double-blinded trial, treatment with BS after LDS statistically improves GIQLI score and steatorrhea-like symptoms.

Keywords Bismuth subgallate · Loop duodenal switch · Steatorrhea · Diarrhea · Quality of life · Malabsorption

Introduction

Biliopancreatic diversion with duodenal switch (BPD/DS) is the most efficacious therapy for morbid obesity [1, 2]. BPD/DS reduces the absorption of digestive juices as it bypasses 90% of the small intestine, resulting in malabsorption. This malabsorption can increase flatulence and stool character which negatively impacts the quality of life (QOL) [3].

Loop duodenal switch (LDS) or stomach intestinal pylorus sparing surgery (SIPS) is a modification of BPD/DS. This

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operation is technically simpler, results in equal or more weight loss [4–6] and reduces the chances of nutritional deficiencies. The main differences between the two surgeries are number of anastomosis (two for BPD/DS and one for LDS), the length of the common channel (150 cm for BPD/DS and 300 cm for LDS), and elimination of mesenteric defect in LDS. The preservation of 3 m of the intestine along with the ileocecal valve reduces the risk of diarrhea, malabsorption, and gastrointestinal side effects of short bowel syndrome. Hence, this technique results in lesser fat and starch malabsorption as compared to standard BPD/DS. However, as with any other malabsorptive surgery, this surgery also produces a relevant qualitative and quantitative change in stools and flatulence usually characterized by steatorrhea-like diarrhea or malodorous flatulence—a side effect that some patients report as disabling because it may give rise to relevant social and family-related conflicts apt to seriously impair QOL if it is not under control [7–9].

Bismuth subgallate (BS) (which has the brand name Devrom®, FDA-approved, over the counter medication) is recognized as safe and effective for use as an aid to reduce odor from flatulence. It is thought to work by acting on odor-producing bacteria in the intestine so that expelled gas and stool are not as malodorous. The main objective of this study is to determine the efficacy and effect of BS on the perceived QOL in patients undergoing LDS surgery. This is the first study of its kind in the literature that assesses the effect of BS after LDS surgery.

Methods

This trial is reported as per the Consolidated Standards of Reporting Trials (Consort) Statement [10]. All patients met the NIH criteria for bariatric surgery and had the preoperative educational process that included dietary and physical education. One surgeon at a single institution did all the surgeries. All patients provided informed consent before their surgical procedure. Standard technique for LDS was used and has been previously described [11]. All patients were seen for regular follow-up at the clinic.

A prospective, randomized, double-blinded, placebo-controlled, crossover study was done in the setting of private clinical practice in patients older than 18 years of age, who reported flatus and/or stool odor changes attributed to malabsorption and had completed at least 6 months post-LDS. Exclusion criteria included (1) female patients who were pregnant or were actively breast-feeding, (2) patients younger than 18 years of age, (3) patients who are considered to be part of a vulnerable population (e.g., prisoners or those with psychological concerns or those without sufficient mental capacity), (4) patients who had LDS as a revisional procedure, (5) patients who were unable or unwilling to comply with the study requirements or follow-up schedule, (6) patients with evidence of active gastrointestinal infection at inclusion, (7) patients with inadequate treatment compliance (forgotten doses, doses higher or lower than prescribed, noncompliance with dose intervals or rest periods, use of other antidiarrheal drugs, or inappropriate compliance with diet as prescribed on discharge), (8) patients taking antidiarrheal for any cause or other medications predisposing to diarrhea, (9) patients with hepatic and renal impairment, and (10) patients who had participated in an investigation drug or device research study within 30 days of enrollment.

The primary study objective was to assess the efficacy of BS on the disabling steatorrhea and to end-related odor in patients who have undergone LDS. The secondary study objective was to assess the effectiveness of the drug on the perceived QOL in these patients.

Target enrollment was 30 patients to account for 30% anticipated dropout rate, leaving 21 available for statistical analysis. This sample size provides 95% power to detect a 25% difference between the groups with a standard deviation of ±0.3 and alpha of 0.05.

This study was approved by Quoram Institutional Review Board (QR no. 31426-1). The purpose of the study and all the benefits and risks of the study were explained to each patient. Patients who agreed to study participation signed IRB-approved informed consent. Patients were given the opportunity to ask the principal investigator (PI) questions so that they were adequately informed about the study.

Patients participated in two treatment periods, each lasting for 1 week, separated by a 1-week washout. Patients randomly received either 200 mg BS, 2 capsules per meal (1200 mg per day), or placebo (a capsule that looks like BS but has no drug in it) for 1 week each. The medication was self-administered by the patients at home. The PI and the patients were blinded about the selection of the treatment patients were receiving. Only the study coordinators were aware of the treatment the patients were taking.

Patients were contacted by telephone or in-person visits at 1 and 3 weeks after the initiation of one of the study drugs.

The Gastrointestinal Quality of Life Index (GIQLI) questionnaire [9] was used to compare the QOL before the initiation of the therapy and after each treatment completion (BS and placebo). GIQLI determines QOL using both generic and specific items about upper and lower gastrointestinal tract symptoms. It contains the 36 questions. These questions are divided into 5 domains that evaluate digestive symptoms (19 questions), physical status (7 questions), emotional status (5 questions), social performance (4 questions), and treatment effects (1 question). Each of these 36 items has 5 possible qualitative answers (all of the time, most of the time, some of the time, a little of the time, and never) and a numeric value ranging from 0 to 4 points is assigned (0 to the least desirable option and 4 to the most desirable option). Additional 4 digestive questions were incorporated that focused on flatus, stool, and related odor into GIQLI. In total, there were 40 questions.

All of these 40 questions were summed up to obtain a maximum total score of 160 that reflects the best QOL and the minimum score of 0 that reflects the worst QOL [9]. Besides this, patients were also asked about the effectiveness of treatment in controlling their pre-existing condition in each follow-up visit. This helped to compare the efficacy of BS with placebo.

Statistical Methods

All data collected was analyzed using Sigma Plot statistical software. We used Student's *t* test for mean comparisons between two groups and one-way ANOVA for mean comparisons between three groups (pre-treatment, post-BS, and post-placebo). Data was collected in the form of mean ± standard deviation. For all analyses that involved inferential statistics, a *P* value < 0.05 was considered statistically significant.

Results

We initially estimated a sample size of 30. However, we were successful in enrolling 36 patients. Of 36 patients, 5 patients were lost to follow-up because of noncompliance with one of the treatment regimens. Of five patients, four did not comply to either of the treatment regimens (forget to take the dose or did not comply with dose intervals or rest period). All these four patients did not finish either treatment nor comply with the study follow-up schedule. The fifth patient did complete one treatment (BS) but did not complete another treatment regime nor followed-up. Additionally, two patients withdrew themselves from the study. As a result, 29 patients were included in the study analysis with a mean age of 49 years (55.1% female). Table 1 presents baseline demographics.

Table 2 shows the comparison of the GIQLI score before the initiation of the treatment and after the treatment with BS. GIQLI scores obtained at BS treatment completion were significantly higher overall ($P = 0.003$) and in the digestive domain ($P < 0.001$) than those obtained before the treatment. GIQLI scores obtained from the other specific domains were also higher compared to the pre-treatment but not statistically significant. The overall increase of score from 93.4 to 109.4 after the treatment with BS reflects an overall improvement in perceived QOL.

Table 3 shows the GIQLI score for the additional four digestive questions that focused on flatus, stool, and related odor which were incorporated into GIQLI. The symptoms of flatus, stool, and related odor improved significantly after BS treatment as compared to pre-treatment ($P < 0.001$).

Table 1 Baseline demographics for study population

	N (%)
Total sample size	36
Age (years)®	48.4 ± 12.8
Male	16 (44.4%)
Female	20 (55.5%)
Days since LDS®	353.3 ± 218
Total sample size included for analysis	29
Age (years)®	49.1 ± 12.6
Male	13 (44.8%)
Female	16 (55.1%)
Days since LDS®	361.7 ± 241.1

®Values are expressed as mean ± standard deviation

LDS loop duodenal switch surgery, *N* number of patients

Table 4 shows the comparison of the GIQLI score before the initiation of the treatment and after the treatment with placebo. The overall score was not statistically significant between the two. The significant placebo effect was only seen in the digestive domain. However, when both treatments were compared with the baseline, QOL after the treatment with BS was higher compared to the other two, and this difference was statistically significant ($P = 0.007$) (Table 5).

One patient complained of darkening of stool (3.4%), and one patient complained of tongue darkening (3.4%). No drug toxicity or hypersensitivity was reported. In order to assess the longevity of BS treatment on GI symptoms, a comparative analysis was performed between the post-placebo GIQLI scores in patients who initially started placebo (group 1, $n = 13$) vs who used placebo after crossover from BS (group 2, $n = 16$). The mean scores between group 1 and group 2 were 95.1 ± 20.8 and 105.1 ± 11.4, respectively. However, there

Table 2 GIQLI score between pre-treatment and post-bismuth subgallate group

	Pre-treatment (mean ± SD) ($n = 29$)	Post-bismuth subgallate (mean ± SD) ($n = 29$)	*P* value
Total	93.4 ± 20	109.4 ± 9.7	*0.003*
Digestive	48.6 ± 10.9	59.8 ± 12.3	*< 0.001*
Emotional	13.5 ± 3.9	15.2 ± 3.4	0.07
Physical	16.5 ± 5.6	18.2 ± 4.9	0.2
Social	11.5 ± 3.1	12.8 ± 3.5	0.1
Treatment effect	3 ± 1.1	3.2 ± 0.9	0.6

All values are expressed as mean ± standard deviation

Italicized entries signifies the statistical significant difference ($P < 0.001$ or $P < 0.05$)

n number of patients, *SD* standard deviation

Table 3 GIQLI score for four additional digestive symptoms related to flatus, stool, and related odor

		Pre-treatment (mean ± SD) ($n = 29$)	Post-bismuth subgallate (mean ± SD) ($n = 29$)	*P* value
Flatus and related odor	Bothered by smelly odor of the flatulence	0.8 ± 0.8	2 ± 1.1	*< 0.001*
	How smelly is the gas	0.4 ± 0.5	1.8 ± 1.3	*< 0.001*
Stool and related odor	Bothered by smelly odor of the stool	0.6 ± 0.7	1.8 ± 1.2	*< 0.001*
	How smelly is the stool	0.5 ± 0.6	1.9 ± 1.3	*< 0.001*

All values are expressed as mean ± standard deviation

Italicized entries signifies the statistical significant difference ($P < 0.001$ or $P < 0.05$)

n number of patients, *SD* standard deviation

was no statistical significant difference between the two groups' GIQLI scores ($P = 0.11$).

Discussion

We showed that BS definitively improved bowel habits and quality of life. This is the first study to report the use of BS to treat steatorrhea and related odor after LDS. The fact that the study is double-blinded makes it more robust. Our protocol had short study periods of 1 week, which detractors may say is not realistic. However, significant findings at 1 week should continue indefinitely because BS does not produce tachyphylaxis and has been shown to be effective long term in patients who have had ileostomy/colostomy. Many randomized blinded trials have small sample sizes. Our study exceeded target enrollment and demonstrated statistically significant improvement in QOL. There is the small possibility that our results are biased by Hawthorne effect—an effect that may bias the outcome when patients know they are being studied. This is difficult to exclude, and ultimately, additional studies are needed to replicate our findings.

In recent years, surgeons around the globe have tried various versions of DS with hope to reduce the complications seen with the surgery while keeping the resolution of comorbid conditions intact [12, 13]. However, all the modifications that aimed at reducing the common channel and total bowel length have led to diarrhea and malnutrition [14]. Drs. Sanchez and Torres performed an alternative version of DS using loop reconstruction with 200-cm efferent limb and named it single anastomosis duodeno-ileal bypass (SADI) [15]. However, patients experienced an increased amount of diarrhea with 200 cm, and therefore, the procedure was modified to increased bowel length to 250 cm [16]. SIPS surgery is a slight modification of SADI and is performed with an efferent limb of 300 cm. It appeared reasonable to extend the common channel to 300 cm with the aim of providing effective weight loss while minimizing gastrointestinal (GI) side effects of short bowel syndrome [11, 17, 18]. This length eliminated protein calorie malnutrition but not the diarrhea in our small subset of patients. BS effectively treats that subset of patients (approx. 4%).

Steatorrhea is not only attributed to the malabsorptive component of the surgery but can also result from patients eating too many carbohydrates after surgery. Many surgeons and patients mistakenly believe that steatorrhea is from high fat intake. This is almost never the case. Part of the treatment plan for patients with GI complaints is teaching them to eliminate most processed carbs from their diet. We recommend use of BS only after no improvement in symptoms after elimination of carbohydrates.

Table 4 GIQLI score between pre-treatment and post-placebo group

	Pre-treatment (mean ± SD) ($n = 29$)	Post-placebo (mean ± SD) ($n = 29$)	*P* value
Total	93.4 ± 20	100.6 ± 16.8	0.1
Digestive	48.6 ± 10.9	55.2 ± 9.4	*0.01*
Emotional	13.5 ± 3.9	12.8 ± 5	0.6
Physical	16.5 ± 5.6	16.7 ± 5.2	0.9
Social	11.5 ± 3.1	12.7 ± 2.2	0.1
Treatment effect	3 ± 1.1	2.9 ± 1.1	0.7

All values are expressed as mean ± standard deviation

Italicized entries signifies the statistical significant difference ($P < 0.001$ or $P < 0.05$)

n number of patients, *SD* standard deviation

Table 5 GIQLI score between three groups—pre-treament, post-bismuth subgallate, and post-placebo

	Pre-treatment (mean ± SD) ($n = 29$)	Post-bismuth subgallate (mean ± SD) ($n = 29$)	Post-placebo (mean ± SD) ($n = 29$)	*P* value
Total	93.4 ± 20	109.4 ± 9.7	100.6 ± 16.8	*0.007*
Digestive	48.6 ± 10.9	59.8 ± 12.3	55.2 ± 9.4	*< 0.001*
Emotional	13.5 ± 3.9	15.2 ± 3.4	12.8 ± 5	0.08
Physical	16.5 ± 5.6	18.2 ± 4.9	16.7 ± 5.2	0.3
Social	11.5 ± 3.1	12.8 ± 3.5	12.7 ± 2.2	0.2
Treatment effect	3 ± 1.1	3.2 ± 0.9	2.9 ± 1.1	0.7
Treatment satisfaction	–	1.3 ± 1.2	1 ± 1.2	0.3

All values are given as mean ± standard deviation

Italicized entries signifies the statistical significant difference ($P < 0.001$ or $P < 0.05$)

n number of patients, *SD* standard deviation

Bismuth salts have been used for more than 300 years, particularly in the treatment of dyspepsia. Bismuth salts have also been used to treat various other GI disorders such as bowel dysfunction, prevention of traveler's diarrhea, management of acute diarrhea, peptic ulcer disease, and more recently for *H. pylori* infection [19–22]. There is only one study done by Hernandez et al. that reports the use of BS to relieve steatorrhea in patients undergoing BPD/DS [23]; we are not aware of any studies that report the use of BS to treat steatorrhea and related odor after LDS.

Bismuth salts are available in several different compounds including bismuth subgallate (BS), colloidal bismuth subcitrate, bismuth subnitrate, and bismuth subsalicylate. All bismuth salts exert their activity in the upper GI tract via local actions from luminal bismuth within the stomach and duodenum. Once the bismuth salts are ingested orally, a small portion of bismuth is absorbed and taken up into gastric mucus, as well as binding to protein and is distributed throughout all the tissues, predominantly the kidneys and liver. Bismuth acts as the bactericidal agent by forming the complexes in the bacterial wall, where it inhibits enzymes such as urease, catalase, and lipase and acts as an antibacterial and antisecretory agent. It also has a cytoprotective effect on the gastric mucosa, protecting gastric mucus from peptic luminal degradation. In the colon, it reacts with hydrogen sulfide to produce bismuth sulfide, the black salt responsible for darkening of the stool [19, 22]. Besides darkening of the stool, darkening of the tongue is the other temporary, harmless side effect seen with this drug. In our study, we only had two patients that complained of darkening of the stool and darkening of the tongue, respectively. In contrast, the study that was published by Hernandez et al. [23] reported 57% of their patients complained of darkening of stool, though most of these patients ingested iron supplement along with the BS. Thus, it is imperative to inform the patient regarding this side effect, so they do not confuse it with hematochezia. Neurological toxicity is another complication that has been seen with high doses of bismuth salts. This toxicity was first seen in France in 1970s and then in Australia with subjects taking unregulated doses (1–3 teaspoons of BS per day) [24–26]. The symptoms seen were ataxia, severe confusion, epileptic seizures, progressive to myoclonic jerks, and even death [22]. However, complete remission was seen with discontinuation of the drug. Sampognaro et al. recently reported a case of encephalopathy in a woman taking BS for gastrointestinal disorder. However, the encephalopathy resulted due to the ingestion of large amount of BS brought through online website without the doctor's recommendation. The encephalopathy improved with the cessation of the drug [27]. The FDA has approved BS 200–400 mg taken by mouth up to four times daily (maximum 1600 mg/day) for flatulence and fecal odor, without restriction on duration of treatment [28]. No neurological toxicity has been reported with the recommended use of BS since its FDA approval. In our pilot study, patients were given only 1 week of BS treatment with the dose of 1200 mg/day. Our sample population (bariatric population) had smaller absorption surface (300 cm) compared to the general population, and yet the recommended dosage was well tolerated by all our patients. It is also important to note that none of our patients developed any neurological toxicity or any drug hypersensitivity.

Beside the studies by Hernandez et al. (rest period of 4 weeks) [23] and Gorbach et al. (rest period of 6–8 weeks) [22], no other studies talk about the absorption, clearance of BS after bariatric surgery to define a set period in which the treatment effect is completely lost. In our study, we used 1-week washout period before the crossover to other treatment option. The comparative analysis between the post-placebo GIQLI scores in patients who initially received placebo vs who used placebo after crossover from BS clearly showed that there might be an effect of BS even after 1 week of washout; this effect is very minimal. Thus, it is important for the physicians to inform the patients about this minimal effect and

advised them to keep more than 1 to 1.5 week of gap between the two treatment periods of BS in order to avoid the toxicity.

To assess the QOL, we used GIQLI questionnaire that was designed in the early 1990s by Eypasch et al. [9]. It is more specific than the SF-36 questionnaire, focusing on GI symptoms in both the upper and lower tracts [29]. It also includes domains of general health that are normally affected in patients suffering from gastrointestinal pathologies. It has also been used for QOL analysis in patients with morbid obesity, although it is nonspecific for them. Since QOL is a very subjective matter, the questions in GIQLI are designed in such a way that it leaves the patients with subjective interpretation. Thus, GIQLI questionnaire works well for patients with bariatric surgery. Digestive symptoms form the largest portion of the GIQLI questionnaire; thus, it serves our study population and study's goals perfectly well. It allows an assessment of how well a treatment works and how the patient looks at the gastric discomfort caused by the surgery. In our study, the digestive domain had the greatest difference in mean values assessed between pre (mean value of 48) and post-BS (mean value of 59), and this difference was statistically significant ($P < 0.001$). Besides the subjective improvement, to judge the objective improvement of the flatulence and stool related odor, four additional questions were incorporated. There was a significant improvement in both of these criteria's post-BS treatment ($P < 0.001$). Similar results were seen with the Hernandez et al. study where they found a significant difference between the total mean as well as means in the digestive domain [23]. Our results showed a significant improvement in QOL with the use of BS in total as well as digestive domain mean scores. The digestive domain was mainly comprised of the questions pertaining to general digestive symptoms such as abdominal pain, bloating, flatus, belching, bowel frequency as well as disease-specific questions such as regurgitation, dysphagia, bowel urgency, diarrhea, constipation, nausea, heartburn, and blood in the stool. These are important complaints after bariatric surgery and especially malabsorptive surgery like SIPS surgery. BS has proven to be effective in alleviating these symptoms [22, 23].

Emotional, social, and physical domain means scores increased post-BS treatment as well with placebo. There were no adverse side effects of any of the treatments, and none of the patients had to discontinue the therapy because of the side effects.

One of the main strengths of this study was its design. Randomized controlled trials are regarded as the gold standard design to determine causality. Additionally, the inclusion of placebo in the trials ideally produces unbiased estimate of the treatment effect. It has been shown that the subjects randomized to placebo-control conditions often report improved outcomes and can manifest physiological responses that mirror those of the subjects who received the bioactive compound [30]. This is termed placebo effect. In our study, we did see slight placebo effect evidenced by improved total mean score and mean scores in digestive and physical domain post-placebo treatment when compared with pre-treatment. Informing participants that they are receiving placebos when delivered within the context of clinical research encounter improves the outcomes in several patients [31, 32]. Reports have also shown that placebo response is not merely from believing one is ingesting a bioactive compound but also from environmental and psychosocial factors [33, 34] associated with the clinical research. These factors may lead to anxiety reduction, expectations, emotional support, and interaction with practitioner/research staff. All these factors in return improve the outcomes even when the participants are not receiving the actual treatment regardless of whether they are aware of this [30, 31, 35]. We observed improvement with a few of our patient. Patients knew that they were going to be assigned in two treatment periods, one with BS and another with placebo. However, they were blinded about which treatment they were receiving first. This might have resulted in slight improvement in their mean scores when compared to pre-treatment. Although differences in the mean scores were seen with the placebo compared to the pre-treatment (mean difference of ±7), the profound difference in mean scores after BS when compared to pre-treatment (mean difference of ±16) as well as placebo treatment (mean difference of ±9) cannot be disregarded.

Conclusion

Treatment with BS improves the disabling steatorrhea and end-related odor in patients undergoing LDS surgery. BS is also effective in improving QOL in these patients with no reported side effects. Further studies are needed to validate our results.

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Compliance with Ethical Standards

Conflicts of Interest Author 3, the corresponding author, reports personal fees and other from Medtronic, outside the submitted work. All the other authors have no conflict of interest to declare.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This study was approved by Quoram Institutional Review Board (QR no. 31426-1).

Informed Consent Informed consent was obtained from all individual participants included in the study.

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