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# Experience of Two-Stage Treatment of Rectal Fistulas Using Low-Thrombin Fibrin Glue "Kriofit"

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**Aim:** to improve the results of treatment of patients with rectal fistula.
**Materials and methods.** Twenty-eight patients with rectal fistulas were included in the study — 20 (71,4 %) men and 8 (28,6 %) women, average age — 40 (24–68) years. Based on examination and transrectal ultrasound data, 13 (46.4 %) patients had intrasphincteric fistulas and 15 (53.6 %) had transsphincteric fistulas. All patients underwent prehospital transrectal ultrasound and sphincterometry to assess the functional state of the anal sphincter, and the SF-36 quality of life questionnaire and Wexner scale assessing the functional status of the anal sphincter were analyzed. All patients, included in the study, had straight fistulous passage, without collections and significant scarring of the anal canal. Patients underwent two-stage surgical treatment using low-thrombin fibrin glue "Kriofit". Follow-up of the patients was carried out on days 7, 14, 21 and included collection of complaints, examination of the perianal area, finger examination of the rectum. In the postoperative period, the intensity of pain syndrome was assessed using the visual analog scale of pain. On days 30 and 90 control transrectal ultrasound, sphincterometry, assessment of Wexner scale and patients' quality of life by SF-36 questionnaire on days 7 and 30 after the operation were performed.
**Results.** There were no intraoperative and early postoperative complications among patients. The average bed-day was 6.8 (5–11) days. The follow-up periods ranged from 1 to 42 months. Disease recurrences were diagnosed in 3 (10.7 %) patients. According to the sphincterometry data, no anal holding dysfunction was detected in any of 28 patients.
**Conclusion.** The results of our study have shown that the division of preliminary surgical treatment of the fistulous passage followed by local anti-inflammatory treatment and filling of the wound canal with two-component fibrin glue with low thrombin content "Kriofit" into two stages effectively increases the results of the proposed technique. The use of fibrin glue as a sphincter-preserving technique makes it possible to exclude the development of postoperative anal incontinence, and new technologies and materials reduce the risk of disease recurrence.
**Keywords:** minimally invasive treatment, chronic paraproctitis, fistula, anal sphincter incontinence, fibrin glue
**Conflict of interest:** the authors declare that there is no conflict of interest.

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## Опыт двухэтапного лечения свищей прямой кишки с применением низкотромбинового фибринового клея «Криофит»

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**Цель исследования:** улучшить результаты лечения пациентов со свищами прямой кишки.
**Материалы и методы.** В исследование включены 28 пациентов со свищами прямой кишки. Из них 20 (71,4 %) мужчин и 8 (28,6 %) женщин, средний возраст которых составляет 40 (24–68) лет. На основании данных осмотра и трансректального ультразвукового исследования (ТРУЗИ) у 13 (46,4 %) пациентов свищи были интрасфинктерные, а у 15 (53,6 %) — транссфинктерные. Всем пациентам на догоспитальном этапе выполнялось ТРУЗИ и сфинктерометрия для оценки функционального состояния запирательного аппарата прямой кишки, также проводился анализ опросника качества жизни SF-36 и шкалы Векснера, оценивающей функциональное состояние запирательного аппарата прямой кишки. У всех пациентов, включенных в исследование, свищевой ход был прямым, без затеков и выраженных рубцовых изменений анального канала. Пациентам проводилось двухэтапное хирургическое лечение с применением низкотромбинового фибринового клея

«Криофит». Последующее наблюдение за пациентами осуществлялось на 7, 14 и 21-й дни и включало в себя сбор жалоб, осмотр перианальной области, пальцевое исследование прямой кишки. В послеоперационном периоде с помощью визуальной аналоговой шкалы боли проводилась оценка интенсивности болевого синдрома. На 30-й и 90-й дни проводилось контрольное ТРУЗИ, сфинктерометрия; на 7-й и 30-й дни после операции — оценка шкалы Векснера и качества жизни пациентов по опроснику SF-36.

**Результаты.** Интраоперационных и ранних послеоперационных осложнений у пациентов не было. Средний койко-день составил 6,8 (5–11) дня. Сроки наблюдения — от 1 до 42 месяцев. Рецидивы заболевания диагностированы у 3 (10,7 %) пациентов. По данным сфинктерометрии у всех 28 пациентов не выявлено нарушений функции анального держания.

**Заключение.** Результаты нашего исследования показали, что разделение предварительной хирургической обработки свищевого хода с последующим местным противовоспалительным лечением и пломбировки раневого канала двухкомпонентным фибриновым клеем с низким содержанием тромбина «Криофит» на два этапа эффективно повышает результаты предлагаемой методики. Применение фибринового клея как сфинктеросохраняющей методики позволяет исключить развитие послеоперационной анальной недостаточности, а новые технологии и материалы снижают риск развития рецидива заболевания.

**Ключевые слова:** малоинвазивное лечение, хронический парапроктит, свищ, недостаточность анального сфинктера, фибриновый клей

**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.

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## Introduction

According to various data, the incidence of rectal fistulas is from 1.2 to 2.8 cases per 10,000 population per year. This pathology most often occurs in the working age from 20 to 50 years, which causes its high social significance. According to statistics, men suffer more often than women in the ratio of 2:1 [1–4].

Surgical treatment — the only way for a patient to recover — involves the elimination of the fistulous passage together with the internal fistulous opening. To date, there is a large arsenal of various surgical techniques for the treatment of rectal fistulas. However, almost all these methods are inevitably associated with traumatization of the anal sphincter, which leads to the risk of anal incontinence. Thus, even when performing plastic surgeries with mucosal-muscular flap relegation, which allows minimizing the trauma of anal sphincter, the incidence of anal incontinence reaches 35 % [6], and when using the ligature method — 63 % [5]. Therefore, the development and introduction into clinical practice of minimally invasive methods of rectal fistula treatment, which could significantly reduce the probability of damage to the anal sphincter, continues. One of such methods is filling the fistulous passage with fibrin glue.

Fibrin glue consists of fibrinogen, thrombin, and calcium ions. When fibrinogen is broken down into fibrin monomers, a fibrin clot is formed and stabilized in the presence of calcium ions and plasma transglutaminase (factor XIII). The fibrin glue stimulates the migration and proliferation of the patient's fibroblasts and pluripotent endothelial cells from adjacent tissues. Within 1–2 weeks, plasmin from surrounding tissues lyses the fibrin clot, replacing it with synthesized collagen [1].

The first results of effective application of biological glue in patients with rectal fistulas were presented by a group of authors led by A. Hjortrup in 1991. The absence of disease recurrence was noted in 52 % of patients, and the authors demonstrated the possibility of repeated application of the technique without risk to the patient [2]. This work showed the potential of this treatment method and gave impetus for several other comparative studies. These studies compared the technique with classical surgical treatment methods and evaluated the effectiveness of the method depending on the type of fistula. Studies have shown that the method is most effective in superficial fistulas without collection and pronounced scarring changes [7–11].

In a study by a group of American scientists led by R. Loungnarath (2004), treatment of rectal fistulas using fibrin glue was performed on 42 patients, three people were subsequently excluded from the study; 12/39 (31 %) patients achieved recovery [12]. The recovery rates in patients with primary interventions were 38 % (8/21 patients), and in the group of patients who had previously undergone surgical interventions, — 22 % (4/18 patients). At repeated application of fibrin glue the treatment efficiency amounted to 12.5 %. According to the authors, the use of fibrin glue in the treatment of complex fistulas has low

efficiency, most recurrences of the disease are diagnosed within three months after the intervention. However, given the low invasiveness and relative simplicity of the procedure, the researchers felt that fibrin glue should be considered as a first-line treatment for patients with complex rectal fistulas.

In a study by J.M.C. Yeung et al. (2010), involving 40 patients with rectal fistulas (28 (70 %) — with complex fistulas and 12 (30 %) — with simple fistulas), 8/28 (29 %) patients with complex fistulas and 5/12 (42 %) with simple fistulas achieved recovery and no recurrence of disease during a follow-up period of up to three months [13].

The authors believe that the use of fibrin glue is most justified as a first-line treatment for simple rectal fistulas, while repeated use of fibrin glue is unlikely to be successful and will require other treatment methods in the future. According to the researchers, the method is minimally invasive and does not affect the structures of the anal sphincter, and the risk of complications is minimal, but its effectiveness is reduced in the treatment of complex rectal fistulas.

In 2011, a two-stage method of surgical treatment of rectal fistulas with the use of biological glue was developed and patented in the National Medical Research Center of Coloproctology named after A.N. Ryzhikh of the Ministry of Health of the Russian Federation (patent No. RU2579629C1). The novelty of the method consisted in dividing the surgical intervention into two parts: the first stage — radio-wave treatment of the fistulous passage, the second one — filling of the wound canal with fibrin glue. Subsequently, a study was conducted that showed the effectiveness of the proposed technique [14]. It should be noted that all studies used fibrin glues of similar composition with high thrombin content (more than 500–1000 IU).

In 2015, a domestic two-component fibrin glue "Kriofit" with low thrombin content (40 IU) was developed. The interaction of keratinocyte cells with low thrombin fibrin glue was studied, which showed a direct correlation between the amount of thrombin and the rate of penetration of the patient's own cells into the clot matrix. Low thrombin content promotes easier penetration of the surrounding tissue cells into the fibrin clot, thereby accelerating the processes of clot implantation and regeneration [15].

However, in the world literature there are no works devoted to the evaluation of the effectiveness of two-stage methods of rectal fistula treatment with the use of low thrombin fibrin glue, so **the aim of our study** was to investigate the effectiveness of the use of two-component fibrin glue "Kriofit" in the treatment of intra- and transsphincteric rectal fistulas and to evaluate the frequency of the development of incontinence of the anal sphincter.

## Patients and methods

From June 2019 to the present time, in the National Medical Research Center of Coloproctology named after A.N. Ryzhikh of the Ministry of Health of the Russian Federation a prospective non-randomized study has been conducted. At present, the experience of treatment of 28 patients with rectal fistulas has been accumulated. Among them 20 (71.4 %) men and 8 (28.6 %) women, average age — 40 (24–68) years. All patients at the prehospital stage underwent transrectal ultrasound and sphincterometry to assess the functional state of the rectal fistula. The use of the SF-36 quality of life questionnaire and the Wexner scale assessing the functional state of the sphincteral closure apparatus was also analyzed. Based on the examination and transrectal ultrasound data, it was revealed that 13 (46.4 %) patients had intrasphincteric fistulas and 15 (53.6 %) had transsphincteric fistulas. All patients included in the study, had straight fistulous passage, without collections and marked scarring of the anal canal (Table).

According to the sphincterometry data, no patient in the preoperative period had anal incontinence. Thus, the average pressure in the anal canal at rest and the maximum pressure in the anal canal during volitional contraction before surgery were 38 (36–46) and 146 (132–239) mmHg, respectively.

## Surgical technique

### *The first stage*

In the position of the patient for lithotomy under local infiltration anesthesia through the external fistulous opening, a ball electrode of the radio-wave device is introduced through the external fistulous opening, which under the control of a finger inserted into the lumen of the intestine, is carried along the fistulous passage to the internal fistulous opening. Then at a speed of 1 mm/s the electrode is withdrawn with simultaneous coagulation of the internal fistulous opening and the fistulous passage (Fig. 1).

After that, with the use of a Folkman spoon, curettage of the treated fistulous passage is performed, and the wound canal is washed with trypsin or chymotrypsin 1–2 times a day for the next 3–5 days, after which the second stage of treatment is performed.

***Table.*** Characteristics of the study group of patients ($n$ = 28)
***Таблица.*** Характеристика исследуемой группы пациентов ($n$ = 28)

| **Parameter / *Показатель*** | | **Number of patients / *Количество пациентов*** |
|---|---|---|
| Gender / *Пол* | Males / *мужчины* | $n$ = 20; 71.4 % |
| | Females / *женщины* | $n$ = 8; 28.6 % |
| Age, years / *Возраст, лет* | | 40 (24–68)* |
| Body mass index, kg/m² / *Индекс массы тела, кг/м²* | | 27.1 (18.3–36.1)* |
| History of illness, months / *Анамнез заболевания, мес.* | | 4 (1–84)* |
| Type of fistula / *Тип свища* | intrasphincteric / *интрасфинктерный* | 13 (46.4 %) |
| | transsphincteric / *транссфинктерный* | 15 (53.6 %) |
| Length of fistula tract, mm<br>*Протяженность свищевого хода, мм* | | 22 (8–45)* |
| Diameter of the internal fistula opening, mm<br>*Диаметр внутреннего свищевого отверстия, мм* | | 3 (1–5)* |

***Note:*** * — mean and interquartile range.
***Примечание:*** * — среднее значение и межквартильный размах.

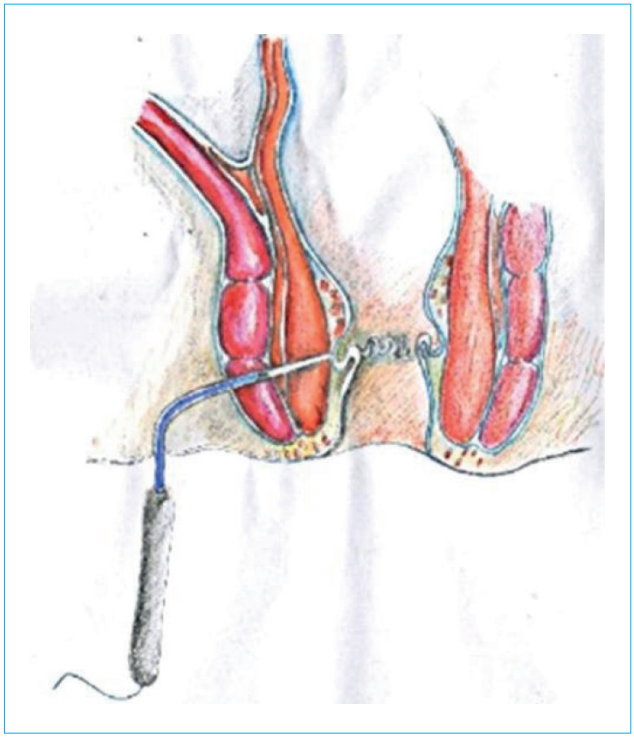

***Figure 1.*** Treatment of the fistula tract with a radio wave apparatus (stage 1)

***Рисунок 1.*** Обработка свищевого хода радиоволновым аппаратом (первый этап)

### *The second stage*

To determine the extent and patency of the wound canal, it is probed, based on which the length of the "guide" is calculated. This is necessary for effective filling of the wound canal with fibrin glue. Using a bulbous-end probe, the length of the wound canal is measured, and 2–3 mm is added to its length. The volume of fibrin glue required to fill the wound canal is calculated based on its length and diameter at the rate of 2 to 4 mL of the drug to treat the fistulous passage. Ten minutes before injection, the fibrin glue is thawed at room temperature to a liquid state, after which the system is assembled to ensure the introduction of the glue into the wound canal (Fig. 2).

In our study, the maximum length of the wound canal was 45 mm and the diameter was 4 mm, so the volume of glue used varied from 1.0 to 2 mL. In the position of the patient for lithotomy without anesthesia, a "guide" is passed through the external opening to the internal fistula opening along the wound channel under the control of a finger, then, when the "guide" is removed, fibrin glue is injected at a speed of 1 mm/s until the wound channel is completely filled. After one minute, clot formation occurs, after which the patient can be activated (Fig. 3).

Follow-up of patients is carried out on days 7, 14 and 21 and includes collection of complaints, examination of the perianal area, finger examination of the rectum. In the postoperative period, the intensity of pain syndrome is assessed using the visual analog scale of pain. On days 30 and 90 a control transrectal ultrasound examination and sphincterometry were performed, on days 7 and 30 after the operation — assessment of Wexner scale and patients' quality of life by SF-36 questionnaire.

The criteria of the method effectiveness were the absence of disease recurrence and signs of anal sphincteric deficiency in the distant terms after the operation.

***Figure 2.*** Two-component fibrin glue “Kriofit”

***Рисунок 2.*** Двухкомпонентный фибриновый клей «Криофит»

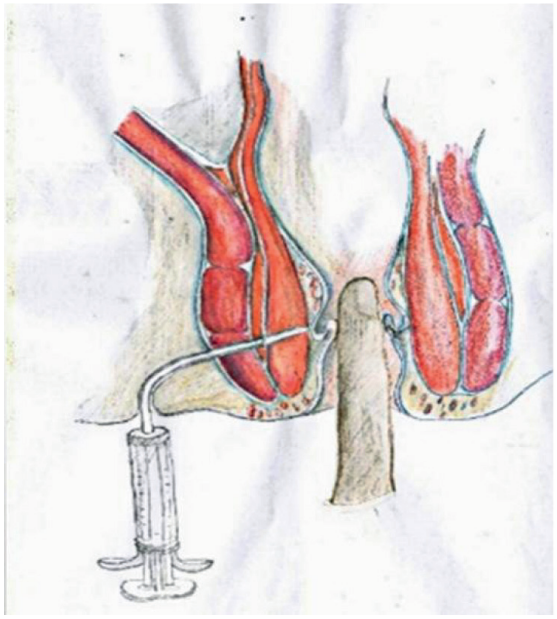

***Figure 3.*** Introduction of fibrin glue into the wound canal (stage 2)

***Рисунок 3.*** Введение фибринового клея в раневой канал (второй этап)

### Statistical processing of data

Office Excel 2016 program (Microsoft Corp., USA) was used to process the obtained data. Before analysis, empirical distributions of variables were tested for agreement with the law of normal distribution using the Shapiro — Wilk criterion. Normally distributed quantitative variables are presented as median (*Me*), and qualitative variables are presented as percentages.

## Results

There were no intraoperative and early postoperative complications in patients. At the stage of mastering the technique the treatment was performed in hospital, and later — in the conditions of day hospital. The average bed-day amounted to 6.8 (5–11) days, including the first surgical stage, washing of the wound canal for several days and its subsequent filling with two-component fibrin glue. After the first stage of intervention 17 (60.7 %) patients had mild pain syndrome (1–3 points on VAS), and 6 (21.4 %) patients had the pain syndrome corresponded to 4 points on VAS and steadily decreased by the third day after the first stage of surgery. The use of non-narcotic analgesics was required for 9 (32.1 %) patients. According to the data of sphincterometry performed one month after the operation, the average pressure in the anal canal at rest and the maximum pressure in the anal canal at volitional contraction were 41 (38–48) and 156 (142–182) mmHg, respectively, which testified to the absence of negative influence of the surgical intervention on the function of the anal sphincter.

The follow-up periods ranged from 1 to 42 months. Disease recurrences were diagnosed among 3 (10.7 %) patients. In 2 and 3 months after the operation 2 (7.1 %) patients with transsphincteric fistulas were diagnosed with recurrence of the disease. Subsequently, these patients underwent a repeat procedure, which was successful in one case. After a patient’s recurrence with a 45 mm long and 4 mm wide fistulous passage, excision of the fistula with suturing of the sphincter was performed. In 1 (3.6 %) patient with an intrasphincteric fistula, spontaneous migration of a fibrin clot occurred on the third day after surgery during the act of defecation. The patient with intrasphincteric fistulous passage, considering the insignificant extent of the wound canal, underwent excision of the fistula into the lumen of the intestine, further recurrence of the disease was not noted.

Thus, the application of two-stage method of treatment with the use of low-thrombin fibrin

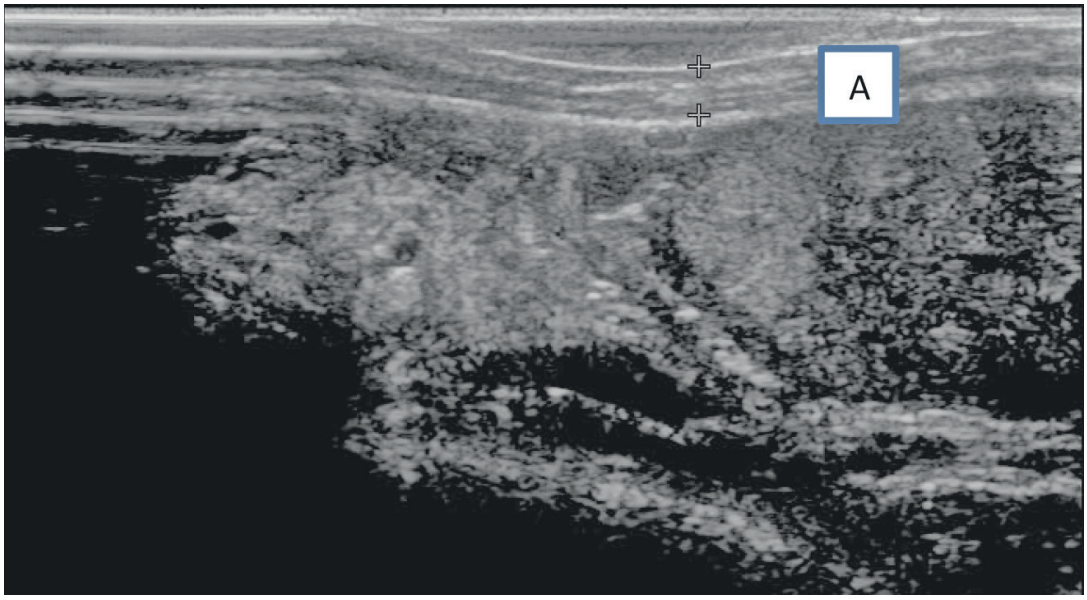


***Figure 4.*** Echogram of the anal canal on day 90 after the surgery (A — connective tissue at the site of the injected fibrin glue)

***Рисунок 4.*** Эхограмма анального канала на 90-й день после операции (А — соединительная ткань на месте введенного фибринового клея)

glue "Kriofit" allowed to achieve good results. Absence of signs of fistula recurrence was noted in 26 (92.8 %) patients.

Three months after surgery, all patients underwent sphincterometry to assess the functional status of the anal sphincter, which showed no signs of anal sphincter insufficiency.

The mean resting pressure was 48 ± 3 mmHg in women and 49 ± 5 mmHg in men. Transrectal ultrasound was performed for possible visualization of fibrin glue in the pararectal tissue. On day 90 after the operation, a hypoechogenic homogeneous in structure fiber band was observed in the pararectal tissue at the site of fibrin glue injection, which was represented by scar tissue (Fig. 4).

## Discussion

Analysis of the literature data shows an increasing interest in the use of minimally invasive techniques in the treatment of rectal fistulas.

In the scientific work conducted by O. Zmora et al. (2003), the use of fibrin glue was performed in 24 patients with complex rectal fistulas, recovery was achieved in 8/24 (33 %), and the follow-up period was 12.1 months. The authors note that the use of this minimally invasive technique made it possible to eliminate the fistula in 33 % of patients, avoiding complex surgical interventions, often associated with the possible development of anal sphincter insufficiency [16]. Also, good results of fibrin glue application in the treatment of rectal fistula in the literature review are reported by M.T. Swinscoe et al (2005). However, the authors, based on the works presented in the review, emphasize that the large difference in the effectiveness of fibrin glue in the treatment of rectal fistulas is associated with a different degree of complexity. The technique is more effective in simple fistulas [9].

Somewhat different results were obtained by British scientists led by I. Lindsey (2002). The study showed the effectiveness of fibrin glue in the treatment of simple rectal fistulas in 50 % of patients, and in complex fistulas — in 69 %. Fibrin glue has many advantages in the treatment of complex rectal fistulas, including the preservation of anal sphincter function, ease of application and the possibility of repeating the technique without risk to the patient, and the development of recurrence of the disease does not affect further treatment. Therefore, the authors believe that the use of fibrin glue is justified in the treatment of complex fistulas of the rectum, because it allows to achieve the elimination of the fistula and, most importantly, to minimize the risk of anal sphincter insufficiency [7].

In the study conducted by T. Adams et al. in 2008, the application of the technique using fibrin glue was performed in 36 patients with transsphincteric fistulas of the rectum. Recovery was achieved in 20 (56 %) after a single application of fibrin glue and in 2 (6 %) by repeating the procedure. At long-term follow-up (*Me* = 17.1 months), no recurrence of disease was noted in 16/17 (94 %) patients. Despite the rapid recovery, replacement of the fibrin clot by connective tissue occurs within several months, which provides reliable elimination of the fistula; only 1 patient developed a recurrence after a 3-month follow-up period [17].

Currently, based on the data of our own studies, we believe that the high incidence of recurrences is associated with the technical features of the technology used. Thus, a one-stage method of treatment, in which immediately after treatment of the fistulous passage is performed its curettage and lavage, followed by the introduction of fibrin glue, leads to a decrease in adhesion. A possible reason for the increased effectiveness of fibrin glue is the low concentration of thrombin ("Kriofit" 40 IU thrombin), which does not inhibit its own regenerative abilities in the area of the formed clot and to a lesser extent prevents biodegradation with replacement by its own tissues. This is also proved by the experimental work of A. Gugerell et al. (2012) [15]. The factors influencing the effectiveness of the technique, in our opinion, may be the length and diameter of fistulous passages. Thus, in the group of patients we studied, recurrence of the disease was noted in three patients. In 2 (7.1 %) of these patients, according to transrectal ultrasound data, the length of the fistulous passage was 45 and 41 mm, and the diameter was 4 and 3 mm, respectively. And in one patient with intrasphincteric fistula its length was 8 mm and width was 3 mm. We attribute the development of the above recurrences in two cases to the large extent of the fistulous passage, which is accompanied by uneven coagulation and difficulties in curettage of the fistulous passage, and in one case – to the small extent of the fistulous passage (< 10 mm), when there was no reliable adhesion of the fibrin clot to the walls of the wound canal, which led to the migration of the fibrin clot.

The results of our study showed that the division of the preliminary surgical treatment of the fistulous passage followed by local anti-inflammatory treatment and filling of the wound canal with two-component fibrin glue with low thrombin content "Kriofit" into two stages effectively improves the results of the proposed technique. The proposed method of rectal fistula treatment is a minimally invasive procedure, local anesthesia is necessary only for the first surgical stage of treatment, which is accompanied by a weakly expressed pain syndrome. According to the sphincterometry data, the intervention does not affect functional state of the anal sphincter and does not lead to the development of anal incontinence. It is also possible to safely repeat this manipulation.

## Conclusion

The minimally invasive method of treatment for rectal fistulas we used is minimally invasive and safe. The advantages of using fibrin glue in the treatment of rectal fistulas are the simplicity of the manipulation and the absence of significant pain syndrome in the postoperative period, which allows to perform the operation in outpatient conditions, without worsening the quality of life of patients. Along with this, the method allows the possibility of multiple reapplications in order to eliminate the recurrence of the disease. In our opinion, the indication for application of the technique is the presence of intrasphincteric and transsphincteric fistulas with a direct fistulous passage and absence of collections. If the indications are exceeded, the effectiveness of the technique decreases, but despite this, it can also be used as the operation of choice for complex fistulas of the rectum. Contraindications to the use of this technique are acute inflammatory diseases of the pararectal tissue.

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