The effect of peppermint essential oil (Supermint Drop) on gastric residual volume among Intensive care unit patients with mechanical ventilation receiving tube (gavage) Feedings: A randomized clinical trial

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Abstract

Background

Delayed gastric emptying is a prevalent problem in intensive care unit (ICU) patients on mechanical ventilation receiving enteral nutrition. This study was aimed to assess the effect of peppermint essential oil (Supermint drops) on gastric emptying in these patients.

Methods

In this clinical trial study, 60 mechanically ventilated ICU patients were randomly assigned to Supermint and control groups. From the first day of their feeding, patients in the intervention and control groups received 20 drops of the Supermint and placebo solutions, mixed with 40 ml of water, three times daily for four days. The gastric residual volume (GRV) was measured at the baseline and during four days of intervention. Data were analyzed using a generalized estimation equation (GEE) regression model.

Results

The mean age of patients was 71.5 (SD = 14.2), and 65.5% were hospitalized for Coronavirus disease 2019 (COVID-19). The GEE regression model results showed that SuperMint significantly reduces the mean of GRV when compared to placebo ($p < 0.001$); for each unit increase in time, the average of GRV in the Supermint group was 1.16 (95% confidence interval: 0.75, 1.57) lower than the placebo group. GRV showed a non-significant increase of 0.07 for each unit increase in time in the control group, whereas it decreased significantly by 1.09 in the Supermint group.

Conclusion

The current study's findings were encouraging and indicated that peppermint essential oil could be used in GVR reduction in ICU patients on mechanical ventilation. Further study are needed to confirm this finding, especially among COVID-19 patients.

Introduction

One of the problems faced by most frequently patients admitted to the intensive care unit (ICU) is the inability to maintain their own nutritional needs because of being unable to orally feed due to an acute condition and a lack of consciousness. Hence, nutritional support is one of the main components of care in this ward and plays a vital role in the patients' recovery process (1–3). Administration of feed and fluid for people who cannot get food by mouth or swallow safely and need nutritional supplements is commonly done via a tube going into the gastrointestinal tract, known as enteral feeding, gavage, or tube feeding (4, 5).

One of the common problems in mechanically ventilated intensive care patients is gastric delay emptying (6), with the main feature of increasing the remaining volume of the stomach and gastric reflux into the esophagus. Gastric delay emptying can lead to vomiting, lung aspiration, and ventilator-induced pneumonia and is associated with the increasing severity of the disease and mortality in these patients (7, 8). The remaining food amount from the previous feeding in the stomach at the beginning of the next feeding, so-called gastric residual volume (GRV) (9), is a determinant parameter for gastric emptying and feeding tolerance. GRV is measured before each feeding time and affects the volume and timing of the next gavage (9, 10). The administration of prokinetic agents such as Metoclopramide, Domperidone, metoclopramide nasal spray, and Cisapride is commonly the first treatment to improve gastric emptying and reduce GRV (11–14). However, prokinetic drugs have several side effects that limit their use. The most important of these side effects include cardiac, hemodynamic, neurological, and gastrointestinal complications (15, 16). In addition, there is no certainty that prokinetic agents could reduce the ICU or hospital length of stay, the risks of reported adverse events, or all-cause mortality in patients admitted to ICU (13). It is, therefore, necessary to provide alternative treatments that are more effective, less invasive, and accompanied by fewer side effects.

Herbal medicine is getting popularized and has experienced exponential growth over the last few decades due to its natural origin and fewer side effects in developing and developed countries (17). Mentha Piperita is one of the medicinal herbs with a long history of use in digestive disorders. In vitro and clinical research supports some of its traditional use for the whole plant and one of the main active components, menthol (18).

The efficacy of peppermint in delaying gastric emptying has been evaluated in rare clinical studies (19–21). Moreover, these studies are small and may not have sufficient statistical power to draw a firm conclusion. So, due to poor pharmacological insight into this issue, this study was performed to assess the effect of peppermint essential oil (Supermint drop) on gastric emptying in ICU patients receiving mechanical ventilation.

Material And Methods

Study Design

This study was a randomized, triple-blinded, parallel-group, placebo-controlled trial conducted on the patients admitted to ICU at Allameh Bohlool Gonabadi Hospital, Gonabad, Iran, from May 2020 to January 2021. The study was approved by the Ethics Committee of Gonabad University of Medical Sciences (Ethical code No: IR.GMU.REC.1398.187, Date: 25/02/2020) and registered at the Iranian Registry of Clinical Trials (IRCT code NO: IRCT20191223045868N1. Date: 28/03/2020).

Participants and setting

The patients admitted to the intensive care unit of Bohlool Hospital were assessed for eligibility. The inclusion criteria were as follows: 1) Age of 18 years or over; 2) Conscious consent of the patient or legal

guardian; 3) Requiring mechanical ventilation and receiving gastrointestinal nutrition; 4) Passing more than 24 hours since the admission to ICU; 5) Having no gallstones; 6) No history of active gastrointestinal bleeding, malignancies, gastrointestinal ulcers, diabetes, and pancreatitis; 7) No pregnancy and breastfeeding; 8) No history of hypothyroidism based on the statement of accompanying person of the patient; 9) No use oral nutrition or use of duodenal catheters. The exclusion criteria were as follows: 1) Start of oral feeding; 2) Mechanical ventilation detachment; 3) Drug allergy and intolerance to gavage during the study; 4) Prescribing and taking medications or other therapeutic interventions, according to the physician's opinion, during the study, which may affect the results of the study; 5) Refusal to proceed with the study; 6) Death of the patient; 7) Transferring patient to other wards or operating rooms for any surgery.

Study Interventions

Patients in the intervention group received 20 drops of the SuperMint solution along with 40 ml of water three times daily for four days from the first day of their feeding. Supermint oral drops contain Mentha spicata, which is standardized based on the presence of 11–15 mg of the Karun per ml of product. Its active ingredients are Karun and methyl acetate. Patients in the control group received 20 drops of water (placebo) along with 40 ml of water three times daily at specific times for four days from the first day of their feeding. The frequencies of gavage and its volume were determined for each patient by the physician. Assessing the Patients' tolerance was also performed by nurses. The containers of Supermint and water were similar-shaped, coded as A and B by the chief researcher, providing to the interveners. Interventions and measurements were performed independently by two trained individuals. Therefore, the evaluator was not aware of the type of intervention.

Study Outcome

The study outcome was GRV volume over time in the Supermint group compared to the placebo group. The GRVs were measured before each gavage during the study (three times daily at specific times for four days) with a 60-milliliter syringe by aspirating gastric contents. All patients were gavaged and lavaged in a 35-degree position. Gavage was performed intermittently and under the influence of gravity.

Randomization

Samples were selected based on the convenience sampling strategy. After controlling the inclusion criteria, the patients were assigned to the intervention and control groups based on a 1:1 allocation ratio and the permuted block randomization with block sizes of 4. The random numbers were generated using the online randomization through the website of Sealedenvelope (https://www.sealedenvelope.com), concealed in sequentially numbered, sealed, opaque envelopes. The statistician provided the random allocation sequence before starting the study. The research coordinators enrolled the patients. Allocation occurred after controlling for the eligibility criteria for the patients by the study investigators, who were different from the intervener and evaluator, based on the pre-determined random allocation sequence concealed in envelopes.

Sample size

The sample size by using the formula for comparison of mean values in two groups, taking into account a test power of 90%, a confidence interval of 95%, and an effect size of 0.91 based on the study by Zarghi et al. (22), was determined 26 patients in each group. We considered a dropout loss of 15%, which resulted in 30 patients in each group.

Statistical analysis

A per-protocol analysis was used to analyze the data of all participants who completed the study. Number (percentage) and mean (standard deviation (SD)) were employed to express the qualitative and quantitative variables, respectively. The Kolmogorov-Smirnov test was used to assess the normality distribution of quantitative variables. Patients' baseline characteristics were compared between the placebo and Supermint groups using the Chi-square test (or exact tests if the Cochran assumptions were violated) and the two independent samples T-test for qualitative and quantitative variables, respectively.

A generalized estimating equation (GEE) regression model with a linear link function and an exchangeable working correlation matrix (23) was used to assess the impact of the interventions over time. GEE regression models are employed to consider the correlation structure of repeated data in longitudinal studies a very flexible approach (24, 25). The model included three main effects (treatments, time, and BMI) and an interaction between time and treatments. BMI was statistically different between the two groups at the baseline. So, its main effect was incorporated into the model as a potential confounder. A two-tailed p-value less than 0.05 was considered significant. All data analyses were performed using SPSS 16.0. Graphical representation of GVR values over time was also presented using a line chart in Excel 2013.

Results

Of the 65 enrolled patients, five patients were excluded before randomization due to not meeting inclusion criteria or declining to participate. Sixty patients were randomized to the Supermint and placebo groups. Finally, 28 and 27 patients completed the study in Supermint and placebo groups, respectively, and their data were analyzed (Fig. 1).

The baseline characteristics of patients in the two groups are described in Table 1. The mean age of the patients in the Supermint and placebo groups were 68.7 (SD = 15.8), ranging from 41 to 99 years, and 74.5 (SD = 11.9), between 43 to 93 years old, respectively. Of the patients, 53.6% and 63.0% were female in Supermint and placebo groups, respectively. Among them, 67.9% in the Supermint group and 63.0% in the placebo group were hospitalized in the ICU due to Coronavirus disease 2019 (COVID-19). There were no statistical differences between the two groups in terms of the baseline characteristics except for BMI.

Table 1
Baseline characteristics of randomized patients in placebo and SuperMint groups

Variables	SuperMint group (n = 28)	Placebo group (n = 27)	P-value
Age, Mean (SD)	68.7 (15.8)	74.5 (11.9)	0.134†
Sex, n (%)			0.480‡
Male	13 (46.4)	10 (37.0)	
Female	15 (53.6)	17 (63.0)	
BMI, Mean (SD)	27.8 (3.8)	24.8 (4.6)	**0.010**†
Disease diagnosis, n (%)			0.241‡
Pneumonia	7 (25.0)	3 (11.1)	
COVID-19	19 (67.9)	17 (63.0)	
Benign prostatic hyperplasia	0 (0.0)	2 (7.4)	
cerebrovascular accident	2 (7.1)	4 (14.8)	
Brain tumors	0 (0.0)	1 (3.7)	
Comorbidities, n (%)			0.289‡
Hypertension	14 (46.7)	15 (50.0)	
Diabetes Mellitus	11 (36.7)	10 (33.3)	
Cancer	3 (10.0)	0 (0.0)	
Chronic kidney disease	1 (3.6)	0 (0.0)	
Seizure	2 (7.1)	0 (0.0)	
Chronic obstructive pulmonary disease	1 (3.6)	0 (0.0)	
Lung disease	1 (3.3)	0 (0.0)	
Deep vein thrombosis	1 (3.3)	0 (0.0)	
Nothing	6 (21.4)	9 (33.3)	
Surgery during hospitalization, n (%)			0.322‡
Yes	13 (46.4)	9 (33.3)	
no	15 (53.6)	18 (66.7)	
Drug abuse, n (%)			0.669‡

Notes: SD, Standard Deviation; * before the study onset; ‡ Chi-square or exact tests; † Two independent samples T-test

Variables	SuperMint group (n = 28)	Placebo group (n = 27)	P-value
Yes	4 (14.3)	2 (7.4)	
no	24 (85.7)	25 (92.6)	
Stimulant drugs use, n (%)			0.111‡
Yes	4 (14.3)	0 (0.0)	
no	24 (85.7)	27 (100.0)	
Sedatives use, n (%)			0.110‡
Yes	5 (17.9)	10 (37.0)	
no	23 (82.1)	17 (63.0)	
Tobacco use, n (%)			0.491‡
Yes	2 (7.1)	0 (0.0)	
no	26 (92.9)	27 (100.0)	
Glasgow Coma Scale, Mean (SD)	7.9 (1.4)	7.4 (1.4)	0.235†
Duration of hospitalization*, Mean (SD)	10.3 (8.7)	9.2 (7.8)	0.612†
Duration of the gavage's onset*, Mean (SD)	5.4 (4.5)	5.1 (4.5)	0.815†
Duration of ventilator connection*, Mean (SD)	5.0 (3.5)	5.1 (3.9)	0.855†
The volume of gavage, Mean (SD)	167.9 (68.3)	196.3 (69.2)	0.131†
Notes: SD, Standard Deviation; * before the study onset; ‡ Chi-square or exact tests; † Two independent samples T-test			

GRV mean values of the randomized patients in the two groups are shown in Table 2. The Baseline of GRV values are similar in the two groups, but over time and after the intervention, the values of GRV in the Supermint group are lower than in the placebo group. Also, in the control group, the mean of GRV values was lowest in the early morning hours and was raised during the day, and this trend was repeated cyclically in the first to fourth days. A similar trend was observed in the Supermint group, except that the increase of the mean of GRV values during the day was very slight, particularly after the third day(Fig. 2).

Table 2
Mean of GVR in ICU patients in control and SuperMint group

Time point		Control group Mean (SD)	SuperMint group Mean (SD)
Baseline		29.41 (10.87)	27.39 (5.74)
First day	6 A.M.	25.59 (15.86)	14.85 (8.71)
	3 P.M.	31.19 (18.81)	17.89 (10.41)
	9 P.M.	31.44 (20.19)	18.28 (14.01)
Second day	6 A.M.	25.07 (22.45)	11.43 (10.87)
	3 P.M.	31.81 (19.15)	16.11 (9.86)
	9 P.M.	31.70 (18.27)	11.79 (10.47)
Third day	6 A.M.	26.22 (16.67)	9.64 (9.75)
	3 P.M.	30.93 (16.10)	12.64 (10.30)
	9 P.M.	28.93 (18.58)	11.79 (11.09)
Fourth day	6 A.M.	23.48 (13.92)	10.18 (10.84)
	3 P.M.	30.19 (17.05)	11.86 (10.84)
	9 P.M.	32.59 (19.97)	10.93 (10.91)

The results of the GEE regression model showed that there was no significant difference between the two groups at the baseline ($p = 0.181$). The interaction between time points and the treatment group was significant ($p < 0.001$); indicating that Supermint significantly reduces the mean of GRV when compared to placebo, so that at each time point of the intervention, the average of GRV in the Supermint group was 1.16 (95% confidence interval: 0.75, 1.57) lower than the placebo group. GRV showed a non-significant increase of 0.07 for each unit increase in time in the control group, whereas it decreased significantly by 1.09 in the Supermint group (Table 3).

Table 3
The results of the GEE regression model to assess the impact of the interventions (SuperMint versus placebo) on GVR over time in ICU patients

Parameter	B (95% CI)	S.E	χ^2	*p*-value
Treatment (SuperMint versus placebo)	-4.23 (-10.44, 1.97)	3.17	1.79	0.181
Time	0.07 (-0.24, 0.38)	0.16	0.18	0.670
BMI	-1.54 (-2.11, -0.96)	0.29	27.28	**< 0.001**
Time X Tretment	-1.16 (-1.57, -0.75)	0.21	30.39	**< 0.001**
Notes: B, Regression coefficient; CI, Confidence interval; S.E, Standard error; BMI, Body mass index				

Discussion

The present study was aimed to evaluate the effect of peppermint essential oil on gastric emptying in ICU patients who are on mechanical ventilation.

In the present study, we observed that the patients who had received peppermint essential oil (Supermint drops) had statistically significantly more acceleration of gastric emptying versus the control group of patients for four days of intervention. The effects of peppermint oil on gastric function and gastric emptying have been previously studied; however, the results have been different. In one study on12 healthy adult volunteers, Goerg and Spilker (2003) (20) reported that 90 mg peppermint oil (in 0.10 mL pill) did not affect gastric emptying time (as measured by ultrasonography and H2 breath tests) when compared to a placebo. Dalvi et al. (19) demonstrated that oral administration of the essential oil (0.2 mL in 25 mL water) accelerated gastric emptying vs. baseline in both adults groups, including healthy and patients with dyspepsia. Hiki et al. (26) in a double-blinded randomized trial on 100 patients, showed that intrathecal administration of peppermint oil solution during upper endoscopy acts as a spasmodic agent and has superior efficacy and fewer side effects than hyoscine-N-butyl bromide. Inamori et al. (21) using 13C-acetic acid breath testing with a liquid test meal, found that ingestion of peppermint oil as a solution resulted in accelerated emptying in the early phase but had no effect on the overall gastric emptying rate in healthy adults. These contradictory results may be related to significant trial heterogeneity, such as the study methods and populations, sample size, dose, and formulation of peppermint oil.

Most of the study patients were infected with COVID-19 due to conducting the present study during the COVID-19 pandemic. The findings of this study suggested that Supermint might help reduce GRV in these patients. Due to frequent, severe feeding intolerance, supplying enteral nutrition for COVID-19 patients has been excessively challenging (27–30). Patients with severe COVID-19 frequently experience decreased energy because of ventilatory attempts and impaired energy use linked to systemic inflammation and hyper-catabolic state. As a result, this population is more prone to the detrimental consequences of insufficient nutrition (30, 31). As a result, individuals are more prone to the detrimental

consequences of insufficient nutrition, such as cardiac, renal, hepatic, and hematologic diseases development during hospitalizations, lengthier ICU stays, and an increased risk of in-hospital death (30).

The main strength of this study is that it is, to our knowledge, the first randomized clinical trial that supports the potential usefulness of peppermint essential oil (Supermint drops) on GRV in ICU patients on mechanical ventilation. The present study was conducted in a single center in Iran and among patients aged 18 years old or over, which is the limitation of the study. Therefore, more clinical trial studies are recommended to find out more about the efficacy and safety of peppermint oil essential among ICU patients of different ethnicity/races and age groups.

Conclusion And Future Development Directions

The results from the present study were very encouraging and indicate that peppermint essential oil could be used in GRV reduction in ICU patients with mechanical ventilation. Further multicenter clinical trials are needed to support this finding, especially among COVID-19 patients.

Abbreviations

ICU
Intensive care unit
GRV
Gastric residual volume
GEE
Generalized estimation equation
BMI
Body Mass Syndrome
GRVs
Gastric residual volumes.

Declarations

Acknowledgement

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Authors' Contribution

MS, SSB, and ADN conceived the presented idea.FM, MT, and ADN contributed to the design and concepts of the work. Data were collected by JASM, SSB, ADN, and HA. FM analyzed data and prepared the draft manuscript. All authors reviewed the manuscript and made amendments before submission.

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Availability of data and materials

Data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Gonabad University of Medical Sciences (Ethical code No: IR.GMU.REC.1398.187). All phases of this study were based on the ethical principles of human medical research (Helsinki declaration). For all patients and/or their legal guardians, described the steps of the research and how the patient's participation in the study was explained, assured that all information was confidential, no cost would be imposed on the patient, at any time it could continue to participate in Research has declined and each question can ask the researcher. The informed consent form of Persian is prepared and signed by the from all study participants and/or their legal guardians, researcher and a witness.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

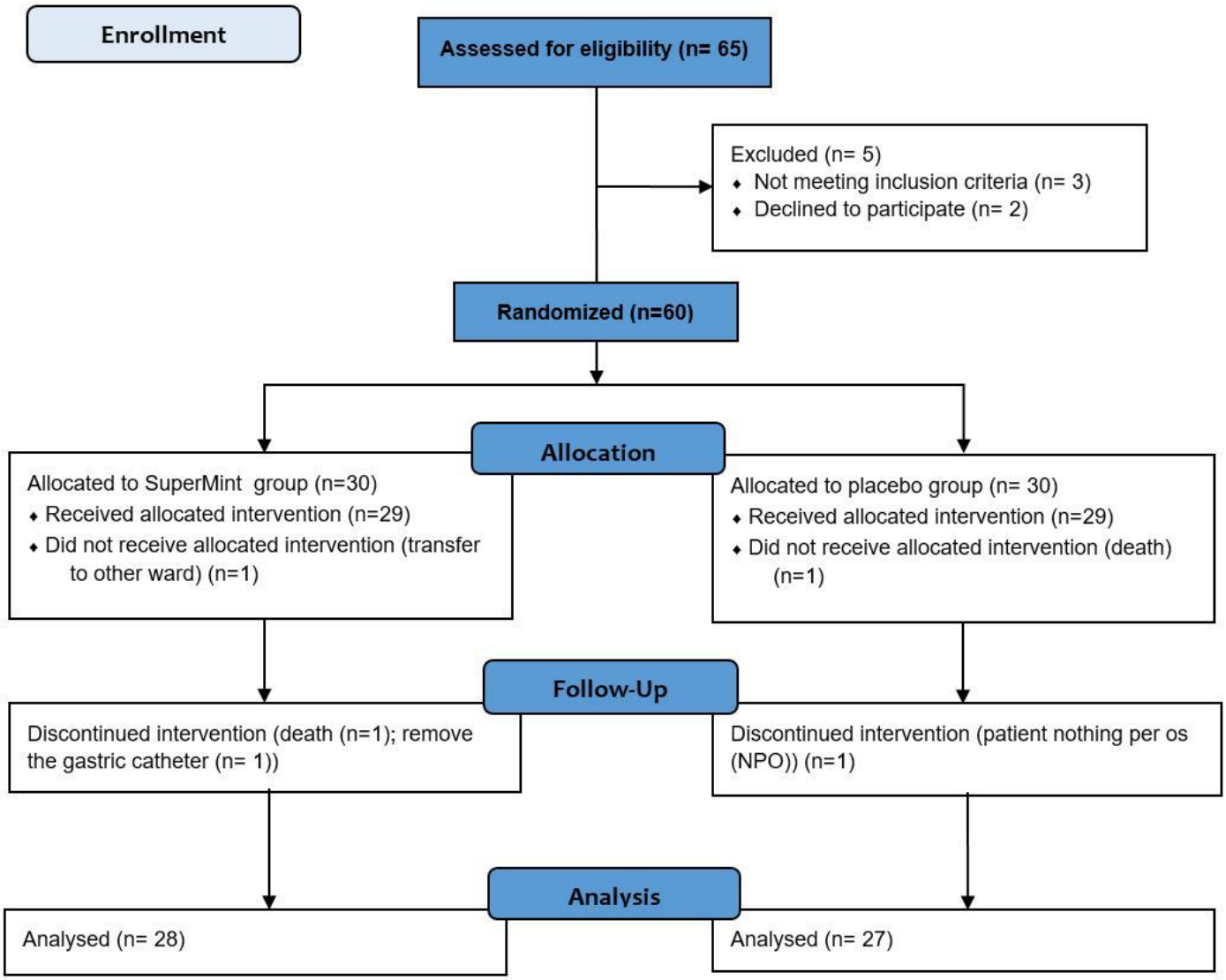

Figure 1

Flow chart trial

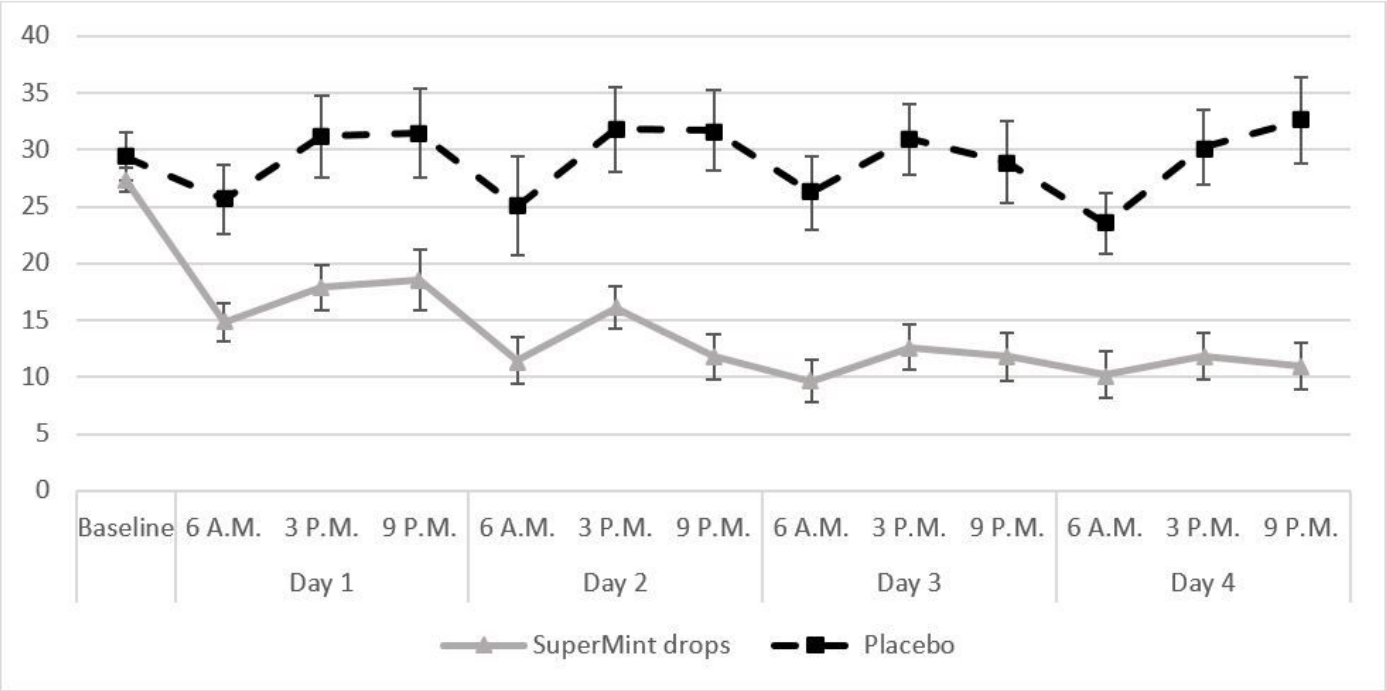

Figure 2

Mean of gastric volume residual (nonadjusted mean with 95% confidence interval)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.doc
- Trials.pdf