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ABSTRACT

Introduction: Many children with acute abdominal pain and suspicion of appendicitis are diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute constipation and acute appendicitis because of similar symptoms and lack of diagnostic criteria. Consequently, constipation is often missed despite repeated consultations at the emergency department. We hypothesize that the diagnostic process can be improved and adequate treatment accelerated by supporting fecal evacuation in children with acute abdominal pain.

Methods and analysis: An unblinded randomized controlled trial including children between 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children who do not receive a diagnosis after the first consultation and who need to return for a second consultation will be randomized. The intervention group will receive laxatives and enemas, while the control group will receive no medication. If, after the second consultation, still no diagnosis is established and a third consultation is needed, then the intervention group will receive only laxatives and the control group will again not receive medication. The primary outcome will be the differences in abdominal pain scores obtained with FACES® Pain Rating Scale and the Visual Analogue Scale at first, second, and possibly third consultation. The secondary outcome will be the number of consultations needed to reach final diagnosis.

Ethics and dissemination: Laxatives and enemas have proven to be safe and effective treatments for constipation in children. Adverse events are therefore not expect, however, should they occur, then the child concerned shall be properly followed and treated until the event is over. The local Medical Research Ethics Committee approved of this study and waived the otherwise mandatory insurance for human test subjects.

Trial registration: Dutch trial register (CCMO): NL44710.042.12. European trial registration (EudraCT): 2013-000498-56.

Keywords: constipation; acute appendicitis; diagnostic method; randomized controlled trial

INTRODUCTION

Acute abdominal pain is the third-leading cause of visits to emergency departments by children under 15 years, and is associated with high costs, especially when hospitalization is required [1]. For instance, in the United States of America, approximately 900.000 children visit an emergency department with acute abdominal pain and suspicion of appendicitis annually [2]. Nevertheless, only 30% of these children are eventually diagnosed with acute appendicitis [3], while constipation is diagnosed in 21% of girls and 18% of boys with acute abdominal pain [3].

It can be difficult to differentiate between constipation with an acute presentation and acute appendicitis, because the symptoms of constipation sometimes mimic those of acute appendicitis. Besides, there are no diagnostic criteria for acute constipation, unlike the Rome IV criteria for diagnosing chronic constipation [4]. In clinical practice, in order to exclude or confirm constipation, most physicians limit their questioning of patients presenting with acute abdominal pain on whether their bowel habits have changed recently or whether they are "normal", even though it is known that many people pay scarce attention to their bowel habits and/or are unaware of what "normal" stool frequencies or consistencies are [5,6]. In addition, to diagnose constipation physicians often avoid performing digital rectal examinations in children because of discomfort or fear on the part of the patients, and their own lack of adequate training or experience [7]. Moreover, additional investigations, such as abdominal X-rays to diagnose children with constipation, was strongly criticized in a number of studies [8,9,10]. Because the abovementioned methods to diagnose constipation are often not performed or carried out insufficiently, an extra consultation the following day can be recommended to determine whether the symptoms improve or worsen. Nonetheless, even after extra consultations many children are diagnosed with non-specific abdominal pain instead of constipation [11]. These misdiagnoses could result in chronic abdominal pain,

because the underlying cause, constipation, is left untreated [12,13]. We believe therefore that a better method is needed to either confirm or exclude constipation in children presenting with acute abdominal pain at the emergency department.

Laxatives and/or enemas are standard treatment for fecal disimpaction in children with constipation [9]. This combination of medications can provide a rapid relief of symptoms and has proven to be safe and adverse events rarely occur [9,14,15,16]. We hypothesize that by supporting fecal evacuation with laxatives and enemas in children suffering acute abdominal pain, but who were not diagnosed after first consultation, the diagnostic process could be accelerated. In case a child does indeed suffer from constipation, laxatives and/or enemas lead to rapid reduction of pain. In addition to the positive effect this has on the child's condition, the reduction of pain also points towards constipation as the cause of the abdominal pain. If a child does not suffer from constipation then laxatives and/or enemas will not provide significant relief of symptoms, indicating to the physician that constipation is less likely to be the cause of the abdominal pain.

Our objective with this randomized controlled trial is to study whether supporting fecal evacuation in children with acute abdominal pain, but without a diagnosis after the first consultation at the emergency department, could accelerate and improve the diagnostic process.

METHODS AND ANALYSIS

Study design and setting

An unblinded randomized controlled trial at the emergency department of an academic hospital, the University Medical Center Groningen, in the Netherlands.

Participants

We intend to include children between 5 and 18 years who are referred to the emergency department with acute abdominal pain and suspicion of acute appendicitis. Exclusion criteria are pregnancy and severe co-morbidity like malignancy, recent abdominal surgery, or known inflammatory bowel disease.

Recruitment

Children presenting at the emergency department with suspicion of acute appendicitis will be approached to participate in the study. First, the researcher will explain the study protocol to the parent(s)/legal guardian and the child. Subsequently, we will hand them the study brochure that was adapted so as to be readily understood by children. If, after having had some time to read the brochure and the opportunity to ask questions, the parent(s)/legal guardian and/or the child agree to participate in the study, we will ask them to sign the consent form. Dutch law requires that in case of children younger than 12 years old, only the parent(s)/legal guardian need to sign the consent form. If children are between 12 and 16 years old, both children and their parent(s)/legal guardian are required to sign the consent form. In case of children older than 16 years, only the children are obliged to sign the consent form. The code of resistance of minors will also be taken into account.

Randomization

Children will be randomized using sealed envelopes without any stratification factors. The researcher will randomly pick a sealed envelope from a sealed box located in the emergency room and will open it in the presence of the child and parent(s)/legal guardian. The study is not blinded for the children, parent(s)/legal guardian, or for the researcher.

Intervention

If children do not receive a conclusive diagnosis after the first consultation at the emergency room and need to return for a second consultation, then they will be randomized. After randomization, the intervention group will receive both laxatives and enemas, while the control group receives no laxatives or enemas. If children need to return for a third consultation, the children in the intervention group will receive only laxatives without an enema, while the children in the control group will again receive no study medication. We decided against prescribing enemas to children in the intervention group twice, because we expect a reduced effect after a second time and adverse events may occur.

The dosage of laxatives and enemas will be adjusted according to the children's ages. Children between 5 and 10 years will receive 4 g Macrogol 4000 twice, while children older than 10 years will receive 10 g Macrogol 4000 twice. In addition, children between 5 to12 years will receive a 10 mL sorbitol enema, while children older than 12 years will receive a 133 mL sodium phosphate enema. As a safety precaution, children under the age of 12 years will receive the enema in hospital. The laxatives and sodium phosphate enemas for children older than 12 years can be administered at home.

Outcome measures

The primary outcome of this study will be the differences in the pain scores for abdominal pain as indicated by the child during the first, second, and possibly third consultation. We will

assess the pain scores by using a combination of the Wong-Baker FACES® Pain Rating Scale and the Visual Analogue Scale (VAS) for pain. The secondary outcome will be the time needed to reach the final diagnosis as expressed in the number of consultations. This involves the number of times a physician decides that an extra consultations is needed in combination with the number of times a child returns to hospital with persistent complaints of abdominal pain.

Additional data we will collect are the patients' characteristics, such as age, sex, weight, height, comorbidities, and medication use. The dosage and type of painkillers will be analyzed and used to correct the pain scores. In addition, we will collect information on stool frequency, stool consistency, and other diagnostic criteria for constipation to evaluate the accuracy of the constipation diagnosis. Finally, we will collect information on whether the children took the study medication correctly and whether children produced stool after taking the medication.

Study protocol

In Table 1 we provide an overview of the study schedule. After arrival at the emergency department, the child and parent(s)/legal guardian will be approached by the researcher and informed consent for the study will be obtained. During the standard clinical examination, the researcher will collect data on the outcome measures (e.g. the pain scores and patient characteristics). If a child receives a diagnosis after the first consultation at the emergency department, the study protocol ends and the child will receive standard care. The children who are not diagnosed after the first consultation and who need to return for a second consultation, will be randomly assigned to the intervention group or the control group. During the second consultation, we will again collect data on the outcome measures. If a child receives a diagnosis after the second consultation, the study protocol ends and the child will receive

standard care. If, after the second consultation, the physician is still unable to establish a diagnosis, and requires the child to return for a third consultation, then the child in the intervention group will receive only laxatives to be administered at home. During the third consultation, we will once again collect data on the outcome measures. After this consultation, the study protocol will end for all children, even if they need to come back for extra consultations. Between two to three months after the first consultation, the researcher will check the electronic patient file to see whether the child had returned to the emergency department with abdominal pain in the meanwhile.

Sample size

This trial will be a pilot study, because the necessary data to perform a sample size calculation are not available in the literature. Nevertheless, we propose to set out by including 30 children before possibly expanding the study.

Statistical analyses

All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain score, is an ordinal variable and will be reported as frequencies per points on the scale. The secondary outcome, the number of consultations required to arrive at a final diagnosis, is a non-parametric variable and will be presented as median with range. Other variables to be analyzed include the patient characteristics and use of painkillers. Categorical data will be reported as absolute numbers and percentages, parametric continuous data as means with SDs, and non-parametric continuous data as medians with ranges.

For the primary outcome, the Mann Whitney test will be used to analyze the difference the pain scores obtained between the first and second consultation by comparing the intervention

group with the control group. An ordinal logistic regression will be used for this comparison to correct for confounding factors, as the use of painkillers. The secondary outcome, the number of consultations required to arrive at a final diagnosis, will also be analyzed using the Mann Whitney test. A *P* value below 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

Data management

All data will be anonymized directly after collection and stored on a secure part of the network drive of University Medical Center Groningen. The hard copies of the informed consent forms will also be stored securely. Only authorized persons will have access to the data. In accordance with Dutch law, the data will be stored for 15 years.

Patient safety

Laxatives and enemas have proven to be safe and effective treatments for constipation in children [9,14]. We therefore do not we expect any adverse events in this study. Nonetheless, should an adverse event occur, then the child concerned shall be followed until the event is over. Depending on the adverse event, follow-up may require additional tests or medical procedures and/or referral to the general physician or a medical specialist. In addition, an annual safety report will be sent to the local Medical Research Ethics Committee of University Medical Center Groningen. As a result of the expected safety level of this study protocol, our local ethics committee waived the otherwise mandatory insurance for human test subjects.

Ethics approval and consent to participate

All interventions discussed in this study protocol are in accordance with the 1964 Declaration of Helsinki. The study is also approved by the Medical Research Ethics Committee of University Medical Center Groningen (2012/393). A written informed consent will be obtained from the parents/legal guardian of eligible children and/or from the children themselves, depending on their age.

DISCUSSION

Laxatives and enemas have proven to be effective and safe treatments for children with constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative attitude of Dutch parents towards such medication for their children, leading to a larger refusal rate on the part of parents than anticipated. In addition, not all children from the intervention group take their study medication according to protocol. Medication adherence is a familiar issue, also for chronic constipation in which case the adherence rate is around 38% for the first month [17]. We therefore decided in advance on a per-protocol analysis instead of an intention-to-treat analysis, so that a possible deviation from the study protocol would not influence the results. Nevertheless, as a result of these problems it is probably necessary to perform a larger multicenter study in the future. Perhaps even in another country where parents have a more positive attitude towards such medication for their children, so as to increase the power of the results. In that case, performing this study protocol with an intention-to-treat analysis could also provide the opportunity to investigate the effect of the new diagnostic method in practice.

Nonetheless, we have every confidence that this study protocol will prove that supporting fecal evacuation with laxatives and enemas will lead to a quicker diagnosis of constipation in children with abdominal pain and a more rapid relief of pain. We are of the opinion that this diagnostic method can reduce the number of misdiagnosed children with non-specific abdominal pain and who are left untreated for their constipation symptoms. In addition, if we were to recognize acute constipation more often in these children, we may prevent the development of chronic abdominal pain or chronic constipation [12,13], both conditions that are associated reduced quality of life [18,19].

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AUTHORS' CONTRIBUTIONS

Marjolijn E.W. Timmerman conceptualized and designed the study protocol, acquires data, and drafted the manuscript.

Monika Trzpis conceptualized and designed the study, and critically revised the manuscript for important intellectual content.

Paul M.A. Broens conceptualized and designed the study, and critically revised the manuscript for important intellectual content.

All the authors read and approved the final manuscript.

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COMPETING INTEREST STATEMENT

The authors declare that they have no competing interests.

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Table 1. Study schedule

	Time points			
	1st consultation at ED	**2nd consultation at ED**	**3th consultation at ED**	**Close-out**
Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

ED: emergency department

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ABSTRACT

Introduction: Many children with acute abdominal pain and suspicion of appendicitis are diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute constipation and acute appendicitis because of similar symptoms and lack of diagnostic criteria. Consequently, constipation is often missed despite repeated consultations at the emergency department. We hypothesize that the diagnostic process can be improved and adequate treatment accelerated by supporting fecal evacuation in children with acute abdominal pain.

Methods and analysis: An unblinded randomized controlled trial including children between 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children who do not receive a diagnosis after the first consultation and who need to return for a second consultation will be randomized. The intervention group will receive laxatives and enemas, while the control group will receive no medication. If, after the second consultation, still no diagnosis is established and a third consultation is needed, then the intervention group will receive only laxatives and the control group will again not receive medication. The primary outcome will be the differences in abdominal pain scores obtained with FACES® Pain Rating Scale and the Visual Analogue Scale at first, second, and possibly third consultation. The secondary outcome will be the number of consultations needed to reach final diagnosis.

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METHODS AND ANALYSIS

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All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain score, is an ordinal variable and will be reported as frequencies per points on the scale. The secondary outcome, the number of consultations required to arrive at a final diagnosis, is a non-parametric variable and will be presented as median with range. Other variables to be analyzed include the patient characteristics and use of painkillers. Categorical data will be reported as absolute numbers and percentages, parametric continuous data as means with SDs, and non-parametric continuous data as medians with ranges.

For the primary outcome, the Mann Whitney test will be used to analyze the difference the pain scores obtained between the first and second consultation by comparing the intervention

group with the control group. An ordinal logistic regression will be used for this comparison to correct for confounding factors, as the use of painkillers. The secondary outcome, the number of consultations required to arrive at a final diagnosis, will also be analyzed using the Mann Whitney test. A *P* value below 0.05 will be considered statistically significant.

ETHICS AND DISSEMINATION

Data management

All data will be anonymized directly after collection and stored on a secure part of the network drive of University Medical Center Groningen. The hard copies of the informed consent forms will also be stored securely. Only authorized persons will have access to the data. In accordance with Dutch law, the data will be stored for 15 years.

Patient safety

Laxatives and enemas have proven to be safe and effective treatments for constipation in children [9,14]. We therefore do not we expect any adverse events in this study. Nonetheless, should an adverse event occur, then the child concerned shall be followed until the event is over. Depending on the adverse event, follow-up may require additional tests or medical procedures and/or referral to the general physician or a medical specialist. In addition, an annual safety report will be sent to the local Medical Research Ethics Committee of University Medical Center Groningen. As a result of the expected safety level of this study protocol, our local ethics committee waived the otherwise mandatory insurance for human test subjects.

Ethics approval and consent to participate

All interventions discussed in this study protocol are in accordance with the 1964 Declaration of Helsinki. The study is also approved by the Medical Research Ethics Committee of University Medical Center Groningen (2012/393). A written informed consent will be obtained from the parents/legal guardian of eligible children and/or from the children themselves, depending on their age.

DISCUSSION

Laxatives and enemas have proven to be effective and safe treatments for children with constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative attitude of Dutch parents towards such medication for their children, leading to a larger refusal rate (23%) on the part of parents than anticipated. In addition, there were some practical problems, especially during the evening and at night, in which many children (27%) had already left the hospital before randomization and/or receiving study medication because they did not want to wait any longer. Also, 37% of the children from the intervention group did not take their study medication according to protocol. Medication adherence is a familiar issue, also for chronic constipation in which case the adherence rate is around 38% for the first month [17]. We therefore decided in advance on a per-protocol analysis instead of an intention-to-treat analysis, so that a possible deviation from the study protocol would not influence the results. Nevertheless, as a result of the abovementioned problems we have only included 10 patients according to protocol since the start of the inclusion in February 2014, so it is necessary to perform a larger multicenter study in the future. Perhaps even in another country where parents have a more positive attitude towards such medication for their children, so as to increase the power of the results. In that case, performing this study protocol with an intention-to-treat analysis could also provide the opportunity to investigate the effect of the new diagnostic method in practice.

Nonetheless, we have every confidence that this study protocol will prove that supporting fecal evacuation with laxatives and enemas will lead to a quicker diagnosis of constipation in children with abdominal pain and a more rapid relief of pain. We are of the opinion that this diagnostic method can reduce the number of misdiagnosed children with non-specific abdominal pain and who are left untreated for their constipation symptoms. In addition, if we were to recognize acute constipation more often in these children, we may prevent the

development of chronic abdominal pain or chronic constipation [12,13], both conditions that are associated reduced quality of life [18,19].

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AUTHORS' CONTRIBUTIONS

Marjolijn E.W. Timmerman conceptualized and designed the study protocol, acquires data, and drafted the manuscript.

Monika Trzpis conceptualized and designed the study, and critically revised the manuscript for important intellectual content.

Paul M.A. Broens conceptualized and designed the study, and critically revised the manuscript for important intellectual content.

All the authors read and approved the final manuscript.

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COMPETING INTEREST STATEMENT

The authors declare that they have no competing interests.

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Table 1. Study schedule

	Time points			
	1st consultation at ED	**2nd consultation at ED**	**3th consultation at ED**	**Close-out**
Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

ED: emergency department

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Using laxatives and/or enemas to accelerate the diagnosis in children presenting with acute abdominal pain: a randomized controlled trial study protocol

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ABSTRACT

Introduction: Many children with acute abdominal pain and suspicion of appendicitis are diagnosed with constipation. Nevertheless, it can be difficult to differentiate between acute constipation and acute appendicitis because of similar symptoms and lack of diagnostic criteria. Consequently, constipation is often missed despite repeated consultations at the emergency department. We hypothesize that the diagnostic process can be improved, and adequate treatment accelerated by supporting fecal evacuation in children with acute abdominal pain.

Methods and analysis: An unblinded randomized controlled trial including children between 5 and 18 years old with acute abdominal pain and suspicion of acute appendicitis. Children who do not have a definitive diagnosis after the first consultation and who need to return for a second consultation will be randomized. The intervention group will receive laxatives and enemas, while the control group will receive no medication. If, after the second consultation, still no diagnosis is established, and a third consultation is needed, then the intervention group will receive only laxatives and the control group will again not receive medication. The primary outcome will be the differences in abdominal pain scores obtained with FACES® Pain Rating Scale and the Visual Analogue Scale at first, second, and possibly third consultation. The secondary outcome will be the number of consultations needed to reach final diagnosis.

Ethics and dissemination: Laxatives and enemas have proven to be safe and effective treatments for constipation in children. Adverse events are therefore not expected, however, should they occur, then the child concerned shall be properly followed and treated until the event is over. The local Medical Research Ethics Committee approved of this study and waived the otherwise mandatory insurance for human test subjects.

Trial registration: Dutch trial register (CCMO): NL44710.042.12. European trial registration (EudraCT): 2013-000498-56.

Keywords: constipation; acute appendicitis; diagnostic method; randomized controlled trial

What is known:

- Constipation is often missed in children with acute abdominal pain, despite repeated consultations at the emergency department.
- Differentiating between acute constipation and acute appendicitis in children with acute abdominal pain is troublesome due to similar symptoms.

What this study hopes to add:

- We hope to show that supported fecal evacuation can accelerate relief from pain in children whose acute abdominal pain results from constipation instead of appendicitis.
- We hope to accelerate and improve the diagnostic process of acute constipation in these children, resulting in less children misdiagnosed with non-specific abdominal pain.

INTRODUCTION

Acute abdominal pain is the third-leading cause of visits to emergency departments by children under 15 years, and is associated with high costs, especially when hospitalization is required [1]. For instance, in the United States of America, approximately 900.000 children visit an emergency department with acute abdominal pain and suspicion of appendicitis annually [2]. Nevertheless, only 30% of these children are eventually diagnosed with acute appendicitis [3], while constipation is diagnosed in 21% of girls and 18% of boys with acute abdominal pain [3].

It can be difficult to differentiate between constipation with an acute presentation and acute appendicitis, because the symptoms of constipation sometimes mimic those of acute appendicitis. Besides, there are no diagnostic criteria for acute constipation, unlike the Rome IV criteria for diagnosing chronic constipation [4]. In clinical practice, in order to exclude or confirm constipation, most physicians limit their questioning of patients presenting with acute abdominal pain on whether their bowel habits have changed recently or whether they are "normal", even though it is known that many people pay scarce attention to their bowel habits and/or are unaware of what "normal" stool frequencies or consistencies are [5,6]. In addition, to diagnose constipation physicians often avoid performing digital rectal examinations in children because of discomfort or fear on the part of the patients, and their own lack of adequate training or experience [7]. Moreover, additional investigations, such as abdominal X-rays to diagnose children with constipation, was strongly criticized in a number of studies [8,9,10]. Because the abovementioned methods to diagnose constipation are often not performed or carried out insufficiently, an extra consultation the following day can be recommended to determine whether the symptoms improve or worsen. Nonetheless, even after extra consultations many children are diagnosed with non-specific abdominal pain instead of constipation [11]. These misdiagnoses could result in chronic abdominal pain,

because the underlying cause, constipation, is left untreated [12,13]. We believe therefore that a better method is needed to either confirm or exclude constipation in children presenting with acute abdominal pain at the emergency department.

Laxatives and/or enemas are standard treatment for fecal disimpaction in children with constipation [9]. This combination of medications can provide a rapid relief of symptoms and has proven to be safe and adverse events rarely occur [9,14,15,16]. We hypothesize that by supporting fecal evacuation with laxatives and enemas in children suffering acute abdominal pain, but who were not diagnosed after first consultation, the diagnostic process could be accelerated. In case a child does indeed suffer from constipation, laxatives and/or enemas lead to rapid reduction of pain. In addition to the positive effect this has on the child's condition, the reduction of pain also points towards constipation as the cause of the abdominal pain. If a child does not suffer from constipation then laxatives and/or enemas will not provide significant relief of symptoms, indicating to the physician that constipation is less likely to be the cause of the abdominal pain.

Our objective with this randomized controlled trial is to study whether supporting fecal evacuation in children with acute abdominal pain, but without a definitive diagnosis after the first consultation at the emergency department, could accelerate and improve the diagnostic process.

METHODS AND ANALYSIS

Study design and setting

An unblinded randomized controlled trial at the emergency department of an academic hospital, the University Medical Center Groningen, in the Netherlands. This protocol describes a study which can be performed as a pilot study and as a final study with an increased sample size. The pilot study will allow to gain data required to perform power analysis, and in this way will allow the performance of adequately powered randomized follow-up study. The final study is required to evaluate our hypothesis and reach the goal of this study.

Participants

We intend to include children between 5 and 18 years who are referred to the emergency department with acute abdominal pain and suspicion of acute appendicitis. If children do not receive a definitive diagnosis after the first consultation, and need to return for a second consultation, then they will be randomized. Exclusion criteria are pregnancy and severe co-morbidity like malignancy, recent abdominal surgery, or known inflammatory bowel disease.

Recruitment

Children presenting at the emergency department with suspicion of acute appendicitis will be approached to participate in the study. First, the researcher will explain the study protocol to the parent(s)/legal guardian and the child. Subsequently, we will hand them the study brochure that was adapted so as to be readily understood by children. If, after having had some time to read the brochure and the opportunity to ask questions, the parent(s)/legal guardian and/or the child agree to participate in the study, we will ask them to sign the consent form. Dutch law requires that in case of children younger than 12 years old, only the

parent(s)/legal guardian need to sign the consent form. If children are between 12 and 16 years old, both children and their parent(s)/legal guardian are required to sign the consent form. In case of children older than 16 years, only the children are obliged to sign the consent form. Furthermore, if a child refuses to cooperate during the study, consent for further participation in the research will be withdrawn.

Randomization

Children will be randomized using sealed envelopes without any stratification factors. The researcher will randomly pick a sealed envelope from a sealed box located in the emergency room and will open it in the presence of the child and parent(s)/legal guardian. The study is not blinded for the children, parent(s)/legal guardian, or for the researcher.

Intervention

If children do not receive a conclusive diagnosis after the first consultation at the emergency room and need to return for a second consultation, then they will be randomized. After randomization, the intervention group will receive both laxatives and enemas, while the control group receives no laxatives or enemas. If children need to return for a third consultation, the children in the intervention group will receive only laxatives without an enema, while the children in the control group will again receive no study medication. We decided against prescribing enemas to children in the intervention group twice, because we expect a reduced effect after a second time and adverse events may occur.

The dosage of laxatives and enemas will be adjusted according to the children's ages. Children between 5 and 10 years will receive 4 g Macrogol 4000 twice, while children older than 10 years will receive 10 g Macrogol 4000 twice. In addition, children between 5 to12 years will receive a 10 mL sorbitol enema, while children older than 12 years will receive a

133 mL sodium phosphate enema. As a safety precaution, children under the age of 12 years will receive the enema in hospital. The laxatives and sodium phosphate enemas for children older than 12 years can be administered at home.

Outcome measures

The primary outcome of this study will be the differences in the pain scores for abdominal pain as indicated by the child during the first, second, and possibly third consultation. Specifically for the pilot study with a small sample size, the primary outcome will be whether or not there is a diminish in abdominal pain in the consecutive consultation, measured as a binary variable. We will assess the pain scores by using a combination of the Wong-Baker FACES® Pain Rating Scale and the Visual Analogue Scale (VAS) for pain. The secondary outcome will be the time needed to reach the final diagnosis as expressed in the number of consultations. This involves the number of times a physician decides that an extra consultation is needed in combination with the number of times a child returns to hospital with persistent complaints of abdominal pain.

Additional data we will collect are the patients' characteristics, such as age, sex, weight, height, comorbidities, and medication use. The dosage and type of painkillers will be analyzed and used to correct the pain scores. In addition, we will collect information on stool frequency, stool consistency, and other diagnostic criteria for constipation to evaluate the accuracy of the constipation diagnosis. Finally, we will collect information on whether the children took the study medication correctly and whether children produced stool after taking the medication.

Study protocol

In Table 1 we provide an overview of the study schedule. After arrival at the emergency department, the child and parent(s)/legal guardian will be approached by the researcher and informed consent for the study will be obtained. During the standard clinical examination, the researcher will collect data on the outcome measures (e.g. the pain scores and patient characteristics). If a child receives a diagnosis after the first consultation at the emergency department, the study protocol ends, and the child will receive standard care. The children suffering from acute abdominal pain, without a definitive diagnosis after the first consultation and who need to return for a second consultation, will be randomly assigned to the intervention group or the control group. During the second consultation, we will again collect data on the outcome measures. If a child receives a diagnosis after the second consultation, the study protocol ends, and the child will receive standard care. If, after the second consultation, the physician is still unable to establish a diagnosis, and requires the child to return for a third consultation, then the child in the intervention group will receive only laxatives to be administered at home. During the third consultation, we will once again collect data on the outcome measures. After this consultation, the study protocol will end for all children, even if they need to come back for extra consultations. Between two to three months after the first consultation, the researcher will check the electronic patient file to see whether the child had returned to the emergency department with abdominal pain in the meanwhile.

Sample size

This trial will be a pilot study, because the necessary data to perform a sample size calculation are not available in the literature. Nevertheless, we propose to set out by including 30 children before possibly expanding the study.

Statistical analyses

All analyses will be conducted in SPSS 23.0 for Windows (IBM SPSS Statistics, IBM Corporation, Armonk, NY) using a per-protocol analysis. The primary outcome, the pain score, is an ordinal variable and will be reported as frequencies per points on the scale. The secondary outcome, the number of consultations required to arrive at a final diagnosis, is a non-parametric variable and will be presented as median with range. Other variables to be analyzed include the patient characteristics and use of painkillers. Categorical data will be reported as absolute numbers and percentages, parametric continuous data as means with SDs, and non-parametric continuous data as medians with ranges.

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DISCUSSION

Laxatives and enemas have proven to be effective and safe treatments for children with constipation [9,14]. Nevertheless, during the inclusion of participants, we noticed a negative attitude of Dutch parents towards such medication for their children, leading to a larger refusal rate (23%) on the part of parents than anticipated. In addition, there were some practical problems, especially during the evening and at night, in which many children (27%) had already left the hospital before randomization and/or receiving study medication because they did not want to wait any longer. Also, 37% of the children from the intervention group did not take their study medication according to protocol. Medication adherence is a familiar issue, also for chronic constipation in which case the adherence rate is around 38% for the first month [17]. We therefore decided in advance on a per-protocol analysis instead of an intention-to-treat analysis, so that a possible deviation from the study protocol would not influence the results. We included the first patient in February 2014, however, as a result of the abovementioned problems we have only included 10 patients, as originally described in protocol. In the future however, it is necessary to perform this study in another country where parents have a more positive attitude towards such medication for their children. One might be surprised by the low number of patients presented in this protocol. We would therefore like to emphasize that this protocol has a twofold application; it can be used firstly as a pilot study in order to gain the data allowing power analysis, and secondly, it can be used for adequately powered follow-up study. The only difference between these the pilot and the final phase of this study will be the number of the included patients.

Nonetheless, we hope that final study performed according to our study protocol, will prove that supporting fecal evacuation with laxatives and enemas can accelerate the relief from pain in these children whose acute abdominal pain results from constipation. Moreover, such a relief from pain, upon supported evacuation, would afterwards allow the confirmation of the

diagnose of constipation in these children. Consequently, usage of our protocol may even reduce the number of misdiagnosed children with non-specific abdominal pain, who are left untreated for their constipation symptoms. In addition, if we were to recognize acute constipation more often in these children, we may prevent the development of chronic abdominal pain or chronic constipation [12,13], both conditions that are associated reduced quality of life [18,19].

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Enrolment	- Standard diagnostic procedures			
	- Eligibility screening			
	- Informed consent			
	- Allocation when diagnosis is unknown			
Intervention	- Intervention group: laxatives and enema	- Intervention group: only laxatives		
	- Control group: no study medication	- Control group: no study medication		
Assessments	- Patient characteristics			
	- Pain score, used medication, stool production	- Pain score, used medication, stool production	- Pain score, used medication, stool production	
				- Number of consultations

ED: emergency department