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Gastric residual volume factors after bowel preparation with mannitol express

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ABSTRACT – **Background** – Bowel preparation with mannitol is a well-established method in Brazil. However, factors that interfere with the gastric emptying time period are yet to be known. Knowing these factors may favor the examination scheduling logistics and the individualized orientation for each patient. **Objective** – Know the factors that can contribute to the gastric emptying time after intestinal preparation with express mannitol. **Methods** – This is a prospective observational study to know factors that may contribute on the gastric emptying timing: predominant type of diet, comorbidities, medication usage, previous surgeries, number of evacuation per week, bearer of bowel obstipation, fecal type, diet type, number of evacuations after the home usage of bisacodyl before the ingestion of mannitol and number of evacuations after the ingestion of mannitol until reaching a proper bowel preparation. Before starting the colonoscopy exam, an upper digestive endoscopy exam was made to aspirate the gastric content. **Results** – Sample was composed of 103 patients, 55 (53.4%) women, medium age 61 (±12.1) years, medium weight 75.3 (±14.1) kg, medium height 1.7 (±10) m and medium BMI of 26.6 (±3.9) kg/m^2. Average gastric residual volume was 120.9 (0–900) mL. Gastric residual volume (GRV) below 100 mL (GRV ≤100 mL) occurred in 45 (43.6%) patients, 24 (53.3%) women, medium age of 61.0 years and medium BMI of 26.7 kg/m^2. Gastric residual volume above 100 mL (GRV >100 mL) occurred on 58 (56.3%) patients, 29 (50%) women, medium age of 61.0 years and medium BMI of 26.2 kg/m^2. Comparing both groups, average fasting time period after the ingestion of mannitol was significantly higher on the group with GRV ≤100 mL than group with GRV >100 mL, 123.1 (60–246) vs 95.3 (55–195) minutes, respectively. There was also statistical significance concerning the usage of ezetimibe 6 (13.7%) in the group with GRV ≤100 mL and statistical significance in the group with GRV >100 mL concerning the usage of paroxetine 3 (6.7%) and tadalafil 3 (6.7%) and surgical history of prostatectomy 3 (6.7%) and bridle withdrawal 3 (6.7%). **Conclusion** – We may conclude in this study that the usage of ezetimibe and fasting above 2 hours after the ingestion of mannitol decrease significantly the incidence of a GRV >100 mL. The usage of paroxetine, tadalafil and surgical history of prostatectomy or bridle withdrawal may contribute to increase de incidence of a GRV >100 mL.

Keywords – Mannitol; sedation; respiratory aspiration of gastric contents; sedation, moderate; moderate sedation; sedation, conscious.

INTRODUCTION

Colonoscopy is a well-established method for diagnostic and therapeutic examination. For its execution, it is of great importance to properly prepare the colon.

Ingestion of mannitol within 2 hours (known as "mannitol express") is the most common way of bowel preparation in Brazil. One of the disadvantages of this method is the large volume of solution that patients must ingest in a short period of time, predisposing to aspiration during colonoscopy in case of considerable amount of liquid present in the gastric chamber.

To perform the colonoscopy it is recommended a 2-hour minimum fasting after the ingestion of liquids[(1)], and there is no knowledge of any factors that may contribute or hinder the gastric emptying of mannitol nor there is any study about the subject.

Knowing the factors that may affect the gastric emptying time period favors the examination scheduling logistics and the individualized orientation for each patient.

METHODS

This is a prospective observational study performed at the Endoscopy Service of Fleury Medicina e Saúde between May 2017 and May 2018, after approval by the institution's Ethics Committee. Indications for colonoscopy were screening or surveillance for colorectal cancer.

Eligible patients were: patients who had agreed to participate the research; age >18 years-old; BMI<40 kg/m^2; ASA 1 and ASA2 and be accompanied by someone of age ≥18 years-old.

Patients received the same instructions for bowel preparation: no ingestion of food containing any sort of seeds 5 days prior to the exam; one day before the exam, have a fiber-free diet and take two pills of bisacodyl at 05:00pm and 10:00pm. At the day of the examination, 4 hours before the colonoscopy, they were asked to ingest 500 mL of mannitol diluted with 500 mL of water.

Bowel cleaning was confirmed by nursery staff by the presentation of watery and light-colored evacuation. Number of evacuations to clean the colon and times of the first, third and last evacuation were all duly noted.

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Before bowel preparation in the institution, patients signed a Free and Informed Consent Form, answered clinical questionnaire and received orientations about the research. Questioned data were: predominant type of diet, comorbidities, medication usage, previous surgeries, number of evacuation per week, bearer of bowel obstipation, fecal type, diet type, number of evacuations after the home usage of bisacodyl before the ingestion of mannitol.

Patients were asked which type of diet they believed to fit in: protein, carbohydrate or vegetables (fibers) predominant diet.

Intestinal obstipation definition was based on the Rome IV Criteria[2] and fecal classification was made according to the Bristol Stool Chart[2].

Upon the confirmation of intestinal cleaning and the await of a 1-hour minimum fasting after the ingestion of mannitol, upper digestive endoscopy was performed for aspiration and volume assessment of the gastric content, followed by colonoscopy. Patients were sedated with midazolam (5 mg), fentanyl (50 µg) and a progressive dose of propofol, until reaching an appropriate level of sedation.

According to the findings in the literature about the subject, gastric residual volume (GRV) of 100 mL[3-8] was determined as the ideal reference value to minimize the risk of bronchial aspiration.

A designated endoscopist made the data gathering and another expert endoscopist performed the colonoscopy exams.

Data were evaluated by means of the Kolmogorov-Smirnov test and answers were converted to binary variables, with residual volumes up until 100 mL and volumes above 100 mL. Mann-Whitney U Test and chi-square distribution were applied with the purpose of verifying the existence of linear relation between the metric variables. A significance level of 5% was considered for the results interpretation. SPSS 22.0 software was used to perform the analyses.

RESULTS

Sample was composed of 103 patients, 55 (53.4%) women, medium age 61 (±12.1) years, medium weight 75.3 (±14.1) kg, medium height 1.7 (±10) m and medium BMI of 26.6 (±3.9) kg/m^2. Average gastric residual volume was 120.9 (0–900) mL.

Gastric residual volume below 100 mL (GRV ≤100 mL) was found in 45 (43.6%) patients and above 100 mL (GRV >100 mL) in 58 (56.3%). Demographic data are demonstrated in TABLE 1.

TABLE 1. Demographic data of the patients.

Total number of patients	103 patients		*P*-value
	GRV >100 mL	GRV ≤100 mL	
N	58 (56.3%)	45 (43.7 %)	
Age (years)	61 (±11.0)	61 (±12.7)	0.99
Male sex	29 (50%)	21 (46.7%)	0.26
BMI	26.2±3.5	26.7±4.02	0.57

GRV: gastric residual volume.

Elapsed time between the ending of mannitol ingestion and the examination was 123.1±49.7 min. with GRV ≤100 mL and 95.3±36.4 min. with GRV >100 mL. There was statistical significance regarding the usage of ezetimibe in the group with GRV ≤100 mL. and the usage of paroxetine and tadalafil, surgical history containing prostatectomy and intestinal bridle surgical treatment for GRV >100 mL. The other variables analyzed are in the TABLES 2 and 3.

TABLE 2. Clinical data of the patients.

	GRV >100 mL	GRV ≤100 mL	*P*-value
N	58 (56.3%)	45 (43.7 %)	
Normal colonoscopy	23(40%)	14 (31.5%)	0.62
Use of ezetimibe	0 (0%)	6 (13.7%)	0.03
Use of paroxetine	3 (6.7%)	0 (0%)	0.02
Use of tadalafil	3 (6.7%)	0 (0%)	0.02
Bridle withdrawal	3 (6.7%)	0 (0%)	0.02
Prostatectomy	3 (6.7%)	0 (0%)	0.02
Obstipation	11 (20%)	5 (9.6%)	0.19
N. evacuations/ week	6.3±2.2	5.8±1.9	0.22
N. evacuations after bisacodil	4±2.3	4.3±3.1	0.67
N. evacuations after manitol	6.4±1.4	6.5±2.0	0.81
Fecal type	Type 1= 2 (3.3%) Type 2= 2 (3.3%) Type 3=6 (10%) Type 4=15 (23.3%) Type 5=25 (43.3%) Type 6=6 (10%) Type 7=2 (3.3%)	Tipo 1=0 (0%) Tipo 2=1 (2.7%) Tipo 3=3 (6.8%) Tipo 4=9 (19.2%) Tipo 5=26 (56.2%) Tipo 6=5 (9.6%) Tipo 7=1 (2.7%)	0.82
Diet type	C=33 (56.7%) F=17 (30%) P=8 (13.3%)	C=24 (53.4%) F=14 (31.5%) P=7 (15.1%)	0.95

C: carbohydrates; F: fibers; P: proteins.

TABLE 3. Evaluated factors after starting mannitol ingestion.

	GRV >100 mL	GRV ≤100 mL	*P*-value
N	58 (56.3%)	45 (43.7 %)	
Mannitol ingestion time period (minutes)	47.2 (SD=13.5)	44.3 (SD=18.2)	0.429
Mannitol starting time and the third evacuation (minutes)	47.8 (SD=28.7)	52 (SD=28.2)	0.498
Total number of evacuations at home	4 (SD=2.3)	4.3 (SD=3.1)	0.676
Total number of evacuations in the institution	6.4 (SD=1.4)	6.5 (SD=2.0)	0.816
End of mannitol ingestion and colonoscopy start (minutes)	95.3 (SD=36.4)	123.1 (SD=49.7)	0.003

Colonoscopy findings per patients were: colon polyp on 41 (39.8%) patients, colon diverticulum on 26 (25.2%), rectal polyp on 5 (4.9%), colon erosion on 5 (4.9%), lateral spreading tumor 3 (2.9%), colon hyperemia on 2 (1.9%), angiectasias on 2 (1.9%), colorectal anastomosis on 2 (1.9%), erosive colitis on 2 (1.9%), scarring in the rectum on 2 (1.9%), colon lipoma on 2 (1.9%) and rectitis on 2 (1.9%).

DISCUSSION

The American Society of Anesthesiologists recommends a 2-hour fasting of liquids, except for alcohol, before starting the sedation, based on the meta-analysis of randomized clinical trials that show a low risk of aspiration when liquids are given to patients in a time period between 2 and 4 hours before the anesthetic procedure (category A1 – evidence B)[1]. Data with human beings shows volumes below 1.5 mL/kg in adults are normal in the fasting, not being related to clinical significant aspiration[4-8].

By nature, liquids for the bowel preparation are light and protocols do not specify how they should react on the patient who is being prepared for colonoscopy examination. Despite that, plenty of anesthesiologists and medical centers request a fasting of 3 to 8 hours before the sedation.

Based on the Roberts and Shirley 1974 experiment[9], in which the injection of acid solution (pH=2.5) directly into lungs of apes would result in adverse effects, it was assumed that the bronquic aspiration of 25 mL of gastric solution could have the same effects on human beings[10-14]. However, patients who submit themselves to elective surgery usually have a gastric fluid volume above 25 mL, even with an overnight fasting[2], once there is still production of saliva and gastric juice by approximately 50 mL/h[10]. This is corroborated by studies that demonstrate that patients who ingest fluids 2 to 4 hours before the surgery do not have a residual gastric volume bigger than the patients who had a longer time period of fasting (25 mL) and patients without pre-anesthetic medication[10,11]. Additionally, adverse events only happen with the aspiration of volumes above 25 mL[9,10,14-22] and patients, while fasting, produce saliva in an amount of nearly 50 mL/h, which will be swallowed and, consequentially, be part of the gastric liquid volume[10].

It was believed that, in the bronquic aspiration, the gastric liquid pH and the amount of volume aspirated would be key factors for the occurrence of chemical bronchopneumonia, and that a prolonged fasting of liquid content would decrease the gastric residual volume. However, studies published up until 20 years ago have shown that the gastric volume and pH do not show significant changes after 2 hours of fasting.

Scarr et al.[10] evaluated 211 patients divided in less than 3 hours, 3 to 4.9 hours, 5 to 8 hours and more than 8 hours of fasting, all of which were submitted to general anesthesia and concluded that there was no significant statistical difference of GRV and gastric pH between the groups.

Juvin et al.[20] compared the pH and GRV of 25 obese patients with 23 thin patients and concluded there was no difference of the GRV (26±13 mL vs 26±8 mL). However, gastric pH in obese patients was slightly lower (pH 2.3 vs pH 2.8).

Schimidt et al.[12], comparing GRV and pH with 1 and 2 hours of fasting after ingesting 5 mL/kg (max. 150 mL) of clear liquid in the pre-general anesthesia period of 131 children between 1 and 16 years old, ASA l and ll without gastrointestinal disorders, concluded that, despite significantly shorter fasting times for clear fluids in group A compared with group B (76/136 min; $P<0.001$), no significant difference was observed regarding gastric pH 1.43 (1.30–1.56) vs 1.44 (1.29–1.68), $P=0.66$ or residual volume 0.43 (0.21–0.84) vs 0.46 (0.19–0.78) mL/kg, $P=0.47$. Perhaps this applies only to children because in our series there was a significant difference in adults (95.3 x 123.1 minutes; $P=0.003$).

Huffman et al.[13] divided 712 patients into two groups: one group submitted to isolated upper endoscopy (n=411) and one group submitted to colonoscopy associated with upper endoscopy, divided in two groups: to one group (n=47), bowel preparation was done with 4L of Polyethylene glycol or sodium picosulfateat at the morning of the exam and to another group, part of(n=254) of the bowel preparation at home and the other part at the morning of the examination. The group with upper endoscopy only was oriented to total fasting over the night before the colonoscopy examination. Comparing all groups, GRV was bigger in the groups in which the colonoscopy was performed ($P=0.0001$) with no difference between both groups with bowel preparation ($P=0.85$). Volumes above 50 mL were found in 8% of the patients that started the bowel preparation at home, in 9% of the patients with whole bowel preparation at the morning of the exam and in 5% whose upper endoscopy only was performed, with no identified factor associated to the raise of gastric volume. Diabetes, use of opioids, use of metoclopramine or the sort of preparation didn't show significance in the GRV when the liquid was aspirated 2 hours after the ingestion of the solution for the bowel preparation, the same results we found. Author didn't identify clinical factors related to the increase of gastric liquid retention, despite having patients with volumes above 100 mL. In our study were found statistical significance to prostatectomy ($P=0.02$) and intestinal bridle surgical treatment ($P=0.02$) for GRV >100 mL.

In 161 patients in use of Percutaneous Endoscopic Gastrostomy, Agrawal D. et al.[14] found an average GRV of 21 mL ±254 mL for the ingestion of 4 liters by PEG at the morning of the exam, with no difference for a fasting of 2, 2,5 and 3 hours (average of 27±29, 16±26 and 17±14, accordingly; $P=0.27$), as well as the coexistence of diabetes, gastroparesis and use of opioids. Five patients presented a volume above 100 mL, without any adverse effects.

Coriat et al.[23], with ingestion of 4 tablets of sodium phosphate diluted in 250 mL of liquid every 15 minutes (total of 16 tablets and 1000 mL) in the morning of the examination, controlled by ultrasound evaluation, observed gastric emptying of 25% after 60 minutes of the ingestion, 70% by 120 minutes and 87% by 150 minutes with no significance for the emptying when considering the body mass index (BMI). Despite results previously described, we observed patients with GRV >100 mL had a shorter average fasting time than those who had GRV ≤100 mL (95.3 x 123.1 min; $P=0.003$).

Paroxetine inhibits the recapture of 5-hydroxytryptamine (5-HT). On rabbits, it causes a dose-dependent decrease on the ileum contractility[15] and on human beings may promote a delay on the gastric emptying, despite accelerating the orocecal transit[16,18,22]. Maybe this effect can explain the result found in our study. Comparing the effects on the gastrointestinal tract by buspirone, paroxetine and venlafaxine, Chial et al.[19] concluded there was no significant difference ($P=0.3$) on the gastric emptying time (t=2h) for solid content. Paroxetine, when compared to placebo, accelerated the orocecal transit time to 6 hours 82 (41.3 to 99)% vs 47 (24.5% to 59)%, $P=0.05$), without alterating the colon transit. Besides that, it did not have effect on the postprandial gastric volume.

Despite not being any directed studies about the effects of tadalafil and ezetimibe, surgery for the withdrawal of bridles and usage of mannitol over the gastric residual volume, Remes-Troche et al.[21] describes effect of tadalafil on the treatment of spastic esophageal disorder due to its muscle relaxation effect over the esophagus' smooth muscle. After de injection of 20 mg of tadalafil on a control group, on four patients with achalasia and on two patients with hypertensive peristalsis, by manometric evaluation of 15, 30,

45, 60 and 120 minutes, 24 and 48 hours, was noticed a progressive resting pressure decrease of the inferior esophageal sphincter after 60 minutes in the control group (18.8±4 mmHg vs 22.1±3 mmHg, *P*=0.019), reaching the lowest point after 2, 24 and 48 hours. Out of the six patients with peristalsis condition, four of them noticed an improvement on their dysphagia between 24 and 48 hours. In tadalafil's medicine leaflet, side effects may include abdominal pain and gastric-esophageal reflux. As for the ezetimibe, the medicine leaflet describes abdominal pain, diarrhea and flatulence as possible side effects. For us, tadalafil is related to GRV >100 mL (*P*=0.02) and the use of ezetimibe is related to decreased GRV ≤100 mL (*P*=0.03).

Studies[2,24,25] point out liraglutide in patients with diabetes mellitus type II as the prompter of gastric emptying delay and inhibitor of duodenal and small intestine motility. We observed patients using this medication did not show statistical significance (*P*=0.146) on the GRV when suspending it seven days before having a colonoscopy examination.

This is the first study with mannitol bowel preparation that tries to define factors related to the time of gastric emptying and can contribute to daily endocopic practice, providing scientific subsidies for those services that have already adopted fasting time reduction, being able to assist the examination scheduling logistics and the individualized orientation for patient. Besides that, it may also provide data for future studies that evaluate factors that can interfere on it.

CONCLUSION

We may conclude the usage of ezetimibe and fasting above 2 hours after the ingestion of mannitol decrease significantly the incidence of a GRV >100 mL. The usage of paroxetine, tadalafil and surgical history of prostatectomy or bridle withdrawal may contribute to increase de incidence of a GRV >100 mL.

Authors' contribution

Brito HP: data acquisition, analysis, data interpretation, article writing, article review. Chaves DM: data acquisition, data interpretation, article review, final approval. Chaves FT: data acquisition, translation, article writing. Sugai B: data acquisition, article writing, article review. Ide E: data acquisition, article writing, article review. Rodrigues RA: data acquisition, article writing, article review.

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RESUMO – **Contexto** – O preparo intestinal com manitol é um método bem estabelecido no Brasil. No entanto, os fatores que interferem no tempo de esvaziamento gástrico ainda não são conhecidos. O conhecimento desses fatores pode favorecer a logística de agendamento do exame e a orientação individualizada para cada paciente. **Objetivo** – Estudar os fatores que podem contribuir para o tempo de esvaziamento gástrico após o preparo intestinal com manitol expresso. **Métodos** – Trata-se de um estudo observacional prospectivo com o objetivo de conhecer os seguintes fatores que podem contribuir no tempo de esvaziamento gástrico: tipo de dieta predominante, comorbidades, uso de medicamentos, cirurgias anteriores, número de evacuações por semana, portador de obstipação intestinal, tipo fecal, tipo de dieta, número de evacuações após o uso domiciliar de bisacodil antes da ingestão de manitol e número de evacuações após a ingestão de manitol até atingir o preparo intestinal adequado. Antes de iniciar o preparo intestinal, os pacientes responderam a um questionário clínico. O endoscópio foi introduzido para aspirar o conteúdo gástrico, antes de iniciar a colonoscopia. **Resultados** – A amostra foi composta por 103 pacientes, sendo 55 mulheres, com média de idade de 61 anos, peso médio de 75,3 kg, altura média de 1,7 m e IMC médio de 26,6 kg/m^2. O volume residual gástrico médio medido foi 120,9 (0–900) mL. Volume residual gástrico inferior a 100 mL (VRG ≤100 mL) foi encontrado em 45 (43,6%) pacientes, sendo 24 (53,3%) mulheres, com média de idade de 61,0 anos e IMC médio de 26,7 kg/m^2. Volume residual gástrico acima de 100 mL (VRG >100 mL) ocorreu em 58 (56,3%) pacientes, sendo 29 (50%) mulheres, com idade média de 61,0 anos e IMC médio de 26,2 kg/m^2. Comparando os dois grupos, notou-se que o tempo médio de jejum após a ingestão de manitol foi significativamente maior no grupo com VRG ≤100 mL do que no grupo com VRG> 100 mL, 123,1 (60–246) vs 95,3 (55–195) minutos, respectivamente. Também houve significância estatística em relação ao uso de ezetimiba 6 (13,7%), sendo maior no grupo com VRG ≤100 mL. Além disso, houve significância estatística no grupo com VRG >100 mL quanto ao uso de paroxetina 3 (6,7%) e tadalafil 3 (6,7%) e história cirúrgica de prostatectomia 3 (6,7%) e retirada de bridas 3 (6,7%). **Conclusão** – Podemos concluir neste estudo que o uso de ezetimiba e o jejum acima de 2 horas após a ingestão de manitol diminuem significativamente a incidência de um VRG> 100 mL. O uso de paroxetina, tadalafil e história cirúrgica de prostatectomia ou retirada de bridas podem contribuir para o aumento da incidência de um VRG >100 mL.

Palavras-chave – Manitol; sedação; aspiração respiratória do conteúdo gástrico; sedação consciente.

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