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Sodium butyrate and short chain fatty acids in prevention of travellers' diarrhoea: A randomized prospective study

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Summary *Introduction:* Travellers' diarrhoea (TD) remains a considerable concern among international travellers. Known methods of prevention include dietary precautions, administration of vaccines and antibiotic agents.
Aim: To assess the efficacy of sodium butyrate (SB) and short-chain fatty acids (SCFA) in prevention of TD.
Material and methods: 67 adult patients planning to travel to subtropical countries were originally enrolled in the study. After eliminating 7 patients for not fulfilling the inclusion criteria, 60 patients were randomized into a study group receiving SB with SCFA and a placebo group. Patients were requested to complete previously distributed questionnaire daily. After

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elimination of 18 patients who did not return questionnaires, 42 patients completed the study (22 study, 20 placebo).
Results: In comparison to the control arm, the study arm noted significantly reduced occurrence of TD (4.5% vs. 40%, $p = 0.008$), was associated with a significant decrease in number of stools per day in travellers (1.9 vs. 4.2, $p = 0.04$), as well as a decrease in gastrointestinal symptoms including pain, bloating and nausea with fevers (0.7 vs. 1.4, $p = 0.01$).
We recorded a trend towards decrease in diarrhoea related utilization of medical care in subjects from the study arm. There were no adverse effects noted regarding the use of SB and SCFA.
Conclusions: Administration of SB with SCFA decreases occurrence of travellers' diarrhoea. It is safe and may constitute a new method of travellers' diarrhoea prevention.

Introduction

Traveller's diarrhoea occurs in tourists travelling from countries with higher hygiene standards to developing countries with lower hygiene standards [1]. Yearly, an estimated amount of 10 million tourists develop traveller's diarrhoea [2]. The most common source is consumption of contaminated food and water. Because the majority of occurrences is of bacterial origin, antimicrobial agents will show efficacy in treatment of existing TD [3].

Although variety of antibacterial agents have been successfully utilized in the treatment of TD, controversy remains regarding an efficient and safe TD prevention. Typically, elementary prevention incorporates dietary precautions, appropriate hand hygiene and avoidance of certain food types exposing a traveller to risk. Foods considered generally safe include hot meals, bottled carbonated beverages, peeled fruits, syrups, jams and honey as well as dry items such as bread, whereas fruits and vegetables with intact skins such as tomatoes or berries, sauces on tabletop, moist foods served at room temperature, food served buffet-style at room temperature and tap water in hotels — have previously been considered unsafe [4].

Pharmacological approaches to prevention of TD revealed that application of bismuth subsalicilate, lactobaccilus, fluoroquinolones and rifaximin can be effective at various rates [5—9]. Although antibiotic prevention of TD is currently not recommended as a standard [2] by CDC, certain selected groups of individuals might benefit from this approach. This group includes travellers with underlying medical illness, such as CHF and malignancy, a condition that might be worsened by a bout of diarrhoea (diabetes mellitus) travellers treated proton pump inhibitors or suffering from chronic GI disorders such as irritable bowel syndrome, as well as travellers whose occupation would not allow occurrence of an acute illness such as politicians, lecturers, professional athletes or artists [4].

In the current study, we are investigating a non-antibiotic agent in the reduction of diarrhoea episodes in travellers. Specifically, we utilize a placebo controlled randomized study to investigate SB, which has previously been associated with protective properties for colonocytes, in a novel application as a potential TD prophylactic agent. Sodium butyrate has proved to provide symptomatic relief in patients suffering from various range of colonic disease, such as IBS, inflammatory bowel disease, diarrhoea, malabsorption and suggestive of preventive role in cancerogenesis of colonocytes [10—12]. While there is no certainty as to what renders sodium butyrate (SB) to be so beneficial in such a wide range of colonic disease, it has been established that SB can act as a regulator of intestinal environment. It is a preferred energy substrate for colonocytes, can moderate intestinal permeability, reduce oxidative stress and reinforce colonic defense barrier leading to decreased inflammation of mucosa, increased cell regeneration rate and promote healing [13—15].

Material and methods

Study group

Sixty seven (67) adult patients planning a trip to tropical countries were initially enrolled in the study. The countries of destination were Egypt, Tanzania, Tunisia and Morocco. Upon initial office visit, the subjects were informed about the purpose of the study and accordance with the local Bioethical Committee and examined medically. Upon the first visit 7 patients were excluded from the study for one of the following: active disease of the gastrointestinal tract, bacterial infection treated with an antibiotic within 14 days before the study, active immunosuppressive treatment, chemotherapy, radiotherapy within the last 6 months, cachexia, active generalized disease, inability to comprehend the nature of study and treatment regimen. Sixty (60) remaining adult patients signed the formal consent for the study, agreed to the daily oral treatment regimen and collected the questionnaire thus meeting the formal criteria of inclusion in the study. Patients were then randomized into a study arm and a placebo arm. Studied patients were provided with health insurance for the planned trip. Patients were instructed to record any potential side effects of administered therapy, and discontinue treatment when side effects were suspected. There were no side effects noticed by the patients during treatment. Out of the randomized patients 18 did not return the study questionnaire (8 study, 10 placebo). A total of 42 patients who returned the trip questionnaires had successfully completed the study (22 study, 20 placebo). The two study

arms were found to be similar in age and gender. A flowchart regarding the course of randomized study is presented in Fig. 1.

Administered substance and regimen

The substances administered to study group was a combination of SB (250 mg), fumaric acid (100 mg), citric acid (60 mg), sorbic acid (50 mg) and malic acid (40 mg) enclosed in a 500 mg trigliceride microcapsule. The daily regimen included oral administration of two capsules three times a day. The control group was administered identical regimen of placebo in identical microcapsule as the study group. The administration of oral regimen was initiated 3 days prior to the trip and continued throughout the trip.

Outcomes assessment

In order to assess the results of the study the participants of both arms were obligated to complete records daily in a previously distributed questionnaire. The details regarding questionnaire records were explained to the participants upon the first visit before the trip. Patients were required to return the completed questionnaires by mail. The questionnaire recorded the observed occurrence of clinical symptoms associated with diarrhoea: amount of stools per day, stool consistency, presence of blood or mucous in stool, abdominal pain, bloating, nausea, vomiting, elevated body temperature, need of medical assistance or treatment during the trip. Based on these findings we sought the diagnosis of TD, which was defined as three or more unformed stools in 24 h passed by a traveller, commonly accompanied by abdominal cramps, nausea, and bloating as defined by Hill [16].

Statistical analysis

Estimated standard deviation (SD) of the study was 1.2 with a confidence interval of 0.05 (two-tailed). With the control group of 20 subjects and the power of the test of 0.95, the number of cases in both arms was estimated for 20—30 participants. The amount of subjects completing the study fulfilled this criteria.

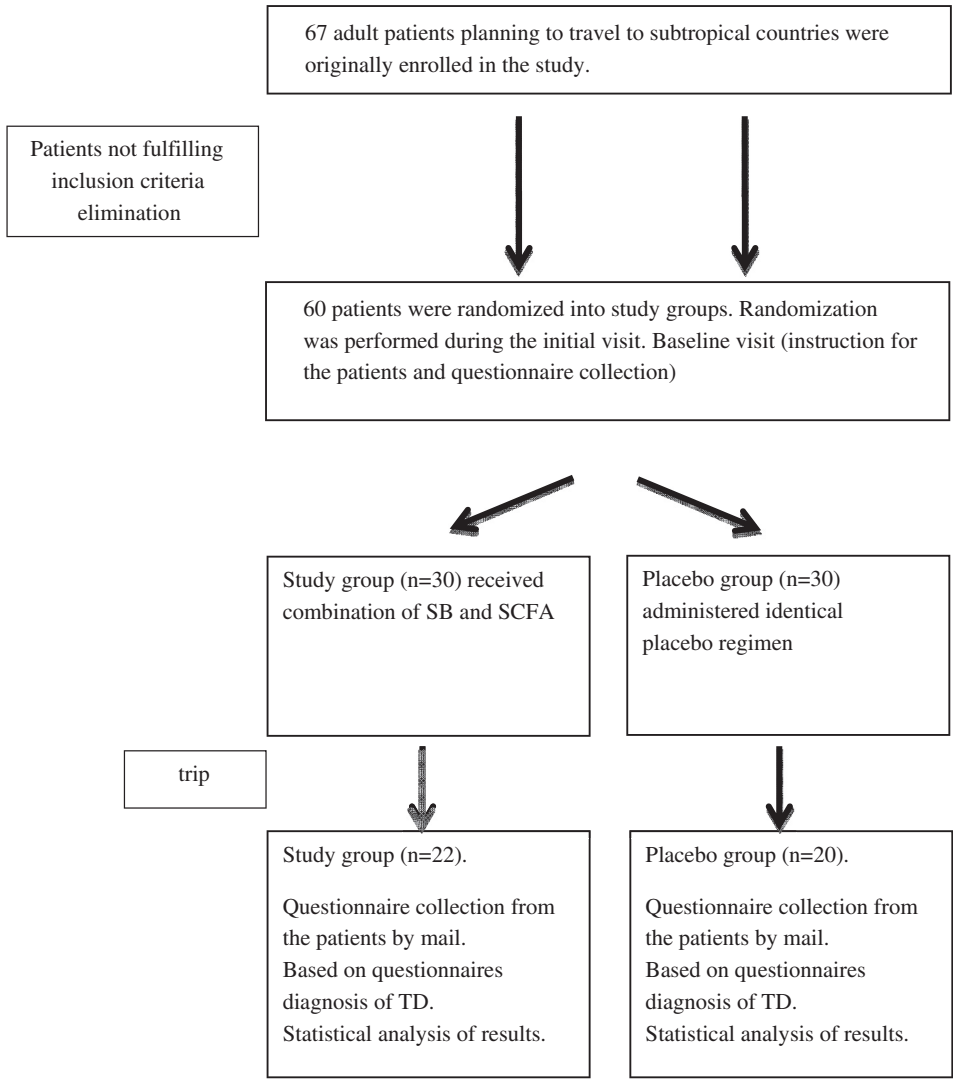

Figure 1 Clinical course of sodium butyrate and short chain fatty acids in prevention of travellers' diarrhea.

As the obtained results were of equal distribution, the results were analysed with a non-parametric test (Kruskal–Wallis test) or a Spearman correlation. The statistical significance was reached with a $p < 0.05$. The size of samples and the power of the test were analysed with GraphPad StatMate 2.0 software (Graphpad, USA). Statistical analysis was performed with Statistica v.9.1 software (Statsoft Inc., USA).

Results

Out of 60 patients enrolled in the study, 42 patients (22 study, 20 placebo) completed the study. Patient in both groups were noted to be of similar age and gender distribution. The comparison of two study arms is presented in Table 1. In comparison to the placebo group, the studied group recorded an average amount of stools per day of 1.9 (4.2 for placebo, $p = 0.04$), the amount of clinical symptoms per day of 0.7 (1.4 for placebo, $p = 0.01$), the diagnosed with TD was recorded in 1 patient (8 for placebo, $p = 0.007$), amount of people recorded to have utilized medical assistance for abdominal symptoms was 0 (2 for placebo, $p = 0.227$). Fig. 2 displays the percentage of occurrence of TD in the study arm and in the control arm. No side effects regarding of medication administered in the study and placebo arms were reported.

Discussion

TD represents a considerable burden on international travellers. In an effort to prevent the disease, several measurements have previously been proposed [17]. With the exception of prophylactic measures and selective nutrition, pharmacological approaches are associated with considerable side effects and are not generally recommended. In the current study we sought potential in prevention of diarrhoea in travellers with the utilization of non-antibiotic agent. We examined the frequency of symptoms and rates of medically diagnosed TD in a randomized placebo controlled study. To the best of our knowledge this represents the first study of the role of SB in reduction of diarrhoea in travellers.

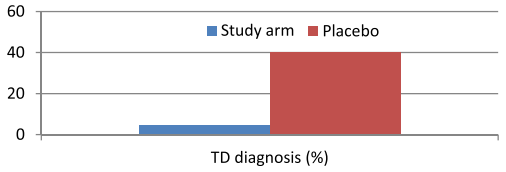

Figure 2 Frequency of TD diagnosis (%). Study arm ($n = 22$) vs. placebo arm ($n = 20$), $p = 0.0077$.

Our results prove several important points. First, efficacy of SB administered for reduction of traveller's diarrhoea episodes has been established. In comparison to the placebo arm there was smaller number episodes of stools per day in the study group (1.9 vs. 4.2, $p = 0.004$), smaller amounts of clinical symptoms reported (0.7 vs. 1.4, $p = 0.012$) with odds ratio of 0.09. With regards to established diagnosis of TD, patients in the study group were less frequently diagnosed with TD than the placebo group (4.5 vs. 40%, $p = 0.007$) with odds ratio of 0.07. In addition, although without reaching statistical significance, there were no occurrences of utilization of pharmacotherapy or medical assistance in the study arm, in comparison to two occurrences in the placebo group. Other previously studied pharmacotherapeutical agents in TD prevention models revealed efficacy of 65% for bismuth subsalicylate administered twice a day, 40% for *Lactobacillus* GG administered daily, 80% for fluoroquinolones administred daily and approximately 75% efficacy for rifaximin administred twice a day [5–8].

Second, the agent we studied was not associated with typical side-effects previously ascribed to other TD preventive agent groups. Antibiotics, although very efficient are not recommended in TD prevention because of systemic side effects and risk of development bacterial resistance [18,19]. Rifaximin, a virtually non-absorbable antibiotic has shown efficiency, but its potential of developing resistance has been recently brought into question when used for prolonged time [20,21]. Widespread use of quinolone can encourage multiclass drug resistance, which reduces prophylaxis and treatment efficacy and can cause induction of quinolone resistant gram negative organisms which can lead to complications such as subsequent infections [22].

Table 1 Cases vs. placebo.

	Study group	Placebo	OR	95%CI	*p*-Value
No of patients enrolled in the study	30	30			
No of patients completed the study	22	20			
Mean amount of stool/day	1.9	4.2	0.11	0.01–1.03	0.0408
Mean amount of abdominal symptoms noted (abdominal pain, bloating, nausea, vomiting, elevated body temperature)	0.7	1.4	0.09	0.01–0.86	0.0122
TD diagnosis (%)	1 (4.5%)	8 (40%)	0.07	0.01–0.64	0.0077
Amount of subjects utilizing medical assistance/pharmacotherapy for TD	0	2			0.2207 (small amount of occurrences)

Although not associated with bacterial resistance typical for antibiotic agents, bismuth administration has previously been associated with encephalopathy and kidney failure [23—26]. Lactobacillus GG administration has been relatively safer but is associated with abdominal cramping [6]. The major drawback of recently studied immunoprophylactic agents and vaccines is the narrower scope of antimicrobials targeted, cost and TD protection rates of approximately 40% [27,28].

Although investigation of the safety profile of SB has exceeded the scope of current study, we did not report any adverse effects associated with administration of SB. Previous studies were uniformly recording no side effects associated with SB and SCFA administration [29,30]. This could be attributed to the natural presence of butyrate in colonic environment, with butyrate being considered the preferred intestinal cell source of energy [31]. Various previous studies associated butyrate with protective properties regarding intestinal mucosa, symptom reduction in various colonic conditions, such as IBS and possible role in prevention of cancerogenesis in colonocytes [10,14,15,32,33]. Nonetheless a dedicated, large sample study focussing on safety profile is lacking.

From a practical perspective use of SB may be an efficient method of reducing episodes associated with diarrhoea in travellers. Lack of side effects typically associated with previously studied agents may revive the idea of wide-spread TD prophylaxis. It seems that in comparison to active treatment of TD, a prophylactic approach could be associated with a significant global cost reduction, as cost of therapy and eventual hospitalization should be estimated along potential revenue losses associated with work absence of patients with TD. Further studies need to be conducted to analyse the details of potential financial benefits. We project that SB has the potential to be a novel agent in prophylaxis against TD, combining efficiency and no detriment to patient safety.

Although we were able to prove efficacy of SB in reduction of rates of TD, our placebo controlled randomized study is not without limitations. Sample size and lack of multiinstitutional input are major weakness of the study. Additionally, our study was conducted in a fairly uniform ethnic environment and might fail to be reproductible in other populations. Lastly, self-reporting of symptoms on a questionnaire might be a source of recall bias. Further investigation in larger cohorts and heterogenous groups may be warranted.

Conclusions

Our placebo controlled randomized study reveals that administration of SB and SCFA is associated with significant decrease in number of stools per day in travellers, a decrease in gastrointestinal symptoms including pain, bloating, nausea and vomiting with fevers and a decrease in occurrence of diagnosed occurrences of travellers' diarrhoea. There were with no adverse effects associated with therapy. Prophylactic utilization of SB in combination with SCFA in travellers may constitute a new method of travellers' diarrhoea prevention.

Conflict of interest

Financial support: This study was funded by Mifarmex. The study sponsor had no role in the study design; collection, analysis, or interpretation of data; or in the writing of the report.

Potential competing interests: None.

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