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Mesenchymal stem cells for perianal fistulizing Crohn's disease (systematic review and meta-analysis)

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ABSTRACT *AIM: to compare the efficacy (fistulas healing rate) and safety (morbidity rate) of mesenchymal stem cells (MSC) and placebo in patients with perianal fistulizing Crohn's disease (PFCD).*
PATIENTS AND METHODS: a systematic review and meta-analysis of clinical trials, comparing the results of treatment of PFCD with single local administration of MSCs or placebo was performed. The meta-analysis included 5 randomized clinical trials and the results of treatment of 289 patients were analyzed.
RESULTS: the meta-analysis demonstrates the high efficacy of a single local administration of MSCs for PFCD compared with placebo (OR = 2.10, CI 1.28–3.46, p = 0.003). The most common postoperative complications — abscesses and fistulas — are probably associated with the natural course of the disease and do not differ significantly between the groups. The results of surgery may be affected by the type, source and concentration of MSCs, the method of delivery and the number of injections.
CONCLUSION: local administration of mesenchymal stem cells is an effective and safe method for perianal fistulas in Crohn's disease, however, the presence of significant limitations in the meta-analysis makes it cautious about the results obtained and requires further randomized trials.

KEYWORDS: *mesenchymal stem cells, anorectal fistula, perianal fistula, Crohn's disease, perianal fistulizing Crohn's disease, PFCD, MSC*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Among all patients with Crohn's disease, the prevalence of perianal fistulas (PFCD) ranges from 25% to 28% [1–3]. Currently, all links in the pathogenesis of PFCD have not been studied completely, while it is known that prolonged genetically determined inflammation in the rectal wall leads to a lesion of the barrier function of the epithelium and further over expression of pro inflammatory cytokines and activation of T-cell immunity [4,5]. The combination of the above factors leads to anorectal fistulas of varying degrees of complexity, while up to 80% of all PFCD are represented by complex fistulas [6,7].

In turn, the best outcomes of treatment of fistulas in Crohn's disease (CD) in relation to the recurrence rate can be achieved only with a combination of systemic conservative therapy to suppress active inflammation in the rectum and surgery [8]. However, currently there is no single algorithm for the treatment of perianal fistulizing CD. Despite the use of various surgical methods, their results are still unsatisfactory. Thus, the rate of wound healing after surgery for PFCD is 37%, and the risk of recurrence of rectal fistula during 10 years of follow-up after treatment reaches 78% [7,9]. In the vast majority of cases, patients with complex rectal fistulas require multi-stage surgical treatment, which certainly increases the risk of postoperative

anal incontinence [9,10]. The absence of a positive effect from the treatment of PFCD can lead to a permanent stoma or proctectomy in 38% of patients, which reduce their quality of life [11].

Mesenchymal stem cells are a promising new direction, which is an alternative to traditional surgery in the multi-stage treatment of perianal fistulizing Crohn's disease. The mechanism of action of MSCs is based on their anti-inflammatory and immunosuppressive effect on surrounding tissues. However, it is currently not fully understood [12]. There are various sources of MSCs, among which bone marrow and adipose tissue are the most common. According to the MSC type, they can be allogeneic (stem cells obtained from a donor) or autologous (the patient's own stem cells) [13]. Currently, sufficient experience in the use of mesenchymal stem cells in patients with PFCD has been accumulated in practice, demonstrating high efficacy (healing) and safety (no complications) of using MSCs. Therefore, the subject of this systematic review and meta-analysis is studies devoted to the treatment of perianal fistulizing CD with mesenchymal stem cells in patients with Crohn's disease [14–18].

AIM

The purpose of the meta-analysis is to compare the efficacy (of PFCD healing) and safety (complication rate) of the use of MSC and placebo in patients with PFCD.

PATIENTS AND METHODS

The systematic review and meta-analysis were performed in accordance with the international recommendations of PRISMA (The preferred reporting items for systematic reviews and meta-analyses check list) [19]. The literature search was carried out in the electronic databases E-library, PubMed and Cochrane Library, had no restrictions on the date of publication and was completed on 04/12/2024. The search query was as follows: "(((‘mesenchymal stem cells’ [MeSH Terms] OR ‘Stromal Vascular Fraction’ [MeSH Terms] OR (‘stem cells’ [MeSH Terms] OR ‘stem’ [All Fields] AND ‘cells’ [All Fields]) OR ‘stem cells’ [All Fields] OR (‘stem’[All Fields] AND ‘cell’ [All Fields]) OR ‘stem cell’[All Fields]) OR (‘fat’ [All Fields] AND (‘grafts’[All Fields] OR ‘grafted’ [All Fields] OR ‘graftings’ [All Fields] OR ‘transplantation’ [MeSH Subheading] OR ‘transplantation’ [All Fields] OR ‘grafting’ [All Fields] OR ‘transplantation’ [MeSH Terms] OR ‘grafts’ [All Fields] OR ‘transplants’ [MeSH Terms] OR ‘transplants’ [All Fields] OR ‘graft’ [All Fields]))) AND (‘fistula’ [MeSH Terms] OR ‘fistula’ [All Fields] OR ‘fistulas’ [All Fields] OR ‘fistulas’ [All Fields] OR ‘fistulae’ [All Fields] OR ‘fistulaes’ [All Fields] OR (‘rectal fistula’ [MeSH Terms] OR (‘rectal’ [All Fields] AND ‘fistula’ [All Fields]) OR ‘rectal fistula’ [All Fields] OR (‘anal’ [All Fields] AND ‘fistula’ [All Fields]) OR ‘anal fistula’ [All Fields]) OR (‘Crohn Disease’ [MeSH Terms] OR (‘crohn’ [All Fields] AND ‘disease’ [All Fields]) OR ‘Crohn Disease’ [All Fields] OR ‘crohn’s disease’ [All Fields]) OR ‘Crohn Disease’ [MeSH Terms])) AND (humans[Filter])", ‘mesenchymal stem cells’, ‘stem cells’, ‘Crohn's disease’, ‘perianal manifestations’, ‘stromal vascular fraction’.

Studies on children and animals were excluded from the request, and language restrictions were not applied. The selected articles were searched for bibliographic references to the subject of research that was not found during the initial search. The systematic review and meta-analysis of the literature included full-text articles describing the results of randomized clinical trials comparing single topical application of mesenchymal stem cells and placebo in patients with perianal fistulizing Crohn's disease.

Criteria for inclusion in the meta-analysis: full-text, randomized clinical trials comparing single topical application of mesenchymal stem cells and placebo in patients with perianal fistulizing Crohn's disease (rectal fistula).

Exclusion criteria: incomparable, non-randomized studies; the use of MSCs in patients with cryptoglandular fistulas; systemic use of MSCs in Crohn's disease; the use of MSCs in patients with rectovaginal fistulas (RVF) on the background of Crohn's

disease; comparison of MSCs with other methods of treatment of PFCD.

Data Obtaining

The data of interest in the comparison groups were: gender, body weight, age, time of Crohn's disease history, use of systemic therapy for CD, source, type and concentration of MSC, method of using stem cells, healing of PFCD, postoperative complications (rate of common complications and their structure: formation of abscesses, fistulas).

Statistical Analysis

Statistical data processing when comparing the groups included in the meta-analysis of the study was performed with the program Review Manager 5.4.1 for MacOS. The total value of the dichotomous data was described with a 95% coincidence interval (CI) in the form of odds ratio (OR). At $p < 0.05$, the difference in the compared indicators was considered statistically significant.

Search Results

A total of 2,738 publications were found (Fig. 1). The first stage excluded non-full-text publications, animal and child studies, and literature reviews. With further screening, studies that do not meet the inclusion criteria were excluded — 100, meta-analyses — 15. Among the selected randomized clinical trials, 2 were excluded due to the use of another treatment method in the comparison group (fibrin glue, N = 1; eruption ligature, N = 1), 1 study with systemic use of mesenchymal stem cells and 1 study in patients with rectovaginal fistula in Crohn's disease were also excluded. When searching the bibliographic data of the studies included in the meta-analysis, no additional articles were found.

Ultimately, 5 randomized clinical trials were included in the meta-analysis. The characteristics of the studies are presented in Table 1. It is worth noting that the studies by Panes et al., done between 2016 and 2018, were devoted to evaluating the results of treatment in one cohort of patients in the compared groups at different follow-up periods and a meta-analysis of the data was carried out depending on the availability of indicators of interest in the publication [14,15]. In turn, in 2/5 studies [17,18] there were 4 comparison groups (patients were

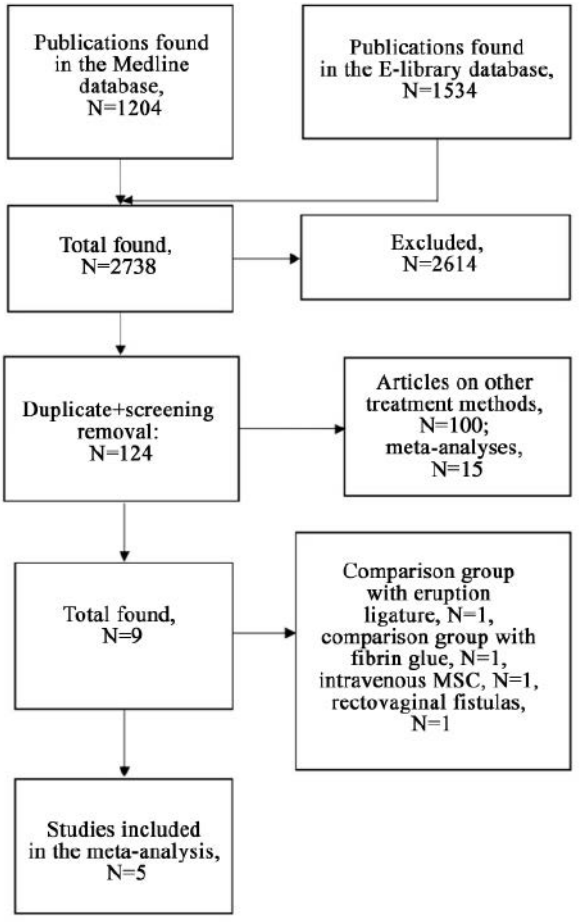


Figure 1. *Search and selection of literature for meta-analysis*

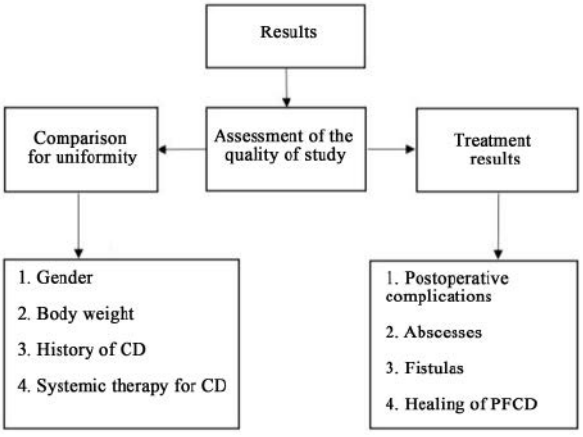


Figure 2. *The structure of the description of the meta-analysis results*

Table 1. *Characteristics of studies comparing the use of mesenchymal stem cells and placebo in patients with perianal fistulizing Crohn's disease*

Author	Year	Country	Type	Observation period (months)	The treatment method	Source of MSC	N	Gender (M/F)	Average body weight (kg)	Anamnesis of Crohn's disease (years)	Lack of systemic therapy for Crohn's disease, N	Postoperative complications, N	PFCD healing, N
Panes et al. [14][1]	2016	Spain	multicenter RCT, double-blind	6	MSC	Allogeneic, adipose tissue	107	60/47	73.9 ± 15.0	12.1 ± 10.0	26/107	18/103	53/107
					Placebo*		105	56/49	71.3 ± 14.9	11.3 ± 8.9	19/105	30/102	36/105
Panes et al. [15][1]	2018	Spain	multicenter RCT, double-blind	12	MSC	Allogeneic, adiposetissue	103	No data	No data	11.6	No data	21/103	58/103
					Placebo*		102	No data	No data	11.6	No data	27/102	39/102
Garcia-Olmo et al. [16]	2022	Spain	multicenter RCT, double-blind	24	MSC	Allogeneic, adiposetissue	25	14/11	73.4 ± 14.8	9.9 ± 7.9	8/25	3/25	14/25
					Placebo*		15	8/7	70.2 ± 11.0	10.7 ± 7.5	3/15	1/15	6/15
Molendijk et al. [17]	2015	Netherlands	RCT, double-blind with dose adjustment	6	MSC1**	Allogeneic, bonemarrow	5	4/1	No data	7.6 ± 1.1	0	No data	4/5
					MSC3***		5	4/1	No data	16.8 ± 4.0	0	No data	4/5
					MSC5****		5	1/4	No data	13.2 ± 4.1	0	No data	1/5
					Placebo*		6	3/3	No data	6.8 ± 2.9	0/6	5/6	2/6
Barnhoorn et al. [18]	2020	Netherlands	RCT, double-blind with dose adjustment	48	MSC1**	Allogeneic, bone marrow	4	3/1	No data	No data	1	No data	3/4
					MSC3***		4	4/0	No data	No data	1	No data	4/4
					MSC5****		5	1/4	No data	No data	2	No data	1/5
					Placebo*		3	No data	No data	No data	No data	No data	No data

*Note: RCT — randomized clinical trial; MSCs — mesenchymals tem cells; PFCD — perianal fistulizing Crohn's disease; *Placebo — 24 ml of 0.9% sodium chloride solution or 2 syringes of 2.5 ml of 0.9% sodium chloride solution or 5% human albumin solution; **MSC1 — in the amount of 1 × 107 cells/ml; ***MSC3 — in the amount of 3 × 107 cells/ml; ****MSC5 — in the amount of 5 × 107 cells/ml: 1 — are interchangeable studies in relation to meta-analysis of data*

divided depending on the MSCs concentration used (1×10^7 cells/ml, 3×10^7 cells/ml, 5×10^7 cells/ml) and, upon meta-analysis of the data, cohorts with different cell concentrations were combined into one group.

RESULTS

Data on 289 patients were analyzed, of whom 160 (55%) patients were treated with MSC and 129 (45%) ones with Placebo (Table 1). The

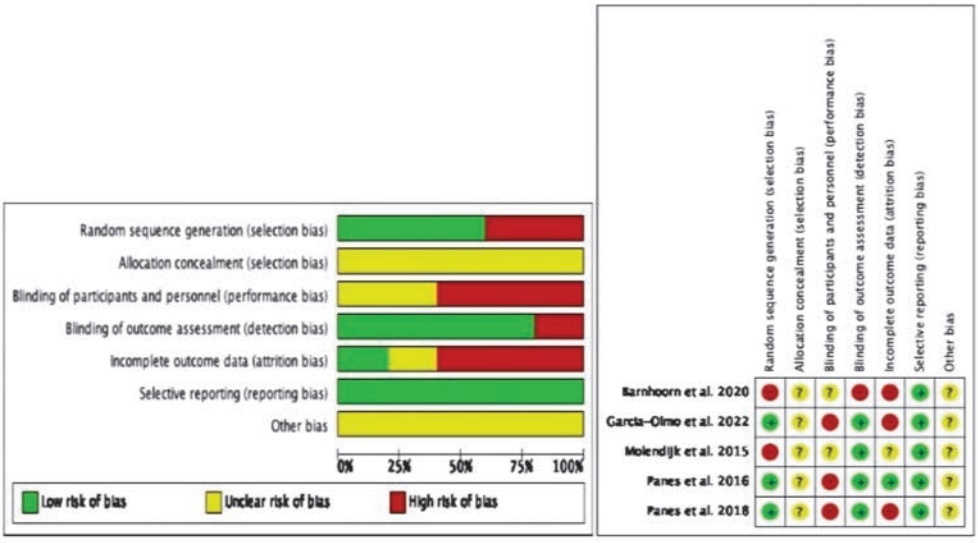


Figure 3. *Assessment of bias risk in studies comparing mesenchymal stem cells and placebo for the treatment of perianal fistulizing Crohn's disease, according to the Cochrane risk of bias check list*

structure of the description of the meta-analysis results is shown in Figure 2.

The assessment of the study quality was carried out in accordance with Cochrane risk of bias check list [20].

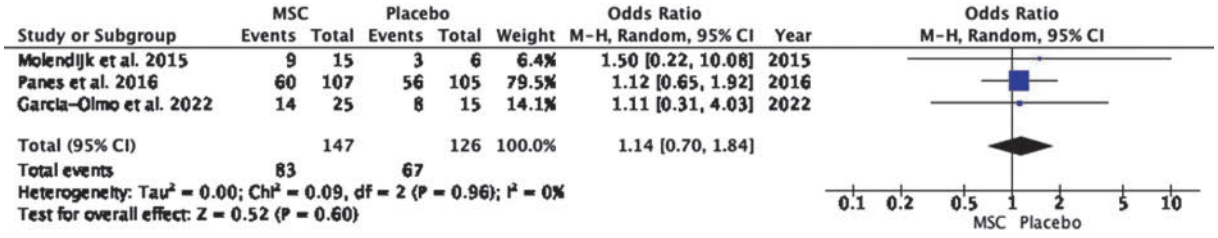
More than 50% of the publications included in the analysis had a low risk of bias according to the criteria of researcher blindness and research reporting. At the same time, in more than 50% of the studies, there was a high risk of bias according to the criteria of patient distribution, blinding of the performer and completeness of the description of these treatment results.

Comparison for Uniformity

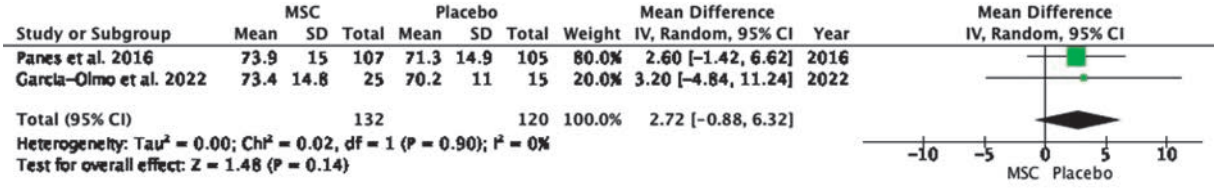
The studies included in the meta-analysis had no statistically significant differences in gender, average body weight, duration of Crohn's disease history and the use of systemic therapy: antibacterial drugs, glucocorticosteroids, immunosuppressants, genetically engineered biological drugs (Fig. 4A–D).

Results of the Treatment.

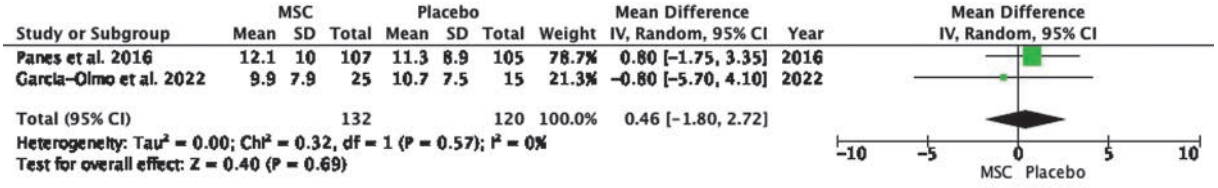
Meta-analysis of Postoperative Complication Rate



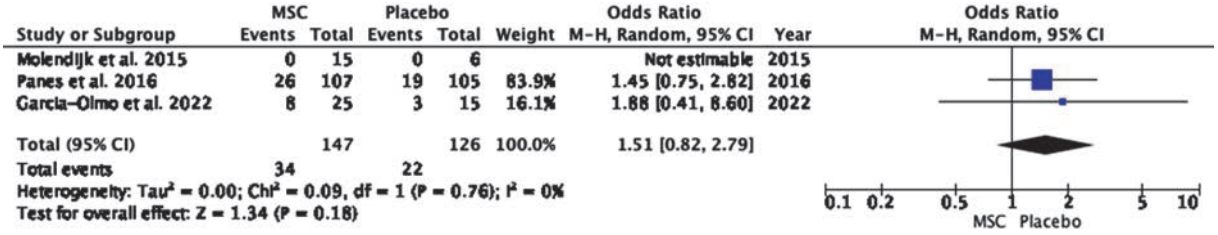
A. Meta-analysis of the sex of patients (male)



Б. Meta-analysis of the average body weight of patients (kg)



B. Meta-analysis of the duration of Crohn's disease history (years)



Г. Meta-analysis of the rate of systemic Crohn's disease therapy (patients who did not receive systemic therapy)

Figure 4. *Clinical and morphological characteristics of patients included in the meta-analysis*
MSCs — mesenchymal stem cells; Placebo — 24 ml of 0.9% sodium chloride solution or 2 syringes of 2.5 ml of 0.9% sodium chloride solution or 5% human albumin solution.

The rate of postoperative complications (formation of abscesses, additional fistulas, blood secretion, pus, exacerbation of Crohn's disease, thrombosis of hemorrhoids, formation of fissure) was described in 3/5 studies (Fig. 5). At the same time, no statistically significant differences were found between the comparison groups (OR = 0.72, CI 0.39–1.33, $p = 0.30$).

Meta-analysis of the Rate of Perianal Abscess Formation after Surgery

Data on the rate of perianal abscesses were presented in 3/5 studies (Fig. 6). There were no statistically significant differences in the compared groups (OR = 0.85, CI 0.41–1.76, $p = 0.66$).

Meta-analysis of the Rate of Additional Perianal Fistula Formation after Surgery

When assessing the rate of new perianal fistula formation after surgery, studied in 2/5 studies (Fig. 7), no statistically significant differences were obtained between the comparison groups (OR = 0.5, CI 0.14–1.77, $p = 0.28$).

Meta-analysis of the Healing Rate of Perianal Fistulizing Crohn's Disease

3/5 studies provide data on the healing of perianal fistulizing Crohn's disease (Figure 8). The criteria for healing in all publications were: the absence of leakage from the external fistula opening when it is compressed with fingers and swelling of no

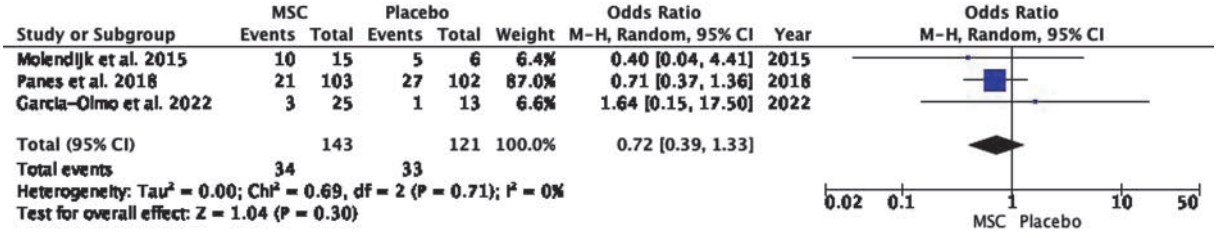


Figure 5. *Meta-analysis of the rate of postoperative complications*

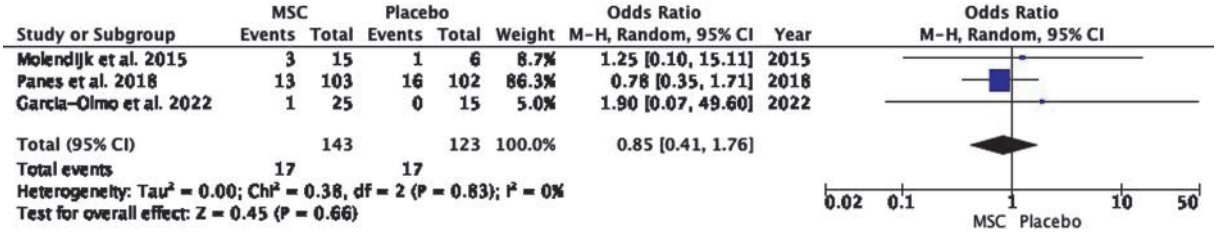


Figure 6. *Meta-analysis of the rate of abscesses formation after operation*

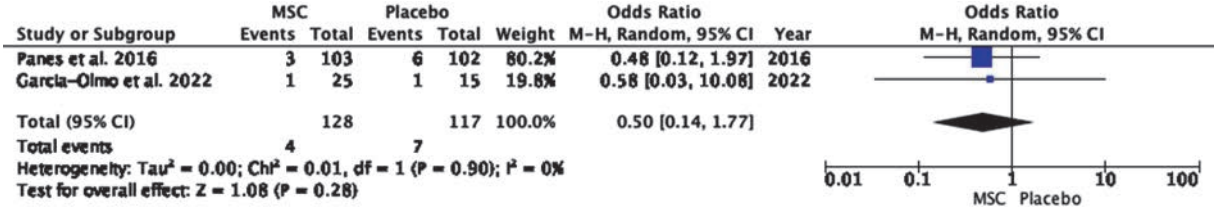


Figure 7. *Meta-analysis of the rate of formation of new fistulas after operation*

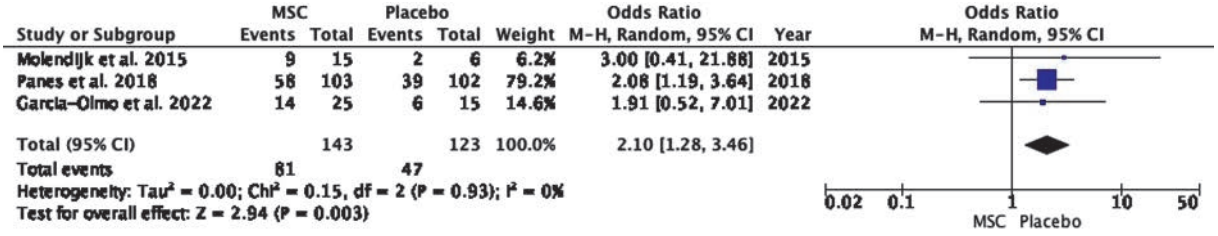


Figure 8. *Meta-analysis of the rate of PFCD healing*

more than 2 cm in diameter according to magnetic resonance imaging (MRI) of the pelvic organs [14–18]. The meta-analysis revealed that the rate of PFCD healing in the group of patients treated with mesenchymal stem cells was statistically significantly higher compared with the group of patients treated with placebo (OR = 2.10, CI 1.28–3.46, $p = 0.003$).

Limitations of Meta-analysis

The limitations of the meta-analysis were: different types (allogeneic and autologous) and sources of mesenchymal stem cells (bone marrow, adipose tissue); heterogeneous follow-up period (from 6 to 48 months); inclusion in the meta-analysis of two studies with the results of treatment of one cohort of patients in the compared groups during the follow-up period of 6 and 12 months; different concentrations of mesenchymal stem cells (from 1×10^7 cells/ml to 12×10^7 cells/ml); there is a high risk of bias in the results due to the absence of performer blindness in more than 50% of studies, incomplete data description; small cohorts of patients in the compared groups in 2/5 studies [17,18].

DISCUSSION

A fairly high recurrence and adverse events rate after surgery for PFCD are prerequisites for the search for more effective and safe methods of treating rectal fistulas in Crohn's disease [21,22]. The relevance of the use of MSCs in PFCD is due to their paracrine effect on tissues, leading to suppression of local inflammation and improvement of reparative processes [23,24]. Also, the use of mesenchymal stem cells will expand the possibilities of treating patients with resistance to systemic therapy of Crohn's disease. In addition, treatment with MSCs is not associated with an increased risk of infections, including tuberculosis, to which patients receiving genetically engineered biological drugs (GEBD) are susceptible [25,26].

Although the exact mechanism of action of stem cells in PFCD has not been studied, numerous studies confirm the safety (absence of complications) of this method [16,18,27]. At the same time, according to the results of the meta-analysis, the rate of postoperative complications in the MSC group had no statistically significant differences compared with the placebo group. The most common complications in the compared groups — the formation of abscesses, additional fistulas — were observed both in patients receiving MSCs and in patients receiving placebo. It is worth noting that these adverse events are characteristic of the natural course of Crohn's disease with perianal fistulizing, and probably may not be directly related to the treatment of PFCD.

In turn, the rate of anal incontinence after surgical treatment of rectal fistulas in Crohn's disease reaches 35% [28,29]. However, none of the studies included in the meta-analysis evaluated the occlusion anal function before and after surgery [14–18]. Given the need in the vast majority of cases for multi-stage surgical treatment in PFCD, in our opinion, an objective assessment of the function of the rectal occlusion apparatus is extremely important in order to determine the effect of a specific surgery on the occurrence of the above extremely undesirable phenomenon. In turn, the use of MSCs can significantly reduce the risk of postoperative anal sphincter incontinence in the studied group of patients, which will undoubtedly improve their quality of life.

The basic goals of the treatment of perianal fistulizing CD are: elimination of symptoms, healing of fistulas and creating conditions for systemic therapy of Crohn's disease, reducing the recurrence rate of PFCD, preserving the function of the anal sphincter, preventing the formation of a stoma and performing proctectomy, improving the quality of patients' life.

The results of this meta-analysis confirm the effectiveness of the use of MSC for the treatment of PFCD (OR = 2.10, CI 1.28–3.46, $p = 0.003$). The healing of PFCD in the studies included in the meta-analysis was evaluated clinically by the absence of pus-like leakage from the external fistula opening when it was compressed with

fingers at various follow-up periods — from 6 to 48 months. Instrumental assessment of healing was performed by MRI (absence of additional tracks > 2 cm in diameter) [14–18]. At the same time, transrectal ultrasound (TRUS) was not performed in any of the publications we analyzed. According to various data, the healing rates of PFCD on the 24th week after treatment vary from 50% to 80%. At the same time, the effectiveness of the MSC does not decrease over time [30,31]. So, in the meta-analysis by Wang, H. et al., when analyzing the long-term effectiveness (more than 1 year), the disease-free healing of perianal fistulizing Crohn's disease in patients was more often preserved after the use of stem cells in comparison with 'traditional treatment' (by this term the authors understood the local use of placebo or fibrin glue) (49% vs. 26%) [32]. In a prospective study by Cho Y.B. et al., it was demonstrated that PFCD remission persisted for 2 years in 83% of patients treated with adipose tissue MSCs [33].

The method of administration of MSC was the same in all studies included in the meta-analysis [14–18]. 2 weeks before the surgery, patients underwent an anal canal revision under general anesthesia, treatment and curettage of the fistula, drainage of existing purulent lumps using a draining latex ligature (seton). On the surgery day, the setons installed earlier were removed, the internal fistula opening was sutured with an absorbable thread. At the same time, 10 ml of saline solution was injected under pressure through the external fistula opening to control the tightness of the previously sutured hole. Next, using a syringe with a thin needle, a solution with MSC was injected through the anal canal into the tissues around the internal fistula opening, but to a depth of no more than 2 mm, and through the external fistula opening along the fistula passage. In the comparison group, a placebo solution was administered in a similar way. Probably, treatment of the fistula course and suturing of the internal fistula opening could enhance the positive effect in the group of patients receiving placebo.

According to the literature, MSCs demonstrate high efficacy in the treatment of PFCD. However, it may differ depending on the type and source of stem cells, their concentration and method of delivery to the treatment area, as well as the number of repeated injections [34]. In the studies included in the meta-analysis, all MSCs were obtained from donors (allogeneic) [14–18], while 3/5 publications used a ready-made drug based on stem cells obtained from donor adipose tissue [14–16]. In general, the available studies confirm the effectiveness of MSC in cryptogenic fistulas [35–37]. According to the randomized trial by Ascanelli S. et al., 4 weeks after the use of stem cells from adipose tissue of patients (autologous MSCs), fistula healing occurred in 63.8% of cases compared with 15.5% in the control group [38].

Also, in the world literature, there is a heterogeneity of delivery options for MSCs in PFCD. So, Garcia-Olmo D. et al. in 2009 conducted a randomized trial using autologous adipose tissue cells together with fibrin glue [39]. At the same time, patients with both cryptoglandular fistulas and fistulas in Crohn's disease were included in the study. In 8 weeks after a single application of MSCs, healing was noted in 46% of patients, after repeated use — in 70% of patients. The use of bioplastic materials for the delivery of MSCs was also described in the study by Dozois E.J. et al. [40]. Autologous MSCs from adipose tissue were absorbed onto a sealing tampon ('fistula plug'), which led to healing in 78% of patients in 6 months after treatment. However, there are currently no studies comparing different methods of delivering MSCs to the area of interest.

PFCD healing also occurs after a single injection of MSC [14–18]. However, it is also possible to repeat the use of MSCs in the absence of healing after the 1st injection — on average, from 1 to 3 times [39,41,43]. More often, the repeated use of MSCs is described in studies using autologous stem cells. In particular, Lee, W.Y. et al. repeated MSC injections up to 6 times, which led to healing of fistulas in all patients in 1 year after the start of treatment [42].

In turn, the question of choosing the optimal number of injections remains open, as well as the concentration of stem cells used. According to a meta-analysis by Cao Y. et al., when using MSCs in the amount of 3 × 10^7cells/ml, the healing of PFCD reaches 71% of cases [44]. These data are confirmed by a study by Hamamoto H. in 2009 on the myocardium of sheep, which described the positive effect of low doses of stem cells on the survival of the studied animals with a simulated heart attack and its decrease with an increase in the MSC concentration [45]. Also, according to the results of a meta-analysis by Cheng F. et al., it is more effective to use the required volume of MSC solution, calculated depending on the number and length of fistula passages, in comparison with using the same volume of graft for each patient — 80% versus 55% ($p < 0.05$) [46].

Another important and unresolved problem of the use of MSCs for the treatment of PFCD at present is the choice of cell type (autologous or allogeneic). According to a meta-analysis by Lightner A. et al., there were no statistically significant differences in the healing of PFCD depending on the origin of mesenchymal stem cells [43]. At the same time, in a meta-analysis by Cheng, F. and co-authors, were obtained data on higher efficiency when using autologous MSCs compared with allogeneic ones — 79% vs. 52% ($p < 0.05$), as well as after using MSCs obtained from adipose tissue compared with stem cells from bone marrow — 64% vs. 57% ($p > 0.05$) [46]. The high efficiency of autologous MSCs has been confirmed in other studies. According to a study by Ciccocioppo R. et al., the PFCD healing was in 88% of patients in 1 year after the use of autologous bone marrow MSCs [47].

It is worth noting that one of the positive qualities of autologous stem cells is the lack of production of antibodies to donor cells, unlike allogeneic ones, which can affect the results of treatment after their use [48–50]. In turn, one of the disadvantages of allogeneic MSCs is the need for their long-term cultivation and storage, whereas autologous mesenchymal cells can be used on the day of their receipt [51–53]. Despite the fact that currently no randomized trials have been conducted comparing the efficacy and safety of stem cells obtained from different sources, according to a number of authors, MSCs from adipose tissue have advantages over mesenchymal cells from bone marrow [48–56]. Firstly, obtaining MSCs from bone marrow is a more invasive procedure compared to liposuction. Secondly, it was found that mesenchymal stem cells derived from adipose tissue have a better ability to proliferate, which is an important pathogenetically justified component in the treatment of PFCD [54–56]. Thus, the use of autologous MSCs from adipose tissue is a fairly promising direction in the treatment of PFCD [57–59]. Given the above limitations of meta-analysis, as well as the lack of a unified approach and method of using mesenchymal stem cells in the treatment of rectal fistulas in patients with Crohn's disease, it is necessary to conduct a randomized clinical trial comparing the use of autologous MSCs obtained from adipose tissue and traditional surgery in order to comprehensively assess the results of treatment and develop recommendations for the use of stem cells in patients with PFCD.

CONCLUSION

The use of mesenchymal stem cells is an effective and safe procedure in the treatment of patients with perianal fistulizing Crohn's disease.

However, the presence of significant limitations in the presented meta-analysis makes us cautious about the results obtained and requires further research.

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