Preemptive Analgesia for Hemorrhoidectomy: Study Protocol for a Prospective, Randomized, Double-Blind Trial

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Study protocol

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Abstract

Background: Hemorrhoidectomy is associated with intense postoperative pain that requires the multimodal analgesia. It includes Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), acetaminophen and local anesthetics to reach the adequate pain control. There are data in literature preemptive analgesia could decrease postoperative pain after hemorrhoidectomy. The aim of this study is to assess the efficiency of preemptive analgesia with Ketoprofen 10 mg 2 hours before procedure per os with spinal anesthesia to decrease postoperative pain and the amount of used
analgesics.

Methods: Patients of our clinic who meet the following inclusion criteria are included: haemorrhoids grade III-IV and the planned Milligan-Morgan hemorrhoidectomy. After signing the consent all participants are randomly divided into 2 groups: the first one gets a tablet with 10 mg Ketoprofen, the second one gets a tablet containing starch per os 2 hours before surgery (72 participants per arm). Patients of both arms receive spinal anesthesia and undergo open hemorrhoidectomy. Following the procedure the primary and secondary outcomes are evaluated: opioid administration intake, the pain at rest and during defecation, duration and frequency of other analgesics intake, readmission rate, overall quality of life, time from the procedure to returning to work and the complications
rate.

Discussion: Multimodality pain management has been shown to improve pain control and decrease opioid intake in patients after hemorrhoidectomy in several studies. Gabapentin can be considered as an alternative approach to pain control as NSAIDs have limitative adverse effects. Systemic admission of ketorolac with local anesthetics also showed significant efficacy in patients undergoing anorectal surgery. We hope to prove the efficacy of multimodal analgesia including preemptive one for patients undergoing excisional hemorrhoidectomy that will help to hold postoperative pain level no more than 3-4 points on VAS with minimal consumption of opioid analgesics.

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Introduction

Anorectal diseases are mostly benign and do not affect life expectancy, so currently both patients and clinicians are extremely interested in performing one day surgery. Anorectal surgery itself causes certain discomfort, especially pain, long recovery period, and a decreasing quality of life for several months.

The pain appears as a result of endogenous and exogenous factors affecting on the peripheral nerves endings, and also the pathological central nervous system excitation. Any surgical intervention activates nociceptors with various stimuli including mechanical factors as a result of a prick or cut of the tissue, chemical factors as a result of exposure to inflammatory mediators, and thermal factors as a result of heating or cooling the tissue. Thus, any surgery is always accompanied by a pain syndrome with various pain severities.

In anorectal surgery, almost every patient experiences moderate/severe pain in the postoperative period, 12% of patients have severe pain throughout the recovery period, control of postoperative pain is still problematic in 5% of cases when a severe pain syndrome continues despite standard pain management. It leads to long hospital admission and to an opioid intake increase. [2] The problem of analgesia is still relevant for patients after anorectal surgery, because the diseases affect more than 50% of the population over 50 years. [6] Excisional hemorrhoidectomy is the most effective method of stage III-IV hemorrhoidal disease treatment. However it is associated with intense postoperative pain which decreases significantly quality of life in postoperative period and overall patients' satisfaction with treatment, increases time spend in hospital and opioid analgesics consumption [1, 4]. The pain after hemorrhoidectomy (HE) and other anorectal surgery depends on anal sphincter and puborectal muscles spasm, the type of intra and postoperative anesthesia, wound healing, surgical technique, the stool type and the patient's subjective perception. [10,11] According to pain management international guidelines the target level of postoperative pain should be 3–4 or less Visual Analogue Score (VAS) points [5].

Preemptive analgesia is aimed to prevent pain after surgery and affects several points of the "pain" cascade. [1] The most common non-narcotic analgesics that block the peripheral pain perception include NSAIDs, corticosteroids, and acetylsalicylic acid. Non-narcotic drugs that inhibit central sensitization include ketamine, acetaminophen, and some anticonvulsants (in particular, gabapentin). So multimodal analgesia could theoretically reduce pain to a minimum due to blocking all kinds of pain receptors. However, the preoperative use of even one type of analgesic contributes to pain relief and to the opioid consumption decrease after the intervention. [2, 7–9] One of the most commonly prescribed painkillers is non-steroidal anti-inflammatory drugs(NSAIDs), which have an adequate analgesic effect and even in acute pain can reduce the opioid dose by 18.3%. [12] Regarding Ketoprofen as an analgesic drug, none of the published studies describes anorectal surgery. However, Ketoprofen is widely used in spinal, orthopedic, general, dental and children surgery with successful outcomes. It significantly reduced opioid consumption (by 33%) and improved postoperative analgesia after spinal and abdominal surgery. [13–15,19] Patients with acute pain who have undergone dental surgery get a meaningful pain relief, a faster onset of effect, the highest peak effect and the longest duration of action using ketoprofen than other NSAIDs and analgesics. [16, 18] It also showed significant efficacy as preemptive analgesia comparing to the other drugs. [17] Ketoprofen is approved for use as an analgesic for treatment of mild to moderate pain in postoperative period and for chronic cancer pain in total daily doses up to 300 mg; the recommended initial dose is 25 to 50 mg every 6 to 8 hours. [20] Comparing Ketoprofen to acitaminophen the first one showed significantly better anti-inflammatory effect on the 3^{rd} and 6^{th} day after surgery and lower pain intensity. [21] In all mentioned above studies adverse effects related to ketoprofen were minor and infrequent.

Therefore adequate postoperative analgesia requires the multimodal approach including opioid analgesics, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), acetaminophen and local anesthetics. But there is no current standard on preemptive analgesia in anorectal surgery, although several studies report some regimens that seem to be effective.

Methods

2.1 Objective

The aim is to assess the effectiveness of preemptive analgesia with Ketoprofen 10 mg 2 hours before hemorrhoidectomy per os with spinal anesthesia to decrease postoperative pain and the amount of used analgesics.

2.2 Study design and setting

This is a prospective, randomized, double-blind, unicenter, superiority, parallel group 2-arm study with 1:1 allocation ratio conducted in Clinic of coloproctology and minimally invasive surgery of Sechenov University and surgical department of University Clinic of Moscow State University. It is on the recruitment stage. We are anticipating 144 patients of all genders from 18 to 75 years old in total who come to clinicы. Thus, in this case, a double-center design can assure sufficient patient recruitment.

2.3 Eligibility criteria

Every patient included in the study must meet the following criteria:

- Symptomatic haemorrhoids grade III-IV
- Planned surgery: Milligan-Morgan hemorrhoidectomy

Patients who had contraindication or technical inability to perform subarachnoid anesthesia or decompensated somatic diseases, or refused to participate and pregnant women are not included. The written voluntary informed consent to participate is obtained from all eligible patients before randomization.

2.4 Interventions

2.4.1 Preoperative preparation.

2 hours before procedure every patient receives a medication. The research group receives Ketoprofen 10 mg per os; the control group receives a placebo.

2.4.2 Surgical technique

Under a spinal anesthesia the patient is placed in a modified lithotomy position on the back, with legs spread apart on supports. The operative field is treated with an antiseptic solution twice and draped. A complex of external and internal haemorrhoid or internal haemorrhoid only is excised with monopolar electrocautery or bipolar electrosurgery device. Haemorrhoid pedicle is tied with absorbable polyfilament suture. One, two or three nodes can be removed per a procedure.

2.5 The main outcome measures

The trial is conducting to evaluate the primary outcome of the opioid administration intake per day during first week postoperatively that are necessary to hold pain level no more than 3-4 VAS points in every patient. The study also assesses the following secondary outcomes: (1) the pain severity before and after defecation according to VAS on the 6, 12 and 24 hours after the procedure, then 2 times per day up to 7th postoperative day, (2) duration and (3) frequency of other analgesics intake (systemically and topically) during the first week postoperatively, (4) readmission rate and (5) overall quality of life on the 7th and 30th days, (6) time from the procedure to returning to work and (7) the complications rate (i.e. bleeding, retention of urine, infectious complications) in early postoperative period (30 days after procedure). Overall quality of life will be assessed with patient-reported questionnaire Short Form 36 (SF-36). A total score in each of 8 sections will be calculated and transformed into a 0-100 scale with a score of zero equivalents to maximum disability and a score of 100 equivalents to no disability.

All patients are scheduled to return to the ambulatory clinic on 7 and 30 days after the surgery. During these visits, postoperative data is collected and digital rectal examination is performed. If a patient fails to follow-up, the researcher may contact the patient by all means available (phone, email, or mail) to ascertain whether the patient has had any complications and/or adverse events that were treated at another hospital. If the researcher is unsuccessful in contacting the patient, the patient will be considered as lost to follow-up.

2.6 Participant timeline

For schedule of enrolment, interventions, and assessments see Table 1.

2.7 Sample size

Considering that this is a superiority study, the sample size was calculated using 1-sided Blackweder test. According to published data, the incidence of opioids intake after hemorrhoidectomy is varies from 20 to 30% [22]. The expected incidence of opioids intake after hemorrhoidectomy with preemptive analgesia is not more than 10%. The purpose of this study is to show that the opioids intake in patients with preemptive analgesia is lower than without it. Considering that a = 0.05; the statistical power of the study is 80%; the patients are randomized into 2 groups with 1:1 allocation ratio; the noninferiority margin D = 5%, the required sample size is 144 patients (72 patients in each of the 2 groups).

2.8 Recruitment

All patients diagnosed with HD II-III stage will be considered for this study.

2.9 Assignment of interventions

Participants will be randomly assigned to either control or experimental group with a 1:1 allocation ratio using cluster randomization with a computerized random number generator. All subjects will be allocated any interventions. The experimental group receives a tablet with 10 mg Ketoprofen, the control one receives a tablet containing starch per os 2 hours before surgery (72 participants per arm). [see Figure1]

The investigator who doesn't operate generates the allocation sequence, enrolls participants and obtain the informed consent, and assigns participants to interventions. The surgeon and the anesthesiology team are blinded.

All relevant data from patient chart except patients' names will be transferred into an electronic case report form (eCRF). The eCRF should contain results of all the screening procedures, including patient history and demographics, imaging studies, filled-out questionnaires, operation note, and postoperative rounds during patient stay in in the surgical ward.

2.10 Data collection, management, and analysis

All data will be collected prospectively using eCRFs designed for this trial. The reasons for withdrawal will be documented. The investigator will attempt to contact each participant at least 3 times during each follow-up window before declaring them lost for observation. The study exit form will be recorded in the eCRF. All prior data will be analyzed within the research.

All patients will receive clarifications of all the study procedures, and will be able to discuss them with the primary investigator. All patient data will be handled according to the principles of doctor–patient confidentiality, the subjects will be anonymized and analyzed with individual identifier numbers transcribed into eCRF.

2.11 Statistics

Quantitative variables are described as means with standard deviations, medians, range or interquartile range as appropriate. Categorical variables are described in absolute numbers and percentages. The statistical analysis of the quantitative variables, with independent groups, is performed with the parametric Student's t-test, provides that its conditions for application are met. Otherwise, the non-parametric Mann-Whitney U-test is used. Statistical analysis for categorical variables is performed using the Pearson $\chi 2$ test or the Fisher exact test. Specifically, the above methods are used to compare the two groups in terms of baseline characteristics in order to assess whether the randomization has been effective.

2.12 Data monitoring.

There is no data monitoring committee designated to this trial. Any adverse and serious adverse events will be immediately reported to the principal investigator and the primary sponsor.

2.13 Ethical approval

This study is conducted in accordance to the principles of the Declaration of Helsinki. The study protocol is approved by the Local Ethics committee of Sechenov University. [see Additional file1]

2.14 Protocol amendments

Any protocol amendments that may influence the conduct of the study, will be communicated to the local ethics committee and study director, and will be uploaded to clinical trials.

2.15 Consent or assent

A member of the research team will obtain the consent form. All participants will be able to address their questions about the study to one of the members of the research team.

2.16 Confidentiality

All patient data will be secured at the study site. No one apart from the members of the research team will have access to any patient data, including anonymized eCRFs with a coded ID, as well as filled out questionnaires.

2.17 Declaration of interests.

The authors declare they have no competing interests.

2.18 Access to data.

No one apart from the members of the research team will have access to the final trial dataset.

2.19Dissemination policy.

Trial results will be e-mailed to all participants of the trial. Trial results will be disseminated to healthcare professionals via publication in a peer-reviewed scientific journal and by mass media, as well as conference papers to inform the public and stakeholders, and will be uploaded to the primary registry. We have no intention of granting public access to the full protocol, participant-level dataset, and statistical code.

Discussion

Multimodality pain management for anorectal surgery has been shown to improve pain control and decrease opioid requirement in several studies. Preoperative oral acetaminophen and gabapentin admission followed by intravenous ketamine in the early postoperative period resulted to significantly less pain level postoperatively and decreased the narcotics intake. [1] The valuable pain-reducing effect of gabapentin was also shown by Poylin [2]. Repressing central neuronal sensitization this anticonvulsant is widely used in acute and chronic pain managing and also as a replacement for opioid analgesics. The efficiency of gabapentin usage as postoperative pain inhibitor has demonstrated in several studies. [4] Gabapentin can be considered as an alternative approach to pain control as NSAIDs have limitative adverse effects. Place RJ [3] showed a significant decreasing of postoperative analgesics requirement in addition with reducing voiding problems by systemic admission of ketorolac with local anesthetics in patients undergoing anorectal surgery.

We hope to prove the efficacy of multimodal analgesia including preemptive one for patients undergoing excisional hemorrhoidectomy that will help to hold postoperative pain level no more than 3-4 points on VAS with minimal consumption of opioid analgesics.

Abbreviations

VAS - Visual Analogue Score

NSAIDs - Nonsteroidal Anti-Inflammatory Drugs

eCRF - electronic case report form

Declarations

Ethics approval and consent to participate:

The study protocol is approved by the Local Ethics committee of Sechenov University. Prior to randomization written informed consent is obtained from all patients.

Consent for publication: Not Applicable

Availability of data and materials: Not applicable.

Competing interests: The authors declare no competing interests.

Funding: The study has no funding.

Authors' contributions: Each author has made substantial contributions: TG, AD and EK to the conception design of the work; HL to the acquisition, EK and SM to analysis, HL to interpretation of data; AD and SM to the creation of new software used in the work; PT and TG have drafted the work or substantively revised it. Study Principal Investigator: PT. All authors have read and approved the manuscript.

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Tables

Table 1 Schedule of enrollment, interventions, and assessments.

Timepoint Action	Enrollment	Randomization	Interventions	Follow-up (1)*	Follow-up (1)**	Follow-up (3)***
Eligibility criteria	●					
Informed consent	●					
Physical examination	●					
Demographic characteristics	●					
Allocation		●				
Drug administration			●			
Procedure			●			
Primary outcome assessment				●	●	
Secondary outcomes assessment				●	●	●

*Follow-up (1) – the first postoperative day

**Follow-up (2) – the first week after procedure

***Follow-up (3) – postoperative day 30

Figures

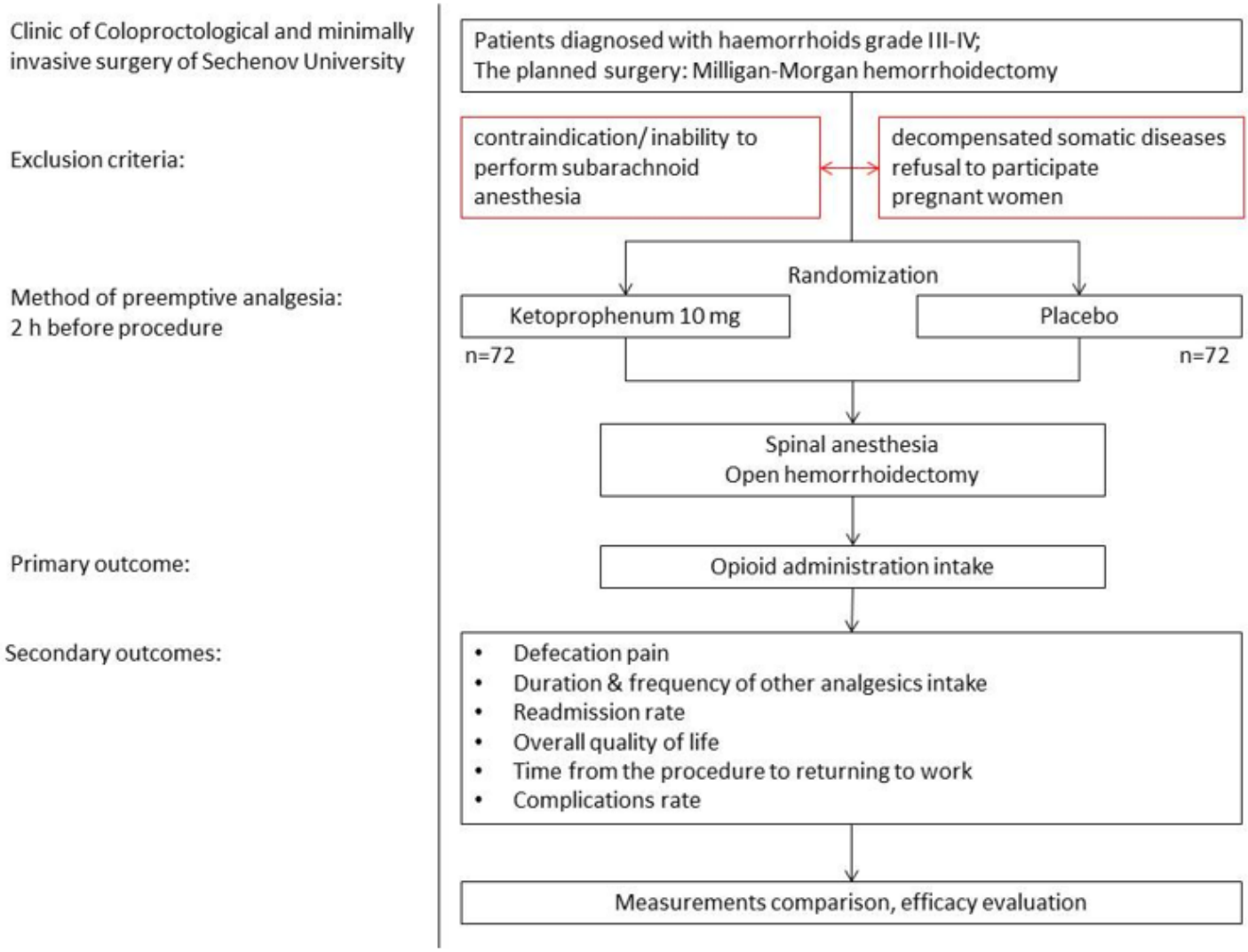

Figure 1

Trial flow diagram

Supplementary Files

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