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Fibrin Glue with Mesenchymal Stem Cells for perianal fistulas: a systematic review and meta-analysis

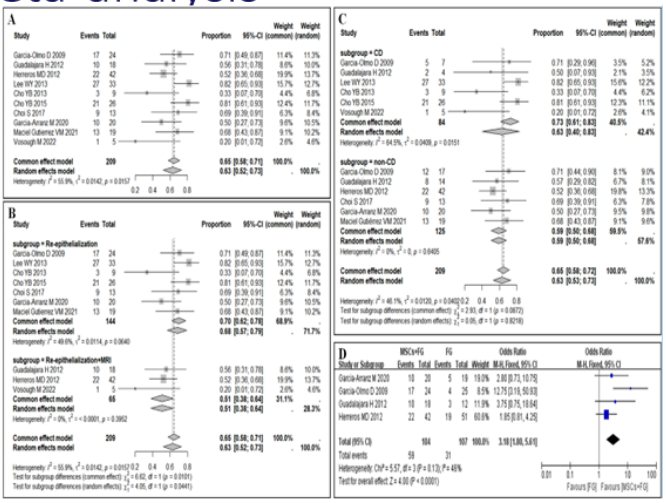
Perianal fistulas (PFs) are often refractory to standard management. Cell therapy strategies using mesenchymal stem cells (MSCs) carried in fibrin glue (FG) have shown promising results in regenerative medicine

The overall clinical healing rate (HR) of PFs after local FG combined with MSCs therapy was 63% (95% confidence interval (CI) 0.52,0.73).

MRI served as the primary modality for assessing fistula healing outcomes, and the pooled HR was 51% (95% CI 0.38, 0.64).

Fistula healing was defined as the complete reepithelialization of external openings, and the pooled HR was 70% (95% CI 0.62, 0.78).

The pooled HR for PFs in the context of Crohn's disease (CD) was elevated compared to PFs not associated with CD (63% vs 59%, respectively). Compared with local FG-alone therapy, local FG combined with MSCs therapy resulted in a higher HR of PFs (odds ratio (OR) = 3.18; 95% CI 1.80,5.61; P < 0.0001).



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Fibrin glue with mesenchymal stem cells for perianal fistulas: a systematic review and meta-analysis

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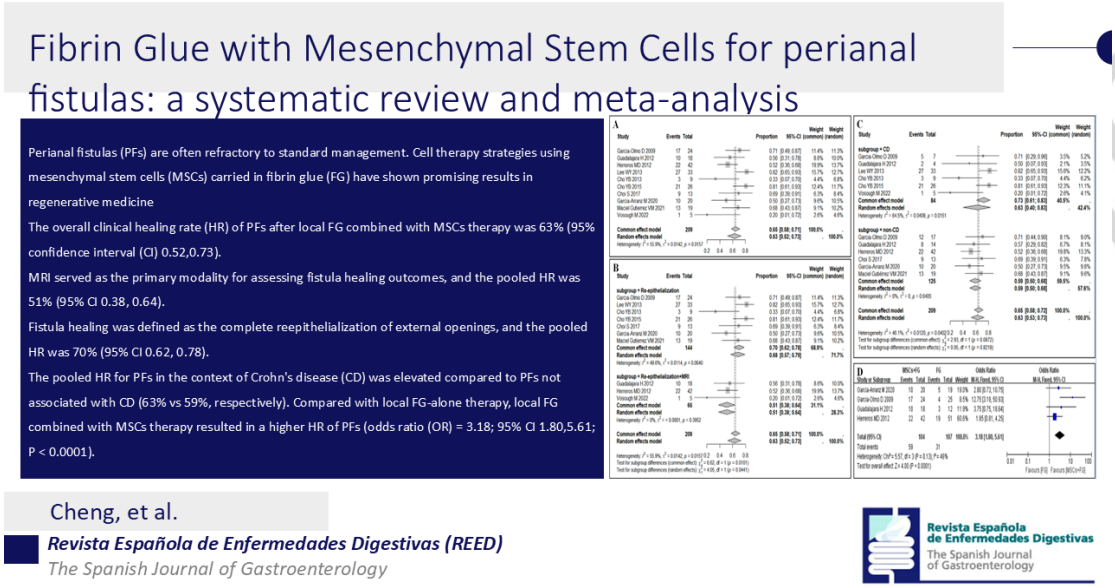
Data availability: all data used for the analysis of this study are included in this article.



ABSTRACT

Objectives: perianal fistulas (PFs) are often refractory to standard management. Cell therapy strategies using mesenchymal stem cells (MSCs) carried in fibrin glue (FG) have shown promising results in regenerative medicine. Thus, the objective of our study was to assess the efficacy and safety of local FG combined with MSCs for PFs.

Methods: electronic databases were searched for studies that reported efficacy and/or safety of local FG combined with MSCs therapy for PFs. The PRISMA guideline was followed. We performed a meta-analysis using the meta package in R and Rev-Man software.

Results: after screening, a total of ten studies were identified. The overall clinical healing rate (HR) of PFs after local FG combined with MSCs therapy was 63 % (95 % confidence interval [CI]: 0.52, 0.73). Magnetic resonance imaging (MRI) served as the primary modality for assessing fistula healing outcomes, and the pooled HR was 51 % (95 % CI: 0.38, 0.64). Fistula healing was defined as the complete reepithelialization of external openings, and the pooled HR was 70 % (95 % CI: 0.62, 0.78). Furthermore, our meta-analysis revealed that the pooled HR for PFs in the context of Crohn's

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disease (CD) was elevated compared to PFs not associated with CD (63 % *vs* 59 %, respectively). Compared with local FG-alone therapy, local FG combined with MSCs therapy resulted in a higher HR of PFs (odds ratio [OR] = 3.18; 95 % CI: 1.80,5.61; p < 0.0001). No major MSCs-related adverse event has been reported.

Conclusion: our study indicated that local FG therapy combined with MSCs treatment for PFs is a promising strategy and that it achieves a higher HR for PFs compared to local FG-alone therapy. This therapy strategy also appears to offer superior treatment for PFs associated with CD. Future assessment in randomized controlled studies is warranted.

Keywords: Perianal fistula. Mesenchymal stem cells. Fibrin glue. Efficacy. Meta-analysis. Systematic review.

INTRODUCTION

A perianal fistula (PF) is an abnormal condition that develops between the anal canal and the perineal skin or in the perianal region; it does not heal spontaneously (1). The clinical manifestations of PF include perianal cellulitis, perineal pain, purulent discharges, and bowel incontinence. Epidemiologically, PF has an incidence of 1.1 to 2.2 per 10,000 persons per year (2,3). It can be caused by surgical trauma, diverticular disease, tuberculosis, ulcerative colitis, Crohn's disease (CD), actinomycosis and anal canal carcinoma. Lifestyle and past medical history may be associated with an increased risk of the disease. Obesity (body mass index [BMI] > 25 kg/m^2), high daily salt intake, diabetes, hyperlipidemia, dermatosis, anorectal surgery, smoking, alcohol intake, sedentary lifestyle, excessive intake of spicy/high-fat food, very infrequent participation in sports and prolonged sitting on the toilet for defecation are recognized independent risk factors for PF formation (4,5). While the majority of PF cases are classified as benign, they cause serious morbidity and result in a negative impact on quality of life and a tremendous burden to the healthcare system. We know PF treatment goals include fistula closure, preservation of the anal sphincter, prevention of recurrence, and maintenance and restoration of quality of life. Currently, several strategies have been proposed to favor the healing

of PF, such as conventional medical treatment strategies (e.g., antibiotics and immunomodulators) and anti-tumor necrosis factor agents (anti-TNF), or surgical treatments. Unfortunately, existing treatments have a high rate of recurrence and are difficult to maintain sustained fistula closure. Besides, all these strategies have advantages and disadvantages. Immunomodulators can have serious side effects. Additionally, there is a risk of opportunistic infection associated with the use of biological treatments. Surgery is also an important component of management of perianal fistulas. But the high incidence rates of complications such as fecal incontinence and fistula recurrence significantly affect patients (6). Consequently, the management of PFs still present significant challenges, highlighting the pressing need for the development of innovative and effective therapeutic strategies to tackle this enduring clinical issue.

In the last 20 years, fibrin glue (FG) combined with cells has been successfully used for tissue engineering applications (7). Mesenchymal stem cells (MSCs) are undifferentiated cells that can be obtained from different sources, such as bone marrow, adipose tissue, and umbilical cord. MSCs have self-renewal and multidirectional differentiation potential, and can exert therapeutic effects on various diseases through directed differentiation, regulation of immunity, anti-inflammatory effects, proangiogenesis, improvement of microenvironment and promotion of regeneration. Research has revealed that MSCs exert their effects on local immune environment through releasing various mediators, such as exosomes, rather than relying on direct cell-to-cell communication (8). Furthermore, exosomes derived from MSCs (MSCs-Exo) have been confirmed to significantly accelerate the healing of cutaneous and other epithelial wounds. Thus, the recognized roles of stem cells in immunoregulation and facilitation of tissue repair are likely facilitated by a paracrine mechanism involving secreted factors, including extracellular vesicles. Therefore, application of MSCs represents a novel approach for enhancing regeneration and/or repair of damaged tissues in an environment particularly unfavorable for wound healing. Now, an increasing number of studies have shown that local MSCs therapy is safe and efficacious for PFs (9,10). FG is a natural polymer involved in the coagulation process. It provides a temporary structure that favors

angiogenesis, extracellular matrix deposition and cell-matrix interactions. Additionally, FG maintains the local and paracrine functions of MSCs, providing tissue regeneration through less invasive clinical procedures. And, in medical practice, FG can be obtained from autologous blood components, which reduces the risk of infection and immunological reactions. Several studies have demonstrated that FG injection represents a simple, effective, and well-tolerated therapeutic option for patients with PFs (11,12). In recent years, cell therapy strategies employing MSCs delivered via FG have demonstrated promising outcomes in the realm of regenerative medicine. Furthermore, some literature has suggested that FG loaded with MSCs possesses the potential to regenerate nervous-system lesions and bone or cartilage (13,14). Currently, a growing number of studies have explored the use of local FG combined with MSC-based therapy for PFs. This treatment strategy may provide a unique treatment modality to suppress chronic inflammation and promote the healing of the fistula for PFs. Therefore, the aim of our study was to evaluate the safety and efficacy of local FG combined with MSCs for the treatment of PFs.

MATERIALS AND METHODS

Data source and search strategies

This systematic review and meta-analysis followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (15). In July 2024, a comprehensive search was performed in the PubMed, EMBASE and Cochrane Library databases for clinical studies written in English regarding local FG combined with MSCs treatment in patients with PFs. The following search terms were used: “mesenchymal stem cell”, “mesenchymal stromal cell”, “stem cells”, “stroma cells”, “perianal fistula”, “fibrin sealant”, “fibrin glue”. We also checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

Study selection

The study design was structured around the selection of clinical trials to evaluate the local FG combined with MSCs for PFs. Inclusion criteria were: a) human studies; b) published randomized controlled trials (RCTs), single-arm intervention trials, cohort studies, case series, and so on; and c) local injection of FG combined with MSCs for PFs, reported outcomes of efficacy and safety. Exclusion criteria were: a) non-human studies; b) repeated studies; and c) studies that were not original research, such as conference abstracts and letters to the editor.

Data extraction and quality assessment

A customized data extraction form was used by two authors to extract data. These authors extracted study data features, including: a) study characteristics (first author, publication year); b) type of study; c) MSCs type and source; d) disease type (CD or non-CD); e) definition of fistula healing (complete re-epithelialization of external openings and/or absence of collection > 2 cm by magnetic resonance imaging [MRI]); f) study outcomes; g) dosage and modalities of intervention administration; and h) adverse events (AEs). Table 1 lists the basic characteristics of the ten identified studies. Quality assessment was performed using Review Manager (version 5.3) according to the recommendations from the Cochrane Collaboration. The following were assessed for each study: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each item was classified as low risk, high risk, or unclear. The risk of bias was determined by taking all items together in a risk-of-bias graph. Any disagreement was resolved through discussion. Disagreements were resolved by discussion between the two authors.

Statistical analysis

The meta-analysis was performed using the meta-prop command of the meta package in R (version 3.4.2) and RevMan5.3 to assess the efficacy. OR and related 95 % CIs were calculated to compare local FG combined with MSCs treatment with control cohorts. The normality test results were used to determine whether the proportions should be applied in untransformed data or transformed with the Freeman-Tukey double arcsine transformation, and confidence intervals were

calculated using the Jackson method. The Chi-squared test ($p < 0.05$ indicating statistical significance) and the I^2 statistical (an I^2 of ≥ 50 %, < 50 % indicating substantial and low heterogeneity, respectively) were used to qualitatively and quantitatively evaluate statistical heterogeneity, respectively. For $I^2 < 50$ %, a fixed-effects model was applied. Otherwise, we used a random-effects statistical model. A value of $p < 0.05$ was considered statistically significant. Lastly, publication bias was evaluated using funnel plots and the Egger test.

RESULTS

Literature search and quality assessment

The literature search process is illustrated in figure 1. A total of 628 references were obtained from the electronic databases. After deduplication, a total of 161 records remained; 132 records were excluded based on reviewing title and abstract. The remaining 29 records were assessed for eligibility by scrutinizing the full text. Ultimately, ten articles were included in our meta-analysis (16-25). Six studies were single-arm trials (19-22,24,25). Four studies were randomized controlled studies (16-18,23). Nine studies used autologous MSCs (16-23,25). One study used allogeneic MSCs (24). Nine studies used adipose-derived MSCs (ASCs) (16-24) and one study used bone-marrow-derived MSCs (BMSCs) (25). Three studies employed MRI for fistula healing assessment (17,18,25). Three studies evaluated the comparative effectiveness of MSCs + FG treatment *versus* the control group (16,18,23). The methodological quality of the included studies was regarded as acceptable, as most of the domains of the included studies were ranked as low. Low risk of bias was mostly detected in selection bias, attrition bias, detection bias, and reporting bias. High risk of bias mostly occurred in selection bias and other bias. Unclear risk of bias mostly occurred in detection bias and performance bias. A summary of the risk of bias in the included articles is presented in figure 2A and B. The potential publication bias is shown by a funnel plot. Finally, the funnel plot was considered roughly symmetric by inspection (Fig. 2C). Egger's test was also performed to detect publication bias for included studies ($p = 0.1595$) (Fig. 2D).

Efficacy of local fibrin glue combined with mesenchymal stem cells for perianal fistulas

Local injection of FG combined with MSCs has emerged as a promising therapeutic approach for PFs. Ten studies reported raw data on the clinical healing of patients after local FG plus MSCs therapy, with substantial heterogeneity (I^2 = 55.9 %). The random-effects pooled rate of healing was 63 % (95 % CI: 0.52-0.73) (Fig. 3A).

The efficacy of local fibrin glue combined with mesenchymal stem cells treatment for perianal fistulas was evaluated using magnetic resonance imaging

In our meta-analysis, MRI was used to evaluate fistula healing in three trials. The fixed-effects pooled rate of healing was 51 % (95 % CI: 0.38, 0.64). Fistula healing was defined as complete reepithelialization of external openings in seven trials, and the fixed-effects pooled rate of healing was 70 % (95 % CI: 0.62, 0.78) (Fig. 3B).

Efficacy of local fibrin glue plus mesenchymal stem cells for different types of perianal fistulas (Crohn's disease *vs* non-Crohn's disease)

Six trials reported raw data on the healing of patients with perianal CD, and the random-effects pooled rate of healing was 63 % (95 % CI: 0.40, 0.83). Additionally, six trials reported raw data on the healing of patients with non-CD, with a fixed-effects pooled healing rate (HR) of 59 % (95 % CI: 0.50, 0.68). Therefore, the pooled HR of PFs in CD was higher than PFs not associated with CD (63 % *vs* 59 %, respectively) (Fig. 3C).

Efficacy of local fibrin glue plus mesenchymal stem cells *vs* fibrin glue treatment in perianal fistulas

Four trials were included in our meta-analysis. Using Rev-Man for meta-analysis, in a fixed-effects model, local FG plus MSCs were more effective for fistulas healing than FG-alone treatment with an OR of 3.18 (95 % CI: 1.80, 5.61; $p < 0.001$), with low heterogeneity between the studies (I^2 = 46 %) (Fig. 3D).

DISCUSSION

The gastroenterology association classified fistula into simple and complex fistula. Complex fistulas are extrasphincteric, suprasphincteric, high intersphincteric, or high transsphincteric or have multiple external openings or are associated with an abscess or with rectovaginal fistula or with anorectal stenosis. Complex PFs are the worst scenario. In our meta-analysis, the majority of fistulas fell into this category. PFs are associated with significant morbidity, resulting in reduced quality of life and increased healthcare costs. The management of PFs aims to eradicate sepsis and the fistula tract while preserving the maximum amount of anal function. A multimodal approach is needed to achieve effective PF treatment, and treatment should be directed towards multiple pathophysiological factors, including obliterating the dead space, removing epithelialization, and altering the pro-inflammatory environment that allows fistulas to persist (24). Now, the treatment of PF is medical or surgical, despite the current range of treatment options in PF (26). Nevertheless, available options are limited by the risk of fecal incontinence, diminished wound healing and high failure rates (27).

Up to now, there have been emerging treatment strategies to be aware of for the management of fistulas. Cell therapy strategies using MSCs carried in FG have shown promising results in regenerative medicine. Now, stem cell-based treatments are gaining a strong foothold in fistula management worldwide. Notably, the European Commission has granted approval for the use of human allogeneic mesenchymal adult stem cells extracted from adipose tissue (Alofisel®, previously Cx601) for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal CD. Furthermore, the 2022 edition of The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula recommends MSCs as one of the treatment options for perianal fistulas with a recommendation grade of 2B (28). Additionally, a study by Georgiev-Hristov T et al. aimed to present a MSCs surgical protocol to optimize the results of this emerging therapy. The study outlines a step-by-step surgical protocol for the treatment of PFs using adipose-derived MSCs, detailing the preparation methods, surgical procedure steps, intraoperative cell handling techniques, and emphasizing the critical importance of adhering to the

surgical protocol for effective fistula management (29). FG has been used as a novel treatment for numerous colorectal conditions, including fistulas in entero-cutaneous fistulas, because it is simple to apply and has minimal complications. Additionally, FG has been considered an optimal vehicle for stem cell delivery. It acts as a temporary matrix that favors cell-matrix interactions and allows MSCs to perform local and paracrine functions (30). Besides, FG can act as a scaffold to hold stem cells in place and fill large defects with MSCs after coring out and curetting the fistula tract, and it can also increase cell transplant survival and enhance the biological function of transplanted cells (31,32).

In the last 20 years, FG combined with cells has been successfully used for tissue engineering applications. More recently, the FG has become the preferred scaffold for stem cell transplantation; different types of stem cells have been combined with FG for cell delivery, such as BMSCs and ASCs (33,34). These stem cells, together with FG, have been successfully used for osteochondral repair, neuroprotection, bone repair, enhancement of nerve regeneration, wound healing and myocardial infarction repair. As a new therapy for PFs, research on FG combined with MSCs was first carried out in 2009 (16). The study showed closure was maintained in 17 (71 %) of 24 patients who received MSCs in addition to FG after eight weeks and in 15 (62.5 %) of 24 after one year of follow-up, during which time no safety issues were identified. Subsequently, an increasing number of studies have attempted to treat PFs with FG plus MSCs. Therefore, our study aimed to evaluate the effectiveness and safety of local FG combined with MSCs in the treatment of PFs.

To our knowledge, this is the first systematic review and meta-analysis to evaluate the safety and efficacy of local FG combined with MSCs therapy for PFs. Findings from our study show that injection of FG plus MSCs in patients with PFs is feasible and safe. Furthermore, our study suggests that local FG combined with MSCs therapy appears to achieve higher HR for PFs than local FG-alone therapy. Additionally, a previous study highlighted that many PFs have some part difficult to inject technically because they are located in a high position, and even the injected MSCs tend to reflux into the tract because the submucosa of the fistulous tract is very soft from chronic inflammation. However, MSCs in FG matrix effectively release

growth factors to enhance wound healing and soluble factors to inhibit immune response by suppressing both T-cell proliferation and secretion of proinflammatory cytokines from the activated T cells (35). So, this evidence collectively supports that combined FG with MSCs has a synergistic effect on the healing of PFs. The study by García-Olmo D (2009), which compared patients with and those without CD, showed no differences in HR between these subgroups (16). But, the study by Cheng F et al. showed that local MSCs therapy showed more promising results in fistulas associated with CD than those associated with non-CD (9). Our meta-analysis indicated that patients with CD appear to obtain a higher HR for PFs compared with patients without CD (79 % *vs* 62 %). Therefore, we think local FG combined with MSCs therapy appears to provides superior treatment for PFs associated with CD. Due to the limitations of the included studies in our meta-analysis, the strength of this conclusion is limited, but this provides guidance for FG plus MSCs therapy in selecting the most suitable types of PFs for treatment. In the future, more RCTs are needed to confirm this conclusion.

MSCs can be isolated from various tissues including the bone marrow, adipose tissue, and human umbilical cord. In our review, most stem cells were autologous adipose-derived MSCs. A study has shown that adipose tissue-derived MSCs are superior to bone marrow-derived MSCs in terms of immunosuppressive capacity (36). Furthermore, the subcutaneous adipose tissue is considered an easily accessible source for obtaining a large amount of cells through minimally invasive procedures (aspiration or liposuction). Obtaining adipose tissue reduces the risk of side effects for donors. A study indicated that autologous MSCs have shown more promising results than allogeneic MSCs in the treatment of fistulas (37). Moreover, the use of autologous MSCs is more acceptable, and there is no ethical conflict. Thus, these facts suggest that there should be more attempts to make use of autologous adipose tissue as a source of MSCs. However, the possibility of disease-related effects on autologous MSCs must be taken into account. In addition, autologous MSCs are not immediately available upon request, because isolation and expansion of MSCs to sufficient numbers of cells require weeks that may result in treatment delay. Allogeneic MSCs, easily obtained from a healthy donor, are a product

accessible to more patients. So, we also need to consider the timeliness and cost-effectiveness of treatment to optimize the treatment. We know that effective treatment and a reduction in recurrence rates depend on accurate detection and characterization of the PFs. With advances in techniques, MRI imaging has been proven to play an important role in PFs evaluation and is currently considered to be the gold standard method (38). In our meta-analysis, three trials evaluated fistula healing on the basis of MRI (long-term MRI can detect deep persistence). Finally, our study revealed that when MRI was utilized to evaluate fistula healing post-treatment, the HR decreased from 70 % to 51 %. This result reminded us that the HR may be overestimated when fistula healing was only defined as complete reepithelialization of the external opening. Therefore, with the goal of optimizing this therapy, we need more objective definitions of the healing of PFs in future studies. Although fistula closure is the primary goal of treatment, it is also important that closure is sustained not only because it reflects the long-term efficacy of treatment but also because recurrences are traditionally considered more difficult to treat subsequently by surgery. The study by Guadalajara H et al. (17) showed that seven out of 12 patients with fistula closure after treatment with MSCs plus FG were free of recurrence over a period of three years. In the future, we need more clinical studies to explore the long-term effectiveness and safety of local FG plus MSCs therapy for PFs. In addition to long-term results, future studies will need to balance the outcomes of these techniques with the capital investment.

Questions persist regarding the safety of MSCs treatment. AEs and serious adverse events (SAEs) are the common indicators for treatment safety. The risk of infection and tumor is of main concern with the use of MSCs. Due to insufficient studies, we could not conduct a meta-analysis for AEs/SAEs. We still consulted the full text of eligible publications to determine whether any AEs/SAEs were related to local FG combined with MSCs therapy, and it delighted us that no AEs/SAEs were directly related to therapy. No unexpected safety event occurred. In addition, this procedure has no extra risk for an anal sphincter injury. Our study did not reveal any specific signs of carcinogenicity. In the future, long-term follow-up must be conducted in more patients to thoroughly evaluate the safety of FG plus MSC treatment for PFs.

Although our study demonstrates the preliminary efficacy of local FG combined with MSCs therapy for PFs, there are still many unsolved areas that require clarification, such as the most appropriate technique for FG and MSCs transplant, which is still controversial. The best treatment dosage, type, and source of MSCs remain unknown. Our study has some limitations. Firstly, there were ten studies, of which the majority were single-arm trials rather than RCTs. Due to this design, inherent biases were exposed, such as selection and information bias as well as confounders, which must be considered when measuring the outcomes in this meta-analysis. Secondly, of the ten studies, some reported raw data on clinical healing of patients after local FG plus MSCs therapy, with substantial heterogeneity (I^2 = 55.9 %). The trials used different cell types and variable definitions of fistula healing, had variable time points for primary assessment of healing (ranging from eight weeks to two years), and included different dosages of MSCs, further adding to study heterogeneity. The diverse differentiation and regeneration capacities of MSCs, different clinical trials for MSCs isolation, different culture programs, and the patients' ages, disease severities, and other factors may also contribute to study heterogeneity. Thirdly, despite the pooling of ten studies, some studies had small patient populations. Furthermore, due to insufficient studies, we could not conduct a meta-analysis for AEs, and we analyzed them in our systematic review. Moreover, each study incorporated additional surgical techniques which, by themselves, have shown a rate of clinical closure and healing. In the future, more RCTs are needed to optimize the efficacy and safety of FG plus MSCs treatment for PFs.

CONCLUSIONS

Overall, our study indicated that local FG combined with MSCs appears to offer a safe and effective treatment approach for PFs. This treatment significantly promoted the healing of PFs when compared to the isolated use of FG. Furthermore, FG combined with MSCs therapy appears to provide superior treatment for PFs associated with CD. However, safety and efficacy must be evaluated through a more rigorous validation with a larger sample size in the future before the therapy is largely applied in clinical practice.

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Table 1.

Study	*Type of study*	*Cell type and source*	*Disease type*	*Outcome assessment*	*Use of MRI*	*Study outcomes*	*Intervention (mean)*	*AEs*
García-Olmo D (16) (2009)	Phase II, trial; RCT	Autologous, ASCs	CD, non-CD	Re-epithelialization	No	17/24 for MSCs+ FG *vs* 4/25 FG at 8 w; (CD: 5/7 *vs* 1/7) (non-CD: 12/17 *vs* 3/18)	2-6 × 10^7 MSCs	MSCs + FG *vs* FG (11 *vs* 17)
Guadalajara H (17) (2012)	Phase II, trial RCT	Autologous, ASCs	CD, non-CD	Re-epithelialization + MRI	Yes	10/18 for MSCs + FG *vs* 3/12 for FG at 1 year (CD: 2/4 *vs* 1/2) (non-CD: 8/14 *vs* 2/10)	First: 2 × 10^7 MSCs Second: 4 × 10^7 MSCs	2 AEs
Herreros MD (18) (2012)	Phase III, trial RCT	Autologous, ASCs	Non-CD	Re-epithelialization + MRI	Yes	24/42 for MSCs *vs* 22/42 for MSCs + FG *vs* 19/51 for FG at 48 w	2-6 × 10^7 MSCs	Most patients had at least 1 AE; 37 SAEs in 30 patients
Lee WY (19) (2013)	Phase II, trial	Autologous, ASCs	CD	Re-epithelialization	No	27/33 MSCs + FG at 8 weeks	First: 15.8 × 10^7 MSCs Second: 19.1 × 10^7 MSCs	No ASCs-related AEs were observed

Cho YB (20) (2013)	Phase I, trial	Autologous, ASCs	CD	Re-epithelialization	No	3/9 MSCs + FG at 8 weeks	3-40 × 10^7 MSCs	13 AEs reported in 7 patients; 3 SAEs in 2 patients
Cho YB (21) (2015)	Phase II, trial	Autologous, ASCs	CD	Re-epithelialization	No	21/26 MSCs + FG at 24 months	9.0-42.0 × 10^7 MSCs	53 AEs, no ASCs-related AEs
Choi S (22) (2017)	Phase II, trial	Autologous, ASCs	Non-CD	Re-epithelialization	No	9/13 MSCs + FG at 8 weeks	14.4 × 107 cells were injected on average	No grade 3 or 4 AEs; 2 patients reported SAEs
García-Arranz M (23) (2020)	RCT	Autologous, ASCs	Non-CD	Re-epithelialization	No	10/20 for MSCs + FG 5/19 for FG at 2 years	First: 10 × 10^7 MSCs Second: 10 × 10^7 MSCs	7/23 for MSCs + FG *vs* 9/21 for FG
Maciel Gutiérrez VM (24) (2021)	Phase I, trial	Allogeneic, ASCs	Non-CD	Re-epithelialization	No	13/19 for MSCs + FG at 24 w	4 × 10^7 MSCs	3 AEs, no ASC-related AEs

Vosough M (25) (2022)	Case Series	Autologous, BMSCs	CD	Re-epithelialization + MRI	Yes	1/5 for MSCs + FG at 24 w	4×10^7 MSCs	No AEs were observed

RCT: randomized controlled trials; MSC: mesenchymal stem cell; ASC: adipose-derived MSCs; CD: Crohn's disease; FG: fibrin glue; w: weeks; MRI: magnetic resonance imaging; AE: adverse events; BMSC: bone-marrow-derived MSC.

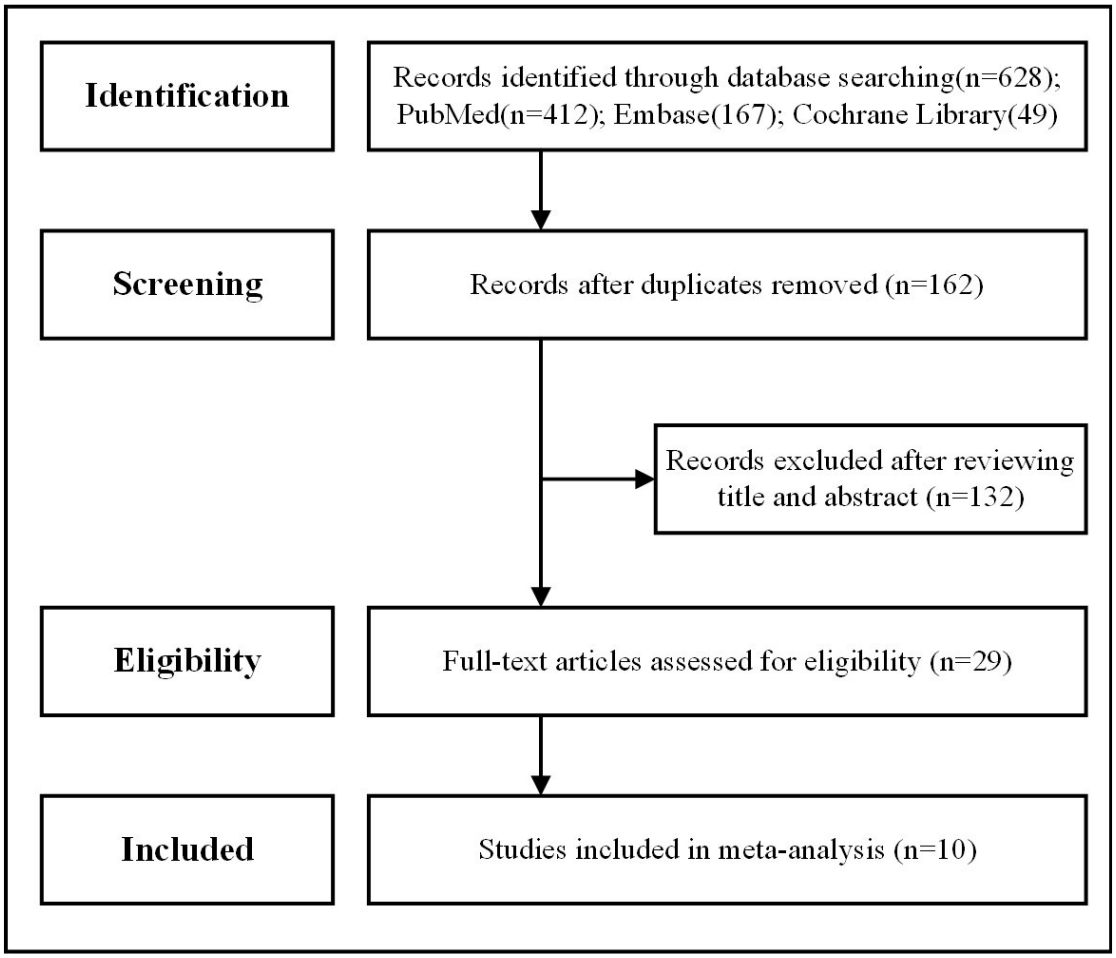

Fig. 1. Flow diagram of included and excluded studies in this meta-analysis.

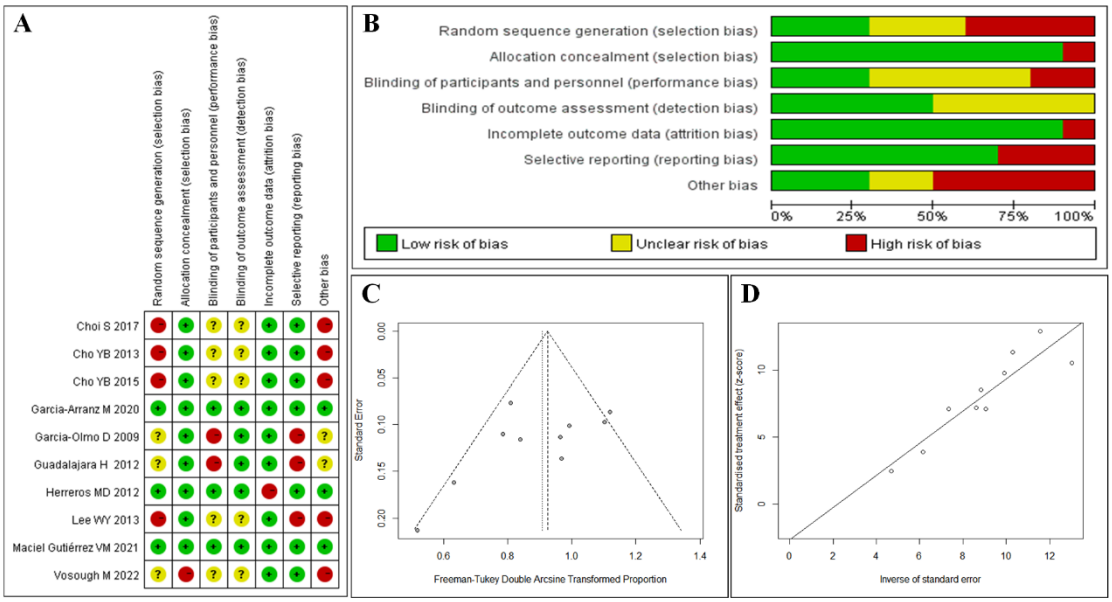

Fig. 2. A and B. Risk of bias of the included studies in the meta-analysis. C. Funnel plot shows no existence of publication bias. D. Egger's test was performed to detect publication bias for included studies.

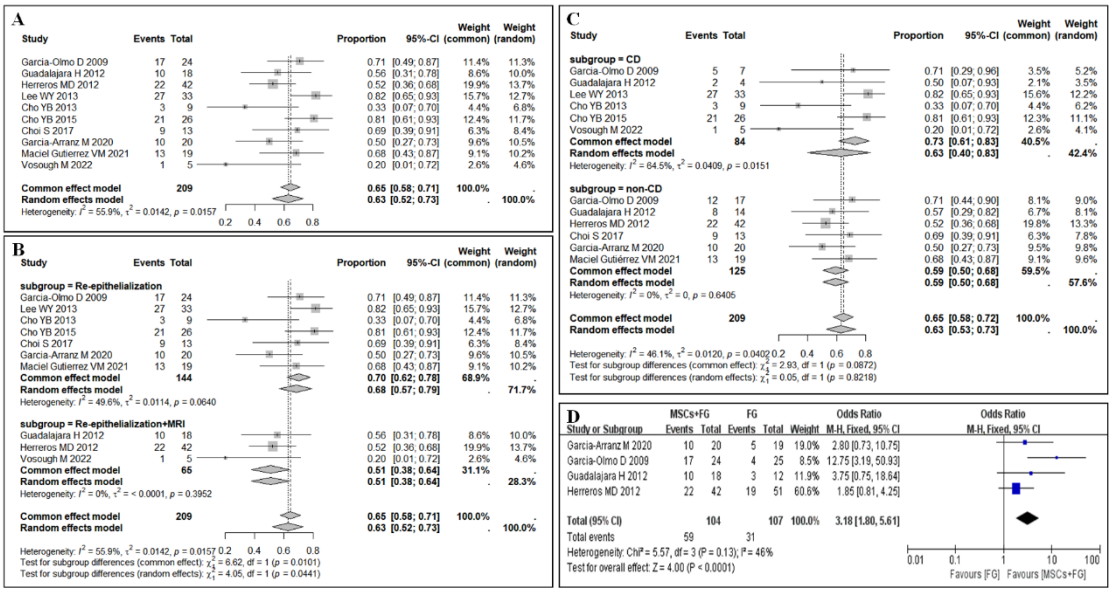

Fig. 3. A. Forest plots about the pooled results of healing rate (HR). B. Forest plot showing changes of HR in different assessment methods. C. Forest plot showing changes in HR by perianal fistulas (PFs) types (Crohn's disease [CD] *vs* non-CD). D. Efficacy of mesenchymal stem cells (MSCs) + fibrin glue (FG) *vs* FG for PFs.