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Agents that can be used in medical treatment of meconium ileus and comparison of their efficacy

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Abstract

Background: Aim: This study was conducted to determine the efficacy of medical agents currently used or potentially used in the medical treatment of meconium ileus and to contribute to the medical treatment of meconium ileus.

Materials and method: In our study, meconium causing meconium ileus or normal meconium obtained voluntarily from healthy newborns at birth was used. A total of 2 g meconium sample was placed in each test tube. Six experimental groups were formed by adding saline solution, N-acetylcysteine, amidotrizoate, pancreatic enzymes, fibrinolytic enzyme, and probiotic bacteria on the meconium samples. All experimental groups were kept at 36 °C and over 90% humidity for 6 h. The resulting mixtures were centrifuged at 2500 rpm for 5 min.

The solid gel-like part and the liquid part were separated. The volumes of the liquid portions and the weights of the gel portions were measured. Gels were placed on a glass substrate to compare the flowability of the gel portions. After 30 min, how much the gel-like meconiums moved from the starting point was recorded. Liquid volumes were measured in milliliters (ml), weights in grams (g), and distance in millimeters (mm).

Results: It was determined that the solid part weights of N-acetylcysteine and amidotrizoate groups increased, while the solid part weights of the other groups decreased. It was determined that the decrease in solid part weights was mostly in the probiotic bacteria group. Test correlation between liquid fraction volume and solid weight was statistically determined. The group that moved the most on the glass substrate was the N-acetylcysteine group.

Conclusions: Our study also showed that the gastrographin and NAC groups do indeed attract liquid to solid meconium. They cause an increase in solid part weight. Probiotic bacteria and pancreatic enzymes were found effective in terms of movement on the glass surface in the meconium samples they were applied to. The fibrinolytic enzyme produced for in vivo environment was found to be ineffective in the in vitro environment in our study.

We think that pancreatic enzymes and probiotic bacteria can also be used in the medical treatment of meconium ileus.

Keywords: Meconium ileus, Medical treatment of meconium, N-Acetylcysteine, Amidotrizoate, Pancreatic enzymes, Fibrinolytic enzymes, Probiotic bacteria

Background

Meconium consists of bile, intestinal mucus secretion, multilayered flat epithelial debris, and swallowed amniotic fluid at the 16th week of intrauterine life [1]. Meconium exit is expected in 94% of normal newborns within the first 24 h after birth [2]. The abnormal meconium

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obstructs the terminal ileum to form ileus is called meconium ileus (MI) [3]. Meconium ileus and cystic fibrosis disease are closely related [4]. However, not all meconium ileus is caused by cystic fibrosis [4]. Meconium, which causes obstruction in meconium ileus, is sticky and dark [4]. The content of meconium, which is the cause of obstruction in the meconium ileus, is less watery than normal meconium, and the amount of albumin is higher [5]. There are also some pancreatic enzyme differences, such as trypsin, in the content of meconium that causes obstruction [5]. Simple meconium ileus is observed in 42% of meconium ileus cases [6]. In 1969, Nobletf described the medical treatment of meconium ileus and successfully treated it [7]. Hydrogen peroxide has also been used before in the medical treatment of meconium ileus. Hydrogen peroxide is no longer used in the treatment of meconium ileus because it causes severe irritation and embolism [8]. Today, diatrizoate (Gastrografin®) and N-acetylcysteine (NAC) (Asist®) are used in the medical treatment of meconium ileus [9]. Both agents are hyperosmal. These agents are presumed to draw water to meconium.

Medicines used in the medical treatment of meconium ileus are still limited. Comparison of these drugs has not been made. New and safe methods are still not found. We created an experimental environment to compare the effectiveness of drugs used in the medical treatment of meconium ileus and to suggest new molecules. We aimed to help in the medical treatment of meconium ileus through the experimental environment we created.

Materials and method

For our study, ethical approval was obtained from the Local Ethics Committee of Selcuk University Faculty of Medicine, dated 24 April 2020 and numbered 08.

In our study, meconium causing meconium ileus or normal meconium obtained voluntarily from healthy newborns at birth was used. These meconiums were used in our study. Meconium samples were weighed as 2 g and put into separate test tubes. Subsequently, the different agents were applied directly on the samples, as in the case of enema in clinical practice. Test tubes were coded with letters and numbers. Thus, double-blind study was provided. The researcher did not know which drug he was administering and to which group. Ten test tubes were used in each group. Groups were created as follows.

1. Control group: A total of 2 ml of saline solution(SF) was applied directly on 2 g of meconium as in the enema practice.
2. Bacteria group: The meconium ileus (MI) agents to be applied in this group are those containing *Lactobacillus rhamnosus* GG 1X109 CFU (Maflor®), which are licensed as drugs in Turkey. Its form licensed as a solution for use by dropping is sold as probiotic in Turkey for use even in newborns. A total of 0.5 cc of probiotic bacteria solution was taken and diluted to 2 ml with 1.5 cc SF. A bacterial group was generated by adding on each meconium.
3. Fibrinolytic enzyme group: In this group, alteplase (Actilyse®), which is a drug licensed as a fibrinolytic in Turkey, was used to dissolve the fibrins in meconium. The vial prepared by combining powder and liquid forms contains 1 mg alteplase per milliliter. In our study, we took 0.5 ml of diluted alteplase and added 1.5 ml of SS to it. We applied the prepared 2 ml enzyme mixture on the meconiums as in the enema practice.
4. Group pancreatic enzymes: In our country, 3150 amylase, 1050 lipase, 210 protease f:I:P units, and 50 mg hemicellulase containing licensed drug agent, oral preparation is sold in the form of enteric-coated Dragee(Pankreoflat®).These capsules were pulverized. A total of 1/10 of the capsule was taken. It was diluted with 2 cc of SF (two capsules were pulverized for this process. It was dissolved in 10 ml of SF. A total of 0.5 cc was taken from this solution). A total of 2 ml pancreatic enzyme solution was applied to the meconium as if enema was being performed.
5. Group sodium diatrizoate (Urografin meconium ileus (MI), Gastrografin®): A form containing 100 mg sodium amidotrizoate and 660 mg meglumine in 1 ml solution is available in Turkey. A total of 0.5 ml was taken from the present liquid form and completed to 2 ml with the addition of 1.5 ml SF and applied to meconiums as an enema similar to the clinical practice.
6. Group N-acetylcysteine (NAC): Preparations containing N-acetylcysteine (NAC) are licensed for many indications as oral and IV forms in our country. In this group, 0.5 ml of the ready-made preparation containing 300 mg NAC in 2 ml ampoule was taken and completed to 2 ml with 1.5 ml of SF. It was applied to the meconiums.

All test tubes were kept at 36 °C for 6 h. Ambient humidity is keeping such 90% and above. The purpose of our keeping in such an environment was to mimic the humidity and temperature of the meconium ileus (MI) human body. After 6 h, the results were centrifuged at 2500 rpm for 5 min. Thus, the solid gel-like part and the liquid part were easily separated. Centrifugation time and cycle were determined as the value at which the gel part and the liquid part separated after several trials. The volumes of the liquid portions were measured. The weights of the gel portions were measured. The gels were then

placed on a glass substrate to compare the flowability of the gel portions. The glass substrate was positioned at room meconium ileus (MI) temperature, with an inclination of 30° from the floor. It was recorded how much the gel-like meconium moved from the starting point in 30 min. Liquid volumes were measured in milliliters (ml), weights in grams (g), and distance in millimeters (mm).

Statistical analysis

SPSS (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY) 22.0 package program was used for coding and statistical analysis of the data. Descriptive statistics of the categorical data in the study were shown using frequency and percentage values, and descriptive statistics of numerical data were shown using median (min–max). Kolmogorow-Smirnov and Shapiro Wilk tests were used to evaluate whether the numerical data fit the normal distribution or not. The Kruskal–Wallis test was used in the analysis of continuous data that did not show normal distribution. Spearman test was performed for the relationship between study parameters. A value of $p < 0.05$ was taken for statistical significance.

Results

In our study, a total of 60 (10 (%16.7) in the control group, 10 (%16.7) in group 2, 10 (%16.7) in group 3, 10 (%16.7) in group 4 (%16.7), 10 in group 5 (%16.7), and 10 in group 6 (%16.7)) samples were taken. There is a statistically significant difference between the amount of movement of the study groups on the glass substrate ($p < 0.001$), solid part weight ($p < 0.001$), and liquid part volume ($p < 0.001$) values (Table 1).

The weights of the gel parts of the groups were compared with each other. In post hoc test, there were statistically significant differences between group 2 and group 4 ($p = 0.002$), between group 2 and group 6 ($p < 0.001$), between group 2 and group 5 ($p < 0.001$), between group 1 and group 6 ($p = 0.001$), between group 1 and group 5 ($p < 0.001$), and between group 3 and group 5 ($p = 0.005$) in terms of solids weight. There is no statistically significant difference between the other groups ($p > 0.05$) (Table 2).

It was determined that the solid part weights of the gastrographin and NAC groups increased, while the solid part weights of the other groups decreased. It was found that the groups treated with Gastrografin and NAC drew water. The group in which the weight of the solid part decreases the most is the probiotic bacteria group.

In post hoc test, there were statistically significant differences between group 3 and group 5 ($p = 0.004$), between group 1 and group 5 ($p < 0.001$), between group 2 and group 5 ($p < 0.001$), between group 2 and group 6 ($p < 0.001$), between group 1 and group 6 ($p = 0.001$), and between group 2 and group 4 ($p = 0.002$) in terms of

Table 1 Comparison of working groups on movement on glass substrate, solid part weight, and liquid part volüme

	Movement on glass substrate (mm)	Solid part weight (g)	Liquid part volume (mm^3)
1st group ($n = 10$)	60.50 (32.00–100.00)	1.50 (1.20–1.90)	2.50 (2.10–2.80)
2nd group ($n = 10$)	83.00 (54.00–260.00)	1.20 (0.30–1.50)	2.80 (2.50–3.70)
3rd group ($n = 10$)	28.00 (1.00–65.00)	2.00 (1.80–2.10)	2.00 (1.90–2.20)
4th group ($n = 10$)	92.00 (57.00–127.00)	2.70 (2.00–3.00)	1.50 (1.00–2.00)
5th group ($n = 10$)	35.00 (20.00–78.00)	3.70 (2.70–3.90)	0.30 (0.10–1.30)
6th group ($n = 10$)	115.00 (63.00–142.00)	3.15 (3.00–3.30)	0.85 (0.70–1.00)
p	< 0.001	< 0.001	< 0.001

Table 2 Relationship between study parameters

	Movement	Solid part weigh		Liquid part volume		
	rho	*p*	rho	*p*	rho	*p*
Movement on glass substrate			− 0.111	0.399	0.117	0.372
Solid part weight	− 0.111	0.399			− 0.998	< 0.001
Liquid part volume	0.117	0.372	− 0.998	< 0.001		

solids weight. There is no statistically significant difference between the other groups ($p > 0.05$). The liquid part volume increased the most in bacteria group. There was a decrease in the liquid part volumes of the gastrographin and NAC groups.

In post hoc test, there were statistically significant differences between group 2 and group 3 ($p = 0.012$), between group 3 and group 4 ($p = 0.001$), between group 3 and group 6 ($p < 0.001$), between group 2 and group 5 ($p = 0.022$), between group 4 and group 5 ($p = 0.002$), and between group 5 and group 6 ($p < 0.001$) in terms of solids weight. There is no statistically significant difference between the other groups ($p > 0.05$). It was found that the most moving group on the glass substrate was the NAC group. The least movement was seen in the fibrinolytic enzyme group.

In the Spearman correlation test, there is no relationship between the movement on the glass surface and the solid part weight (rho = -0.111 $p = 0.399$) and the liquid part volume (rho = 0.117, $p = 0.372$), while there was a negative relationship between the solid part weight and the liquid part volume (rho = -0.998, $p < 0.001$).

Discussion

Agents accepted in the medical treatment of meconium ileus are still limited [9, 10]. The most efficient method in the treatment of constipation is to increase the intestinal content and the liquid ratio of the stool so that the stool dissolves and excretes it from the body. In constipation, when saline solution or tap water is given directly to the intestinal contents, it can be discharged with bowel movements by making the stool sufficiently hydrated. However, normal meconium and abnormal meconium that cause meconium ileus are different from stool in content. For this reason, it was necessary to add various substances to saline solution to ensure the removal of meconium. The main purpose of the medical treatment of meconium ileus is that the meconium, which causes meconium ileus, by making it more liquid and disposing of it in normal ways. The main purpose is to make meconium more liquid to allow normal evacuation.

In our study, the agents that can be applied directly to meconium as in the enema procedure were compared using an in vitro method instead of being compared to the in vitro method. The agents used in our study were Gastrografin, NAC added to saline, and probiotic bacterias with potential use; pancreatic enzymes and fibrinolytic enzymes were used in our study. Pancreatic enzymes and fibrinolytic enzymes are drugs that are still used for different purposes, but they are not used in the medical treatment of meconium ileus.

Until now, it was thought that NAC and gastrographin could draw fluid into meconium because they are hyperosmolar. Our study showed that the Gastrographin and NAC groups do indeed attract liquid to solid meconium. They make meconium more gel-like. In previous studies, it has been shown that gastrographin has no effect on intestinal histology in animals with constipation [10]. Our study has shown that the currently used Gastrografin and NAC cause to make meconium a more gel-like consistency by drawing liquid into the solid part of meconium.

NAC is another molecule commonly used in the medical treatment of meconium ileus. NAC has many uses in modern medical practice. It is known that cases of meconium ileus are associated with cystic fibrosis disease. NAC is an agent that can be used orally or intravenous treatment of cystic fibrosis. In our study, it was shown that the acellular NAC added to meconium in vitro caused an increase in the gel consistency of meconium. When comparing NAC and gastrographin, no difference was found in terms of fluid absorption into meconium.

Oral drop forms of probiotic bacteria for newborns have obtained medicine licensed in Turkey. Probiotic bacteria can be used in cases where the intestinal flora of newborns is impaired. Considering that the newborn does not have intestinal flora but that the flora will develop rapidly, we concluded that bacteria should also be included in our study. In our study, we found that the probiotic bacteria group was the group that decreased the weight of the solid part the most. The movements of the probiotic bacteria group on the glass substrate is compared to the other groups; this group was found to be moving fast.

There are also publications showing that insufficiency of pancreatic enzymes may cause meconium ileus [11, 12]. In our study, we found that the application of pancreatic enzymes on meconium as an enema was effective, even though normal meconium and meconium causing meconium ileus were not compared.This effect was especially in the form of increasing the action of gel-like meconium. In our study, we found that pancreatic enzyme group is the group that moved the fastest in terms of gel movement on analyzing the movement of the glass substrate. This finding suggested that pancreatic enzymes could also be used in our study; we found that the application of pancreatic enzymes on meconium as an enema was effective in the medical treatment of meconium ileus in the form of an enema.

Meconium ileus is easy to treat medically, but it is not always possible. Since it is easier than surgical treatment, medical treatment in meconium ileus is tried in every possible case. Our study showed that Gastrografine and NAC are effective agents that can be used for this purpose. In addition, probiotic bacteria and pancreatic enzymes may be tried/used in the medical treatment of

meconium ileus. Since our study is not an in vivo study or an animal experiment, it must be supported by further studies. The agents we used in our study are molecules with existing medicine licenses.

The fibrinolytic agent we use is an enzyme. It is likely that the most suitable environment for the functioning of the fibrinolytic enzyme we use is the intravenous environment. Application of this enzyme on meconium, which is very different in content from the intravenous environment, will adversely affect the enzyme's activity. It was expected that the fibrinolytic agent would be probiotic bacteria, and pancreatic enzymes may be useful in the medical treatment of meconium ileus. lt caused a serious reduction in the solid part of the meconium. However, it was found that the fibrinolytic agent did not cause dissolution in the solid part of the meconium compared to the control group.In our study, fibrinolytic agents were not found suitable for medical treatment of meconium ileus. Although we think that fibrinolytic agents are ineffective in the medical treatment of meconium ileus in our study, they are still powerful potential theoretical therapeutic agents for in vitro animal experiments.

We think that probiotics or pancreatic enzymes can be used in the medical treatment of meconium ileus as off-label drugs in selected cases.

Conclusions

Our study showed that the gastrographin and NAC groups did indeed draw the liquid to solid meconium. (Such a claim is present in all books, but there is no scientific study to prove this claim. Our study proves that gastrographin and NAC draw liquid to meconium.)

In our study, we found that the application of pancreatic enzymes on meconium as an enema was effective.

Probiotic bacteria and pancreatic enzymes can also be used in the medical treatment of meconium ileus.

Fibrinolytic agents were not found suitable for medical treatment of meconium ileus.

Abbreviations

MI: Meconium ileus; NAC: N-Acetylcysteine; SPSS: Statistical Package for the Social Sciences.

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Authors' contributions

Hasan Madenci, Concept: The idea for research or article/hypothesis generation. Design: Planning the methods to generate hypothesis. Supervision: Supervision and responsibility for the organization and course of the project and the manuscript preparation. Resources: Supplying financial resources, equipment, space, and personnel vital to the project. Materials: Biological materials, reagents, and referred patients. Data collection and/or processıng: Responsibility for conducting experiments, management of patients, and organizing and reporting data. Analysis and/or interpretatıon: Responsibility for presentation and logical explanation of results. Literature search: Responsibility for conducting literature search. Writing manuscript: Responsibility for the creation of an entire or the substantial part of the manuscript. Critical review: Reworking the final, before submission a version of the manuscript for intellectual content, not just spelling and grammar check. The author(s) read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

For our study, ethical approval was obtained from the Local Ethics Committee of Selcuk University Faculty of Medicine, dated 24 April 2020 and numbered 08.

Consent for publication

We accept the publication of our article in your journal.

Competing interests

The author declares no competing interests.

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