CLINICAL STUDY PROTOCOL

The treatment of chronic anal fissures with fissure excision and Botulinum Toxin Type A injection

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1 Background and rationale

Chronic anal fissure is a linear ulcerative defect of the anoderm. Intense pain syndrome and resulting sphincter spasm create a vicious circle that prevents its epithelialization, the relaxation of the internal sphincter is therefore a required, pathogenetically justified step in any method for treating anal fissure. This disease is mostly affecting young people aged 30 to 50, irrespective of gender. Also, there was a trend towards increase in the number of patients hospitalized with a diagnosis of chronic anal fissure, by 35.6% over the past 5 years.

The “golden” standard for the elimination of the internal sphincter spasm in world practice is a lateral subcutaneous sphincterotomy. The disadvantage of this method is the development of anal incontinence in some patients, which incidence is 8-30% based on the existing original studies.

The study performed by Parellada C. et al. (2004) showed the highest incidence of anal sphincter insufficiency, in 44% of patents. In a meta-analysis by Chen H. L. et al. (2017), the use of this method is associated with the development of persistent insufficiency of the anal sphincter in 19.5% of cases. The severity of insufficiency by the Wexner scale ranges from 1 to 14 points and persists for 6 years. Therefore, the treatment of anal fissure remains one of the unresolved problems of modern medicine and makes us to search new less traumatic methods.

In 1992, Sohn N. et al. proposed the method of pneumodivulsion instead of sphincterotomy.

In a study comparing 2 methods the incidence of insufficiency after sphincterotomy was 16% after 6 weeks, and 12.5% after pneumodivulsion, and 14% and 0% in a year ($P < 0.0001$), respectively. The severity of anal incontinence after 6 weeks by the Wexner scale in the pneumodivulsion group did not exceed 3 points, in the sphincterotomy group it reached 6 points, after a year - 0 points and 13 points, respectively.

In 2010, Bagdasaryan L.S. proposed a modified technique, the essence of which is dosed pneumodivulsion adjusted for the initial diameter of the anal canal. This clinical prospective study showed that a year after pneumodivulsion no case of anal sphincter insufficiency were found, in contrast to sphincterotomy, after which incontinence disorder was in 12% of patients. However, this study does not show the severity of anal sphincter insufficiency in the early postoperative period.

In 1995, Li L. et al. conducted a study to investigate the damaging effect of anal stretching on the external anal sphincter. The study showed that anal divulsion leads, first of all, to swelling of the nerve fibers and impaired blood circulation in the external anal sphincter, and further to traumatization of muscle tissues and necrosis of the fibers.

The drug relaxation of the internal sphincter allows to avoid irreversible damage to the rectal obturator. For this purpose, organic nitrates and calcium channel blockers are most commonly used. Their significant disadvantage is their low efficiency compared to placebo (the effectiveness of nitroglycerin ointment is 48.9%, placebo - 35.5%), as well as significant side effects and the need for frequent use.

The injection of botulinum toxin type A for the treatment of patients with chronic anal fissure was firstly used in 1993. According to the latest literature data, the efficcasy of neurotoxin ranges from 33% to 96%, but there is still no unified standard method for drug injection. From the meta-analysis, the dosage of botulinum toxin and the number of injection points do not affect the treatment efficacy. Thus, it was decided to conduct a randomized study with a minimum dosage of 10 IU BoNTA.

There is also evidence in the literature that the anal sphincter pneumodivulsion technique effectively eliminates the internal sphincter spasm without anal incontinence. It was therefore chosen as the reference method.

Considering the above facts, we conducted this study.

2 Objectives

Study objective: To improve treatment outcomes in patients with chronic anal fissure.

Study tasks

1. To compare the treatment efficacy in patients after anal fissure excision with the total dose of 10 IU botulinum toxin type and anal sphincter pneumodivulsion with anal fissure excision.

2. To assess the pain syndrome in patients with chronic anal fissure and sphincter spasm after fissure excision using total dose of 10 IU BoNTA and anal sphincter pneumodivulsion with fissure excision.

3. To access the effect of botulinum toxin type A and the method of pneumodivulsion on the severity of clinical manifestations of anal sphincter insufficiency.

4. To perform a comparative assessment of the functional treatment outcomes in patients by profilometry and their dynamics after the elimination of the internal sphincter spasm by profilometry using total dose of 10 IU BoNTA and anal sphincter pneumodivulsion.

5. To compare the long-term treatment outcomes in patients with chronic anal fissure and sphincter spasm after injection of botulinum toxin type A in a total dose of 10 IU and after anal sphincter pneumodivulsion.

6. To evaluate the effect of increased dose of botulinum toxin type A (total of 40 units) on immediate treatment outcomes in patients with chronic anal fissure and sphincter spasm.

3 Study design - Data to be collected

The FSBI A.N. Ryzhikh Scientific Medical Research Center for Coloproctology of the Ministry of Healthcare of Russia has conducted a prospective, single-center, randomized study enrolling 80 patients with chronic anal fissure and sphincter spasm. Patients were randomized in groups by a random number generation using computer software. The main group included 40 patients subjected to the internal sphincter relaxation with botulinum toxin type A; the control group included 40 patients subjected to pneumodivulsion of the anal sphincter using the standard procedure.

The primary end point of the study is to achieve significant differences in the incidence of anal incontinence on day 60 of the postoperative period. Secondary end points are the intensity of the pain syndrome after surgery; the incidence and structure of postoperative complications; the incidence and severity of weakening of the anal sphincter by the Wexner scale on day 60; the duration of transitory postoperative incontinence; outcomes of the functional state of the rectal obturator according to profilometry data before surgery and in the postoperative period on days 7 and 60; the incidence and time of postoperative wound epithelization.

All patients included in the study underwent profilometry: before the surgery, on days 7 and 60 after the surgery. Before surgery and daily afterwards, the patients assessed the pain syndrome using VAS and answer questions using Wexner scale. On day 60, the treatment outcomes were evaluated, and the patients underwent anoscopy. For two months after the surgery, taking painkillers was assessed.

The patients in the main group after fissure excision were injected with botulinum toxin type A, free of complexing proteins, at 3 and 9 o'clock position with 5 units of the drug (total of 10 units) using U100 insulin syringe. The patients in the control group underwent surgical removal of the anal fissure with pneumatic balloon dilation to relax the sphincter. Under spinal anaesthesia at lithotomy position the appropriate graduated cone was inserted in anus by rotating motions under pressure not exceeding 2 kg until the maximum contact with anal canal walls. Each cone graduation corresponded to the certain diameter of the anal canal. Thereafter, the measuring device was removed and replaced with pneumatic balloon of the appropriate diameter covered with latex and lubricated with liquid paraffin. The balloon was gradually opening under air pressure (for 1 minute) up to 0.7 bar until reaching its maximum diameter and pneumatic balloon dilatation of anal sphincter was performed for 7 minutes. Thereafter, the balloon was deflated and removed from the anus. After that the anal canal and then surgical site were treated with aqueous chlorhexidine solution. Then, sparing surgical removal of anal fissure without internal anal sphincter incision was performed using electrocoagulation via a rectal speculum.

Further 28 patients were excluded from the study for various reasons. Twenty-eight patients of the main and 24 patients of the control groups met the Protocol and passed all tests, which allowed to reach the primary end point of the study.

3.1 Inclusion criteria

Subject enrolled must meet the following criteria:

- Patients with chronic anal fissure and internal sphincter spasm;
- Patients aged 18 to 70;
- Informed consent of the patient to participate in the study;

3.2 Exclusion criteria

The subject who meets the following criteria are excluded:

- Presence of rectal fistulas;
- Necessity of sclerotherapy of internal hemorrhoids;
- Refusal of examination.

4. Forms and procedures for collecting data and data managing

Data collection was carried out using MS Access DBMS.

Nonparametric continuous data were described by medians and quartiles. The Mann-Whitney test was done for intergroup comparison. Parametric continuous data were described by mean and standard deviation. t-test was used for intergroup comparison. The type of distribution of continuous data was determined by the Shapiro-Wilk test. Binary data were compared by a two-tailed Fisher test. The analysis was carried out in the statistical program Statistica v. 13.0 (Tibco, USA). Bonferoni multiple-comparison correction was used when comparing more than two groups. The analysis of continuous data in dependent groups was performed by the signed test. Factor analysis was carried out using logistic regression.

4.1. Patient protection

The study was approved by the local ethics committee and fully complies with GCP criteria.

4.2. Subject identification – Personal Data protection

Patient data was blinded, and an identification number was used to identify patients.

4.3. Informed consent

All patients were informed about the study objectives, possible adverse events, procedures, and possible hazards. They were informed of the strict confidentiality of their data, but that their medical records could be reviewed for research purposes by authorized persons other than their physician. It should be emphasized that participation is voluntary and that the patient may opt out of further participation in the study whenever they wish. This will not affect the subsequent treatment of the patient. Documented informed consent was obtained for all patients included in the study. The written informed consent form is signed and dated personally by the patient or the patient's legal representative. It should be highlighted, that participation is voluntary and that the patient may withdraw from the study at any time. It will not affect the further treatment of the patient. Documented informed consent was obtained for all patients included in the study. The written informed consent form is signed and dated personally by the patient or the patient's legal representative.

5. Conflict of Interest

Any investigator and/or research staff member who has a conflict of interest with this study (patent ownership, royalties, or financial gain more remarkable than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest.

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