Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

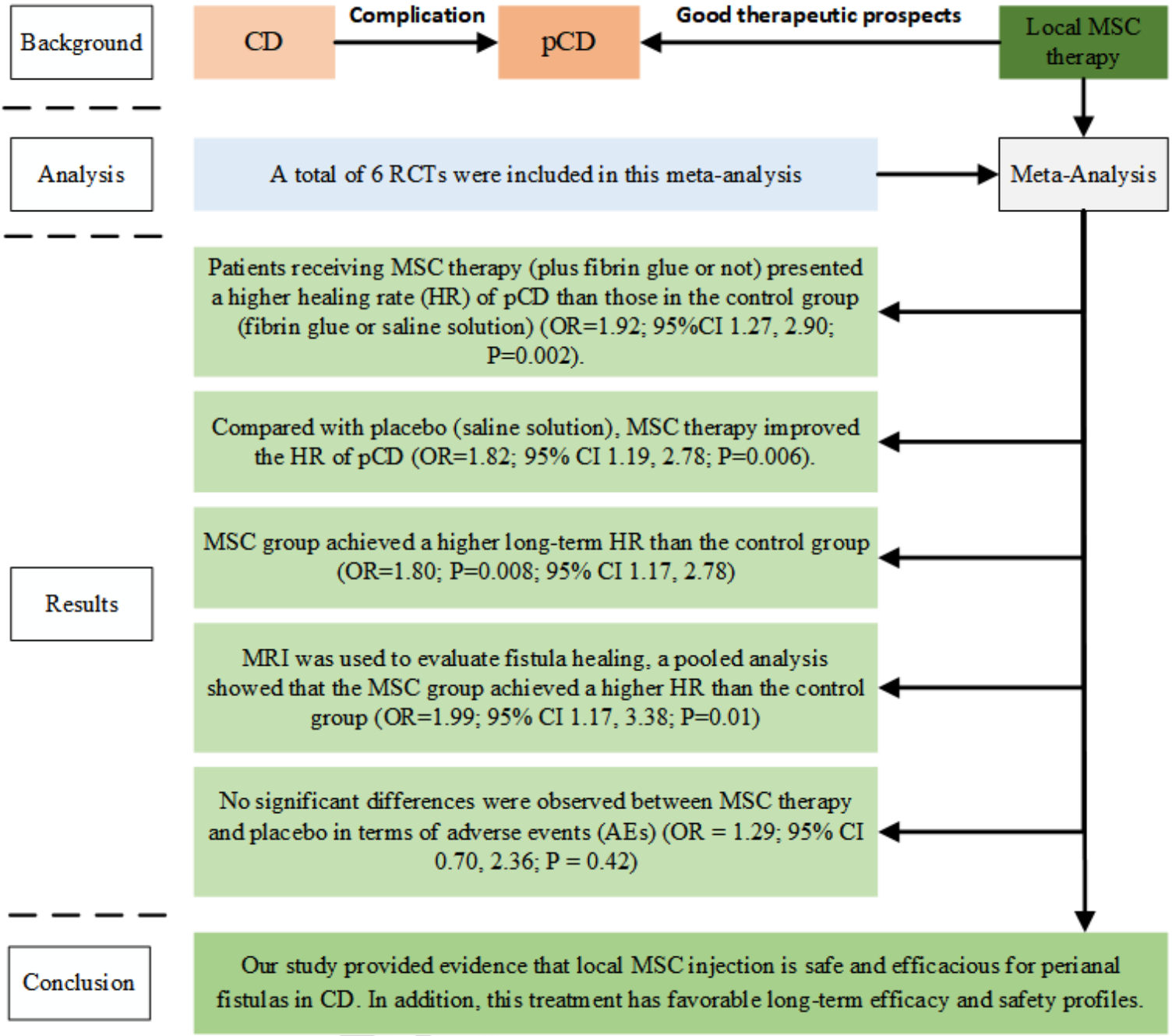
Title:
Efficacy and safety of mesenchymal stem cells in the treatment of perianal fistulas in Crohn's disease: a meta-analysis of randomized controlled trials

Authors:
Fang Cheng, Zhong Huang, Wei Wei, Zhi Li

DOI: 10.17235/reed.2023.9213/2022
Link: PubMed (Epub ahead of print)

Please cite this article as:
Cheng Fang, Huang Zhong , Wei Wei, Li Zhi. Efficacy and safety of mesenchymal stem cells in the treatment of perianal fistulas in Crohn's disease: a meta-analysis of randomized controlled trials. Rev Esp Enferm Dig 2023. doi: 10.17235/reed.2023.9213/2022.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology



Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Efficacy and safety of mesenchymal stem cells in the treatment of perianal fistulas in Crohn's disease: a meta-analysis of randomized controlled trials

Fang Cheng, Zhong Huang, Wei Wei, Zhi Li

Department of Gastroenterology, Zigong First People's Hospital Zigong, Sichuan Province, China.

Corresponding author: Fang Cheng, Department of Gastroenterology. Zigong First People's Hospital, 42 Shangyihao Road, Zigong 643000, Sichuan Province, China.
E-mail: 1072893878@qq.com.

Author´s contributions:

FC, ZH and WW contributed to study concept and design, acquisition, analysis, interpretation of the data and drafting of the manuscript. FC and ZH contributed to data collection and manuscript review. FC and ZL contributed to study concept and design, analysis and interpretation of data and critical revision of the manuscript for important intellectual content. WW and ZL supervised the study. All authors read and approved the final manuscript.

Abbreviations list: MSC: mesenchymal stem cell; CD: Crohn's disease; RCTs: randomized controlled trials; pCD: perianal CD; OR: odds ratio; CI: confidence interval; AEs: adverse events;

ABSTRACT

Objectives: Local mesenchymal stem cell (MSC) therapy for perianal fistulas in Crohn's disease (CD) has yielded promising results, but it still remains controversial. In this study, we aimed to conduct a meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of both autologous or allogeneic MSC therapy for perianal CD (pCD).

Methods: RCTs reporting MSC therapy for perianal fistulas in CD were searched and included. The effectiveness and safety data were analyzed using RevMan 5.3.

Revista Española de Enfermedades Digestivas
The Spanish Journal of Gastroenterology

Results: A total of 6 RCTs were included in this meta-analysis. The analysis showed that patients receiving MSC therapy (plus fibrin glue or not) presented a higher healing rate (HR) of pCD than those in the control group (fibrin glue or saline solution) (odds ratio (OR)=1.92; 95% confidence interval (CI) 1.27, 2.90; P=0.002). Compared with placebo (saline solution), MSC therapy improved the HR of pCD (OR=1.82; 95% CI 1.19, 2.78; P=0.006). In thous studies, our study confirmed that significant long-term efficacy at least 52 weeks post MSC therapy (OR=1.80; P=0.008; 95% CI 1.17, 2.78). When MRI was used to evaluate fistula healing, a pooled analysis showed that the MSC group achieved a higher HR than the control group (OR=1.99; 95% CI 1.17, 3.38; P=0.01). Furthermore, no significant differences were observed between MSC therapy and placebo in terms of adverse events (AEs) (OR = 1.29; 95% CI 0.70, 2.36; P = 0.42). None of the AEs were judged to be related to MSC treatment.

Conclusions: This meta-analysis of RCTs provided evidence that local MSC injection is safe and efficacious for perianal fistulas in CD. In addition, this treatment has favorable long-term efficacy and safety profiles.

Keywords: c

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder that can involve the entire gastrointestinal tract. Approximately one-quarter of patients with CD present symptoms associated with perianal lesions, and half of the lesions are fistulizing [1]. Although the pathophysiology of fistula formation in the course of CD has not yet been fully elucidated, defects in the inflamed intestinal endothelium are of key significance in this mechanism [2]. Perianal fistula is estimated to affect up to 28% of patients with CD in the first two decades after diagnosis [3]. The presence of perianal fistulas at diagnosis has been shown to be an independent predictive factor for the development of a disabling disease course [4]. Patients with perianal fistulas suffer from pain, embarrassing discharge, fecal incontinence and a significant reduction in quality of life [5]. Some studies have also shown that the risk of tumors is increased

among patients with CD [6-7]; for example, CD patients have an increased risk of developing anal cancer [8]. Therefore, perianal CD (pCD) is a serious and frequent complication and has a heavy negative impact on patients' quality of life. Today, combined medical and surgical therapy is understood to perform better than either treatment alone in healing fistulas. However, the benefit in terms of sustained fistula closure has proven to be limited [9]. Surgical procedures may increase the risk of fecal incontinence [10]. Furthermore, only approximately one-third of patients treated with biological agents achieve fistula remission, and high rates of fistula recurrence have been reported one year after discontinuation of infliximab treatment [11]. The need to use biological agents creates an increased risk of opportunistic infections and other complications [12]. In addition, most treatments are unable to achieve long-term healing of fistulas. Therefore, the management of pCD and the realization of long-term healing have remained challenging problems. In this context, stem cell–based therapies have become an attractive approach for pCD.

In recent years, mesenchymal stem cells (MSCs) have been recognized as a good candidate for regenerative medicine. MSCs are multipotent cells capable of self-renewal and differentiation. They can be isolated from different tissues, such as bone marrow, adipose tissue, and umbilical cord, and are expanded under in vitro conditions to obtain large quantities. MSCs can upregulate Tregs, migrate to inflammation sites, and cause regeneration and healing of damaged tissues [13]. In addition, the lack of substantial immunogenicity of MSCs allows them to be used across human leukocyte antigen (HLA) barriers without inducing immune rejection after transplantation [14]. Taken together, the evidence suggests that MSCs can downregulate immune responses and anti-inflammatory properties and promote tissue healing. They may achieve long-term healing of fistulas, significantly improving patients' quality of life. Multiple studies have been conducted to assess the efficacy and safety of MSC therapy in pCD, but the outcomes remain controversial. Our meta-analysis was designed and conducted to evaluate the efficacy and safety of MSC therapy for pCD based on direct evidence from previous randomized controlled trials (RCTs).

METHODS

This review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Search strategy.

A comprehensive literature search was performed in PubMed, Embase, and the Cochrane Library for RCTs published up to and including March 2022, with no language restrictions. The keywords for the search were “inflammatory bowel disease”, “Crohn’s disease”, “Crohn disease”, “mesenchymal stem/stromal cells”, “stem cell”, “stromal cell”, “perianal fistula”, “Crohn’s perianal fistula”, “cryptoglandular perianal fistula”, “randomized controlled trial”, “controlled clinical trial”, and “randomized”.

Study selection.

The inclusion criteria were as follows: (1) human subjects; (2) RCT design; (3) patients with pCD; (4) patients aged ≥18 years; (5) intervention with local MSC therapy; (6) comparison with placebo, standard of care, or a different MSC treatment regimen; and (6) outcome: efficacy and/or safety. The exclusion criteria were (1) nonhuman studies; (2) nonrandomized trials or trials with inaccurate randomization methods; (3) studies for which the full text was unavailable; (3) systemic infusion of MSCs for perianal fistulas; (4) non-CD; and (5) duplicate publications. Two investigators (FC, ZH) participated in the literature selection and data extraction, if there were any disagreements, a third investigator was consulted (WW).

Data extraction and quality assessment.

Two investigators(FC,ZH) independently extracted the following data from the included studies: (1) first author; (2) publication date; (3) number of patients; (4) type and source of allogeneic vs autologous MSCs; (5) outcome assessment; (6) results; (7) dosage and modality of administration; (8) refractory disease; (9) adverse events (AEs); and (10) concurrent use of anti-TNF agents. The baseline characteristics

of the RCTs included in this study are summarized in Table 1. The Cochrane risk-of-bias assessment tool was used to determine the methodological quality of RCTs [16]. The assessment for each study included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each item was classified as low risk, high risk, or unclear risk. The risk of bias was determined by compiling all the items in a risk-of-bias graph. Any disagreement among investigators was resolved through discussion.

Statistical analysis.

The healing rate (HR) of pCD was regarded as the main endpoint. Statistical analysis was performed using Review Manager 5.3 software. The odds ratios (ORs) and related 95% confidence intervals (CIs) were calculated to compare the treatment and control groups. Statistical heterogeneity between the clinical trials was assessed via I^2 statistics (with I^2 values ≥ 50% and < 50% indicating substantial and low heterogeneity, respectively). For I^2 < 50%, a fixed-effects statistical model was applied. Otherwise, we used a random-effects model. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Literature search and quality assessment.

The literature search process is illustrated in Fig 1. A total of 507 references were obtained from the electronic databases. After deduplication, a total of 368 records remained. 343 records were excluded based on reviewing title and abstract. The remaining 25 records were assessed for eligibility by scrutinizing the full text. Ultimately, 6 RCTs were included in our meta-analysis [17-22]. The studies were published from 2009 to 2022. All included patients suffered from complex CD with treatment-refractory perianal fistulas. The route of MSC administration was local injection. Four studies investigated the HR of pCD based on reepithelization of the external opening and absence of collection >2 cm by MRI [18-20]. Two studies administered autologous MSCs [17-18], while four studies used allogeneic MSCs [19-22]. Five studies compared MSCs to saline solution [19-22], while 2 studies

compared MSCs plus fibrin glue to fibrin glue alone [17-18].

The included RCTs were estimated to be of moderate quality. A low risk of bias was mostly detected in selection bias, performance bias, detection bias and attrition bias. A high risk of bias was mostly found in performance bias, reporting bias, and other bias. An unclear risk of bias mostly occurred in selection bias and other bias. A summary of the risk of bias in the included studies is presented in Fig 2A-B. The funnel plot does not indicate publication bias (Fig. 2C).

Efficacy of MSC therapy for pCD.

The healing of fistulas was the primary endpoint of our meta-analysis. In all 6 of the RCTs involved, the patients who received MSC therapy (MSCs/MSCs + fibrin glue) had a markedly higher HR than the control group (saline solution or fibrin glue), and the difference was statistically significant (OR=1.92; 95% CI 1.27, 2.90; P= 0.002) (Fig. 3A). Fibrin glue is being studied as a vehicle for MSCs in regenerative medicine and is capable of stimulating cellular adhesion and growth. Some studies have indicated that fibrin glue injection is an efficacious treatment for perianal fistulas in CD [23-24]. Therefore, the HR of pCD may be overestimated when MSCs are combined with fibrin glue therapy. In our study, 4 of 6 articles compared MSCs with placebo (saline solution). The results showed that the patients who received MSCs had a markedly higher HR than the placebo group, and the difference was statistically significant (OR=1.82; 95% CI 1.19, 2.78; P= 0.006) (Fig. 3B).

Efficacy of MSCs for pCD evaluated by MRI.

Pelvic MRI is a noninvasive, highly accurate examination for the diagnosis and classification of anal fistulas. In our meta-analysis, MRI was used to evaluate fistula healing in 3 RCTs. The pooled analysis showed that the MSC group had a higher HR than the control group (OR = 1.99; 95% CI 1.17, 3.38; P=0.01) (Fig. 3C).

Long-term effectiveness of MSCs for pCD.

With the currently available treatment options for perianal fistulas in CD, long-term healing remains a challenge, and it is uncertain whether MSCs provide long-term

improvement. Our meta-analysis included 4 studies that assessed the long-term efficacy of MSC treatment for at least 52 weeks. The pooled analysis showed that MSCs provided greater long-term efficacy than control treatments for pCD (OR = 1.80; 95% CI 1.17, 2.78; P=0.008) (Fig. 3D).

Different sources of MSCs for the treatment of pCD.

Autologous MSCs from the recipient and allogeneic MSCs from donors have their own advantages and disadvantages in their medical therapy. The therapeutic benefits of using autologous vs. allogeneic MSCs for pCD are inconclusive. In our systematic review, 2 of the 6 studies reported the use of autologous stem cells for pCD treatment, while 4 of the 6 studies reported the use of allogeneic stem cells. A fixed-effects model was applied, and the allogeneic MSC group also had a higher HR than the control group (OR = 1.82; 95% CI 1.19, 2.78; P=0.006) (Fig. 3E).

Adverse events.

This study included two RCTs that determined the safety of pCD. There were no significant differences in AE rates between the MSC and control groups (OR = 1.29; 95% CI 0.70, 2.36; P=0.42) (Fig. 3F).

DISCUSSION

Perianal problems, which are common features of CD, are associated with great morbidity and place a great financial burden on healthcare systems. Patients with pCD experience a reduced quality of life and a high risk of poor long-term outcomes [25]. Despite the vast advances in surgical and medical treatments over the last decade, it remains challenging to identify the optimal therapeutic method for pCD. This condition generally has low long-term remission rates. The low success rate of existing methods may be related to the complex pathophysiology of perianal fistulas, damage to multiple tissues after a complicated immune process in the gastrointestinal (GI) tract, infectious pathology due to the overgrowth of bacterial flora, and continuous flow of fecal matter through the sites of mucosal injury [26]. MSCs have the capacity to differentiate into various mesodermal cell lineages,

downregulate immune responses, exert anti-inflammatory effects, and promote tissue healing. Therefore, the injection of MSCs is emerging as a new therapeutic option for pCD.

To date, this study is the first meta-analysis of RCTs on local MSC therapy for perianal fistulas in CD. Our meta-analysis demonstrated that MSC therapy alone or combined with fibrin glue treatment is an effective and safe treatment for pCD. At present, MSCs are usually injected systemically (for intravenous transplantation) or locally. However, the delivery of stem cells directly to fistula tracts can increase cell numbers locally to aid fistula healing. Therefore, our study focused exclusively on local administration of MSCs. Although cell-based therapy using MSCs represents a new treatment prospect for pCD patients, little has been reported on its long-term efficacy. In our study, we evaluated the long-term effectiveness of MSC treatment for perianal fistulas in patients with CD. The results showed that MSCs were associated with improved long-term healing compared with the control (OR = 1.36; 95% CI 1.08, 1.71; P=0.009). The benefit over placebo was sustained at least 52 weeks after the local injection of MSCs. Our results also indicate a possible delayed effect of MSCs. The results are encouraging. Additionally, our study provides evidence of that MSC therapy has a good long-term safety profile as a treatment for pCD. In the future, additional well-designed RCTs are needed to evaluate the long-term efficacy of MSC therapy for pCD.

In our study, all the included patients were concomitantly treated with biological therapy. Cheng F et al. showed that treatment with anti-TNF agents did not appear to affect the long-term efficacy of MSCs for treatment-refractory patients [27]. Another study indicated that the exposure of MSCs to physiological concentrations of anti-TNF agents did not affect their survival or their capacity to inhibit peripheral blood mononuclear cell proliferation [28]. However, a study showed that maintenance dosing of biological therapies is necessary to preserve the initial treatment response of perianal fistulas [29]. Therefore, it remains unknown whether MSCs interact with anti-TNF agents when used in combination with them. In the future, more studies are needed to address this question. Cell therapy strategies using MSCs carried in fibrin glue have shown promising results in regenerative

medicine. One study indicated that fibrin glue promoted the adhesion, proliferation and differentiation of MSCs, which perform important biological functions at the injury site [30]. Increasingly many studies aim to establish an approach to treat injured tissue using fibrin glue and MSCs [31-32]. In our study, the HR of pCD may be overestimated after local injection of MSCs plus fibrin glue. We are interested in whether fibrin glue and MSCs have a synergistic effect in pCD treatment. In the future, more studies are needed to evaluate the effect of fibrin glue combined with MSCs on perianal fistulas in CD.

MSCs can be harvested from autologous or allogeneic sources. The selection of an appropriate cell source is a practical issue that greatly impacts the success of cell therapy for pCD. It has been long debated whether self-derived or donor-derived MSCs should be applied clinically, and the relative therapeutic benefits of these two cell sources are inconclusive. It has been reported that MSCs isolated from CD patients are functionally analogous to those of healthy individuals, and no differences were found in terms of phenotype, in vitro growth kinetics, or response to IFN-γ [33]. Autologous MSCs are easy to obtain, unsusceptible to immune rejection after infusion, and free of ethical concerns. However, it is time consuming to isolate MSCs and expand them ex vivo to a clinically relevant number of cells . In addition, donor-site pain and age-associated dysfunction in proliferation and differentiation may limit the broad application of autologous MSC therapy [34]. Additionally, MSCs from patients or even donors with known or suspected disease susceptibility–related genetic backgrounds may not benefit recipients in the long term because such cells may remain in the body of the recipient for many years. Allogeneic MSCs can be rapidly administered from a completely validated cell bank and provide affordable therapy to large numbers of patients. In our study, the pooled OR for studies of autologous MSC therapy was 5.20 (95% CI 0.75, 35.82; P=0.09), while studies of allogeneic MSCs had a pooled OR of 1.97 (95% CI 1.40, 2.75; P <0.0001). Therefore, considering the need for timely and cost-effective treatment, allogeneic MSCs may be optimal for the treatment of pCD.

Perianal fistulas represent one of the most critical complications of CD. Their management and treatment call for a multidisciplinary approach with an accurate

description of imaging findings. MRI plays a crucial role in the evaluation, detection and follow-up of CD perianal fistulas [35]. In fact, MRI is the gold standard imaging technique for evaluating these lesions. This modality can capture the fine anatomical details of the anal sphincter. MRI has 100% sensitivity and 86% specificity in the detection of perianal fistulas [36]. In our meta-analysis, 4 RCTs used detailed physical examination complemented by pelvic MRI to evaluate the course of fistulas. The pooled analysis showed that the MSC group achieved a higher HR than the control group (OR = 1.95; P=0.0007). To optimize this emerging therapy, future studies must define the healing of perianal fistulas in more objective ways (e.g., endoscopy, MRI).

Questions persist regarding the safety of MSC treatment in pCD patients; indeed, safety is a major concern in MSC therapy. In our study, there was no difference in AEs between the MSC and control groups. The risk of AEs is relatively low, and no adverse effects related to the stem cells themselves have been reported. Common AEs such as anal pain, anal bleeding, fever, abdominal pain, diarrhea, and perianal abscess are mostly associated with local MSC injection procedures rather than MSCs themselves. Additionally, this minimally invasive procedure avoids the unnecessary risk of fecal incontinence. The risk of tumors is the main concern with the use of MSCs. Some studies have indicated that MSCs may promote the development of cancerous tumors by inducing neoplastic cell proliferation and promoting angiogenesis [37-38]. To date, there have no reported cases of neoplasms developing after perianal MSC treatment. However, it is important to consider that the development of tumors is a long-term process. In the future, long-term follow-up must be conducted in more patients to thoroughly evaluate the safety of MSC treatment for pCD.

In this study, we aimed to evaluate the efficacy and safety of MSC therapy through a meta-analysis of RCTs. However, this analysis had several limitations: (1) The studies used different types and sources of MSCs, including adipose tissue and bone marrow from autologous as well as allogeneic sources. (2) The timepoint for the assessment of fistula healing varied significantly (8 weeks to 40 months). (3) Different studies applied different criteria to define fistula healing. (4) More studies are needed to evaluate the long-term efficacy of MSC therapy. (5) There is still

controversy in the literature over the most appropriate technique for MSC transplantation. (6) The HR of pCD may be overestimated after local injection of MSCs plus fibrin glue. In the future, more RCTs are needed to optimize the efficacy and safety of MSCs for pCD.

CONCLUSION

Our study yielded evidence that local MSC therapy is a safe and effective treatment for perianal fistulas in CD. This innovative strategy is effective in producing a long-lasting healing effect. Allogeneic MSCs had relatively high rates of clinical healing and may be the optimal donor cells for the treatment of pCD.

ACKNOWLEDGMENTS

None.

REFERENCES

1. Bell SJ, Williams AB, Wiesel P, Wilkinson K, Cohen RC, Kamm MA. The clinical course of fistulating Crohn's disease. Aliment Pharmacol Ther. 2003;17(9):1145-1151.）

2. Scharl M, Rogler G. Pathophysiology of fistula formation in Crohn's disease. World J Gastrointest Pathophysiol. 2014;5(3):205-212.

3. Schwartz DA, Loftus EV Jr, Tremaine WJ, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. Gastroenterology. 2002;122(4):875-880.

4. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of Crohn's disease. Gastroenterology. 2006;130(3):650-656.

5. Vollebregt PF, van Bodegraven AA, Markus-de Kwaadsteniet TML, van der Horst D, Felt-Bersma RJF. Impacts of perianal disease and faecal incontinence on quality of life and employment in 1092 patients with inflammatory bowel disease. Aliment Pharmacol Ther. 2018;47(9):1253-1260.

6. Katsanos KH, Tatsioni A, Pedersen N, et al. Cancer in inflammatory bowel disease 15 years after diagnosis in a population-based European Collaborative follow-up

study [published correction appears in J Crohns Colitis. 2012 Feb;6(1):132-3]. J Crohns Colitis. 2011;5(5):430-442.

7. Algaba A, Guerra I, Castano A, et al. Risk of cancer, with special reference to extra-intestinal malignancies, in patients with inflammatory bowel disease. World J Gastroenterol. 2013;19:9359–9365.

8. Thomas M, Bienkowski R, Vandermeer TJ, Trostle D, Cagir B. Malignant transformation in perianal fistulas of Crohn's disease: a systematic review of literature. J Gastrointest Surg. 2010;14(1):66-73.

9. Molendijk I, Nuij VJ, van der Meulen-de Jong AE, van der Woude CJ. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm Bowel Dis. 2014;20(11):2022-2028.

10. Lightner AL, Ashburn JH, Brar MS, et al. Fistulizing Crohn's disease. Curr Probl Surg. 2020;57:100808.

11. Lee MJ, Parker CE, Taylor SR, et al. Efficacy of medical therapies for fistulizing Crohn's disease: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018;16:1879-1892.

12. Ford AC, Peyrin-Biroulet L. Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol. 2013;108(8):1268-1276.

13. Salem HK, Thiemermann C. Mesenchymal stromal cells: current understanding and clinical status. Stem Cells. 2010;28(3):585-596.

14. Jones BJ, McTaggart SJ. Immunosuppression by mesenchymal stromal cells: from culture to clinic. Exp Hematol. 2008;36(6):733-741.

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. Published 2021 Mar 29. doi:10.1136/bmj.n71.

16. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. Cochrane Database Syst Rev. 2019;10:ED000142.

17. D. Garcia-Olmo, D. Herreros, I. Pascual et al., "Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial," Diseases

of the Colon and Rectum, vol. 52, no. 1, pp. 79–86, 2009.

18. Guadalajara H, Herreros D, De-La-Quintana P, Trebol J, Garcia-Arranz M, Garcia-Olmo D. Long-term follow-up of patients undergoing adipose-derived adult stem cell administration to treat complex perianal fistulas. Int J Colorectal Dis. 2012;27(5):595-600.

19. Molendijk I, Bonsing BA, Roelofs H, et al. Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cells Promote Healing of Refractory Perianal Fistulas in Patients With Crohn's Disease. Gastroenterology. 2015;149(4):918-27.e6.

20. Panés J, García-Olmo D, Van Assche G, et al. Long-term Efficacy and Safety of Stem Cell Therapy (Cx601) for Complex Perianal Fistulas in Patients With Crohn's Disease. Gastroenterology. 2018;154(5):1334-1342.e4.

21. Garcia-Olmo D, Gilaberte I, Binek M, et al. Follow-up Study to Evaluate the Long-term Safety and Efficacy of Darvadstrocel (Mesenchymal Stem Cell Treatment) in Patients With Perianal Fistulizing Crohn's Disease: ADMIRE-CD Phase 3 Randomized Controlled Trial. Dis Colon Rectum. 2022;65(5):713-720.

22. Panés J, Bouma G, Ferrante M, et al. INSPECT: A Retrospective Study to Evaluate Long-term Effectiveness and Safety of Darvadstrocel in Patients With Perianal Fistulizing Crohn's Disease Treated in the ADMIRE-CD Trial [published online ahead of print, 2022 Jan 31]. Inflamm Bowel Dis. 2022;izab361.

23. Vidon M, Munoz-Bongrand N, Lambert J, et al. Long-term efficacy of fibrin glue injection for perianal fistulas in patients with Crohn's disease. Colorectal Dis. 2021;23(4):894-900.

24. Grimaud JC, Munoz-Bongrand N, Siproudhis L, et al. Fibrin glue is effective healing perianal fistulas in patients with Crohn's disease. Gastroenterology. 2010;138(7):2275-2281.e1.

25. Maconi G, Gridavilla D, Vigano` C, et al. Perianal disease is associated with psychiatric co-morbidity in Crohn’s disease in remission. Int J Colorectal Dis 2014; 29:1285–1290.

26. Wei X, Yang X, Han ZP, et al. Mesenchymal stem cells: a new trend for cell therapy. Acta Pharmacol Sin. 2013;34:747–754.

27. Cheng F, Huang Z, Li Z. Mesenchymal stem-cell therapy for perianal fistulas in

Crohn's disease: a systematic review and meta-analysis. Tech Coloproctol. 2019;23(7):613-623.

28. Duijvestein M, Molendijk I, Roelofs H, et al. Mesenchymal stromal cell function is not affected by drugs used in the treatment of inflammatory bowel disease. Cytotherapy. 2011;13(9):1066-1073.

29. Lopez N, Ramamoorthy S, Sandborn WJ. Recent advances in the management of perianal fistulizing Crohn's disease: lessons for the clinic. Expert Rev Gastroenterol Hepatol. 2019;13(6):563-577.

30. Ortiz AC, Fideles SOM, Pomini KT, et al. Effects of Therapy with Fibrin Glue combined with Mesenchymal Stem Cells (MSCs) on Bone Regeneration: A Systematic Review. Cells. 2021;10(9):2323. Published 2021 Sep 5.

31. Wang K, Guan Y, Liu Y, et al. Fibrin glue with autogenic bone marrow mesenchymal stem cells for urethral injury repair in rabbit model. Tissue Eng Part A. 2012;18(23-24):2507-2517.

32. Blázquez R, Sánchez-Margallo FM, Álvarez V, Usón A, Marinaro F, Casado JG. Fibrin glue mesh fixation combined with mesenchymal stem cells or exosomes modulates the inflammatory reaction in a murine model of incisional hernia. Acta Biomater. 2018;71:318-329.

33. Carvello M, Lightner A, Yamamoto T, Kotze PG, Spinelli A. Mesenchymal Stem Cells for Perianal Crohn's Disease. Cells. 2019;8(7):764. Published 2019 Jul 23.

34. Ahmed AS, Sheng MH, Wasnik S, Baylink DJ, Lau KW. Effect of aging on stem cells. World J Exp Med 2017;7(1):1–10.

35. Tozer PJ, Burling D, Gupta A, Phillips RK, Hart AL. Review article: medical, surgical and radiological management of perianal Crohn's fistulas. Aliment Pharmacol Ther. 2011;33(1):5-22

36. Beets-Tan RG, Beets GL, van der Hoop AG, et al. Preoperative MR imaging of anal fistulas: Does it really help the surgeon?. Radiology. 2001;218(1):75-84.

37. Widder M, Lützkendorf J, Caysa H, et al. Multipotent mesenchymal stromal cells promote tumor growth in distinct colorectal cancer cells by a β1-integrin-dependent mechanism. Int J Cancer. 2016;138(4):964-975.

38. Tsai KS, Yang SH, Lei YP, et al. Mesenchymal stem cells promote formation of

Revista Española
de Enfermedades Digestivas
The Spanish Journal
of Gastroenterology

colorectal tumors in mice. Gastroenterology. 2011;141(3):1046-1056.

Table 1. Summary of the baseline characteristics of the included participants.

Study	N	Cell type and source	Outcome	Results (healed)	Intervention (mean)	Refractory	AEs	Concurrent use of anti-TNF
Garcia-Olmo D [17] (2009)	14	Autologous, ASCs	Reepithelization	CD: 5/7 for MSCs+ fibrin glue vs. 1/7 for fibrin glue at 8 w	Fixed cell dose First: 2×10^7 MSCs Second: 4×10^7 MSCs	Yes		Yes
Guadalajara H [18] (2012)	6	Autologous, ASCs	Reepithelization + MRI	CD: 2/4 for MSCs+ fibrin glue vs. 1/2 for fibrin glue at 40 m	Fixed cell dose First: 2×10^7 MSCs Second: 4×10^7 MSCs	Yes		Yes
Molendijk I [19]	21	Allogeneic, BMSCs	Reepithelization	7/15 for MSCs vs. 2/6 for saline solution at 12 w	Fixed cell dose	Yes		Yes

(2015)			+MRI		A: 1×10^7 MSCs B: 3×10^7 MSCs C: 9×10^7 MSCs			
Panés J [20] (2018)	212	Allogeneic, ASCs	Reepithelization +MRI	58/103 for MSCs vs. 39/101 for saline solution at 52 w	Fixed cell dose 12×10^7 MSCs	Yes	79/103 for MSCs vs. 74/102 for placebo at 52 w	Yes
Garcia-Olmo D [21] (2022)	40	Allogeneic, ASCs	Reepithelization	(1) 16/25 for MSCs vs. 7/15 for saline solution at 24 w (2) 20/25 for MSCs vs. 7/15 for saline solution at 52 w (3) 14/25 for MSCs vs. 6/15 for saline solution at 104 w	Fixed cell dose 12×10^7 MSCs	Yes	3/25 for MSCs vs. 1/15 for placebo	Yes
Panés J [22]	89	Allogeneic, ASCs	Reepithelization	(1) 29/43 for MSCs vs. 24/46 for saline solution at 52 w	Fixed cell dose	Yes		Yes

(2022)	(2) 23/43 for MSCs vs. 20/46 for saline solution at 104 w (3) 23/43 for MSCs vs. 21/46 for saline solution at 156 w	12×10^7 MSCs

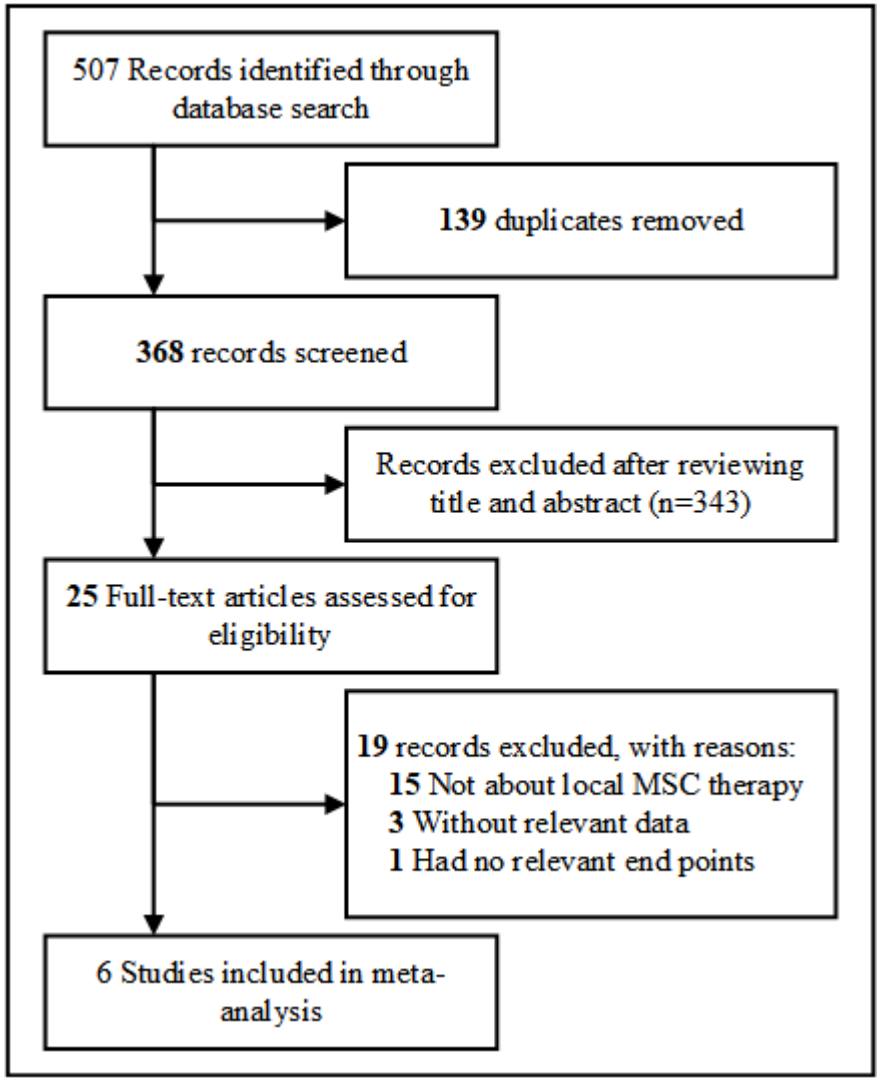

507 Records identified through database search
139 duplicates removed
368 records screened
Records excluded after reviewing title and abstract (n=343)
25 Full-text articles assessed for eligibility
19 records excluded, with reasons:
15 Not about local MSC therapy
3 Without relevant data
1 Had no relevant end points
6 Studies included in meta-analysis

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

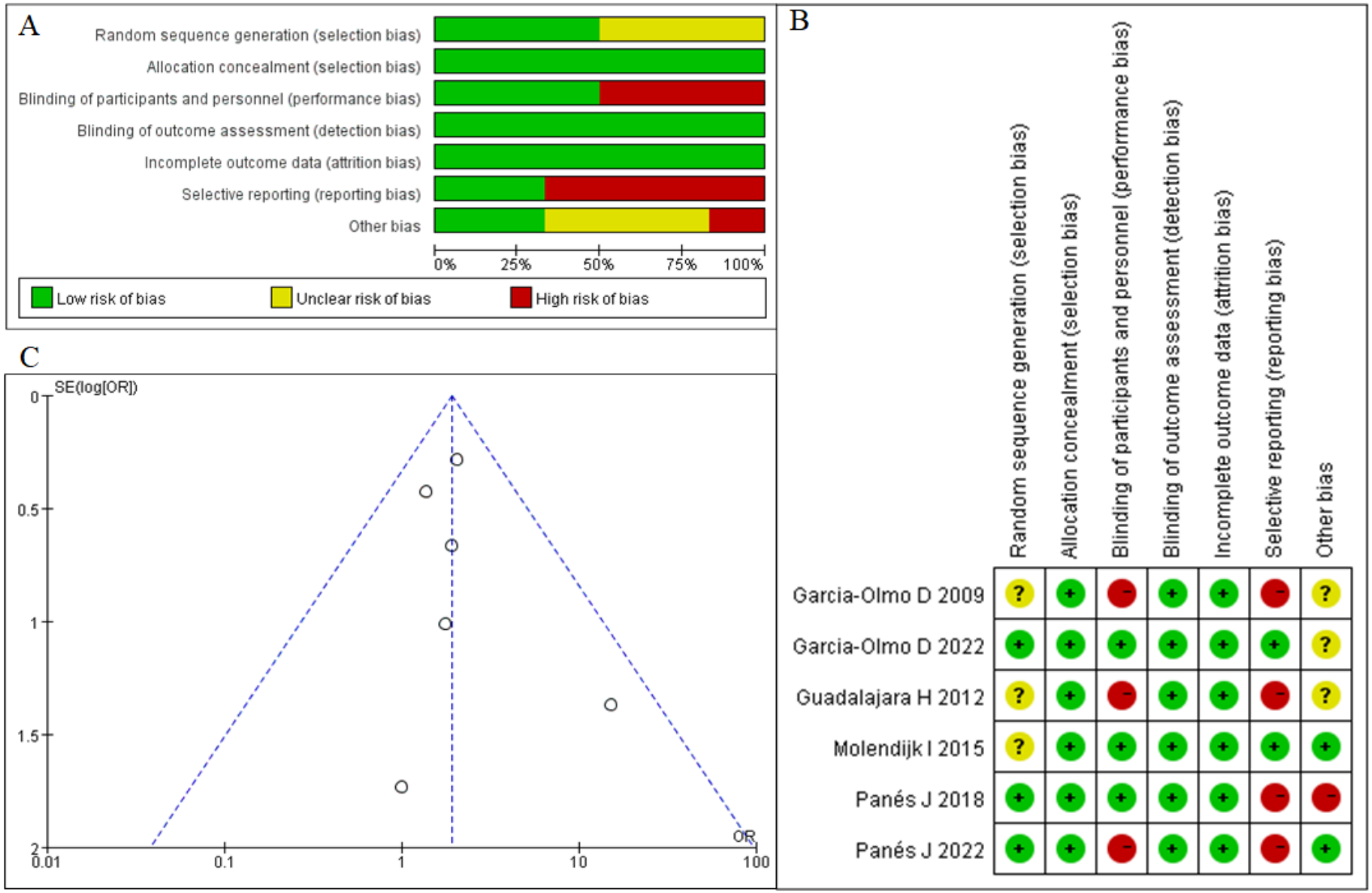
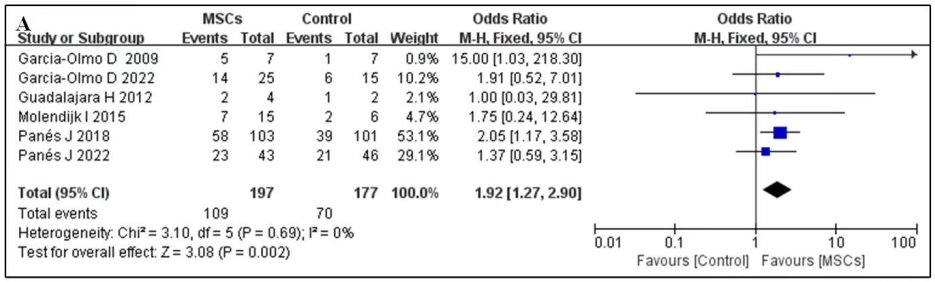
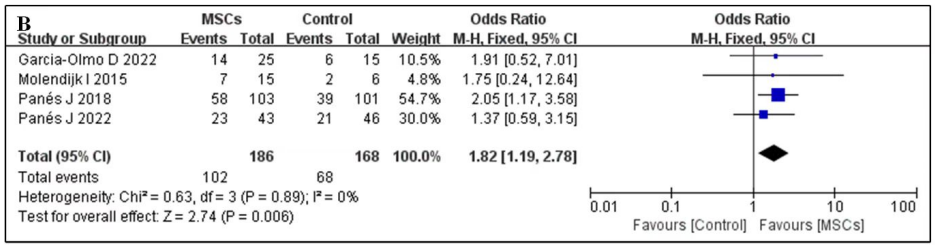
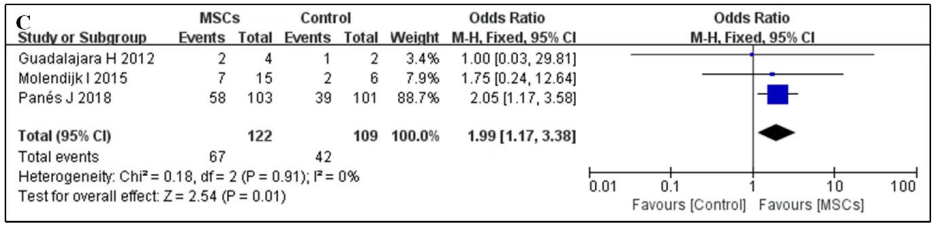
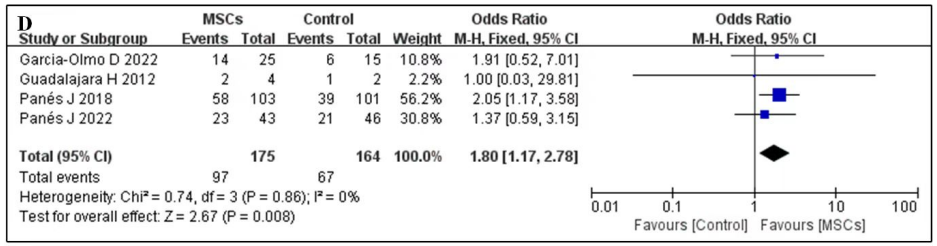

A
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias
B
Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Garcia-Olmo D 2009
Garcia-Olmo D 2022
Guadalajara H 2012
Molendijk I 2015
Panés J 2018
Panés J 2022
C
SE(log[OR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
OR

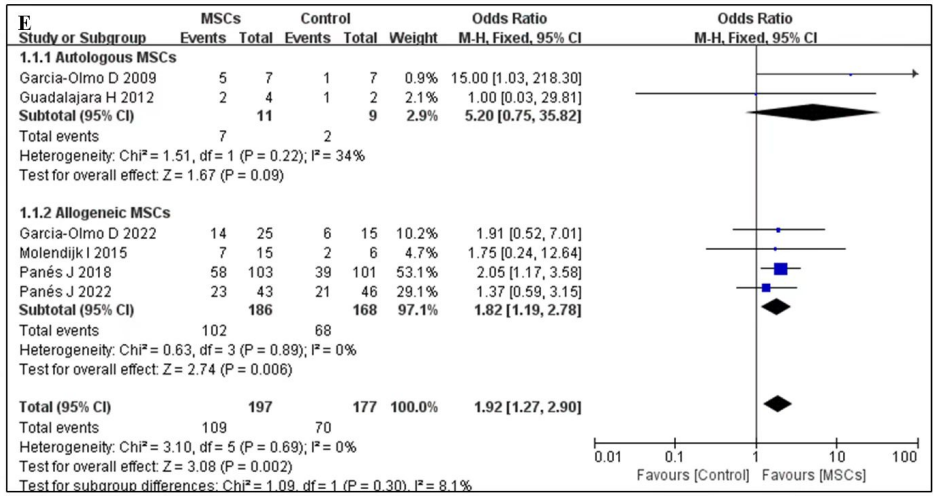
Fig 2A-B. Risk of bias of the RCTs included in the meta-analysis; 2C.The publication bias of our study.


A
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Garcia-Olmo D 2009 5 7 1 7 0.9% 15.00 [1.03, 218.30]
Garcia-Olmo D 2022 14 25 6 15 10.2% 1.91 [0.52, 7.01]
Guadalajara H 2012 2 4 1 2 2.1% 1.00 [0.03, 29.81]
Molendijk I 2015 7 15 2 6 4.7% 1.75 [0.24, 12.64]
Panés J 2018 58 103 39 101 53.1% 2.05 [1.17, 3.58]
Panés J 2022 23 43 21 46 29.1% 1.37 [0.59, 3.15]
Total (95% CI) 197 177 100.0% 1.92 [1.27, 2.90]
Total events 109 70
Heterogeneity: Chi² = 3.10, df = 5 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]


B
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Garcia-Olmo D 2022 14 25 6 15 10.5% 1.91 [0.52, 7.01]
Molendijk I 2015 7 15 2 6 4.8% 1.75 [0.24, 12.64]
Panés J 2018 58 103 39 101 54.7% 2.05 [1.17, 3.58]
Panés J 2022 23 43 21 46 30.0% 1.37 [0.59, 3.15]
Total (95% CI) 186 168 100.0% 1.82 [1.19, 2.78]
Total events 102 68
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]


C
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Guadalajara H 2012 2 4 1 2 3.4% 1.00 [0.03, 29.81]
Molendijk I 2015 7 15 2 6 7.9% 1.75 [0.24, 12.64]
Panés J 2018 58 103 39 101 88.7% 2.05 [1.17, 3.58]
Total (95% CI) 122 109 100.0% 1.99 [1.17, 3.38]
Total events 67 42
Heterogeneity: Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.54 (P = 0.01)
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]


D
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Garcia-Olmo D 2022 14 25 6 15 10.8% 1.91 [0.52, 7.01]
Guadalajara H 2012 2 4 1 2 2.2% 1.00 [0.03, 29.81]
Panés J 2018 58 103 39 101 56.2% 2.05 [1.17, 3.58]
Panés J 2022 23 43 21 46 30.8% 1.37 [0.59, 3.15]
Total (95% CI) 175 164 100.0% 1.80 [1.17, 2.78]
Total events 97 67
Heterogeneity: Chi² = 0.74, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 2.67 (P = 0.008)
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]


E
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
1.1.1 Autologous MSCs
Garcia-Olmo D 2009 5 7 1 7 0.9% 15.00 [1.03, 218.30]
Guadalajara H 2012 2 4 1 2 2.1% 1.00 [0.03, 29.81]
Subtotal (95% CI) 11 9 2.9% 5.20 [0.75, 35.82]
Total events 7 2
Heterogeneity: Chi² = 1.51, df = 1 (P = 0.22); I² = 34%
Test for overall effect: Z = 1.67 (P = 0.09)
1.1.2 Allogeneic MSCs
Garcia-Olmo D 2022 14 25 6 15 10.2% 1.91 [0.52, 7.01]
Molendijk I 2015 7 15 2 6 4.7% 1.75 [0.24, 12.64]
Panés J 2018 58 103 39 101 53.1% 2.05 [1.17, 3.58]
Panés J 2022 23 43 21 46 29.1% 1.37 [0.59, 3.15]
Subtotal (95% CI) 186 168 97.1% 1.82 [1.19, 2.78]
Total events 102 68
Heterogeneity: Chi² = 0.63, df = 3 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.74 (P = 0.006)
Total (95% CI) 197 177 100.0% 1.92 [1.27, 2.90]
Total events 109 70
Heterogeneity: Chi² = 3.10, df = 5 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.08 (P = 0.002)
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.1%
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]

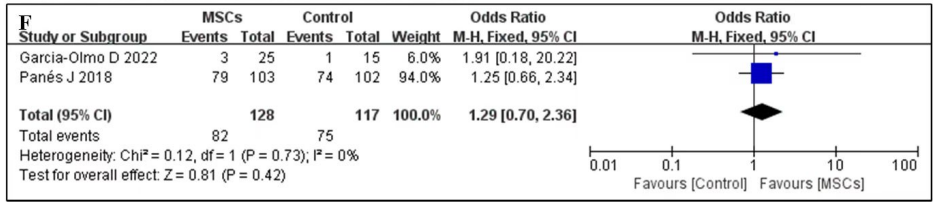

F
MSCs
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Garcia-Olmo D 2022 3 25 1 15 6.0% 1.91 [0.18, 20.22]
Panés J 2018 79 103 74 102 94.0% 1.25 [0.66, 2.34]
Total (95% CI) 128 117 100.0% 1.29 [0.70, 2.36]
Total events 82 75
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.81 (P = 0.42)
0.01 0.1 1 10 100
Favours [Control] Favours [MSCs]

Fig. 3. A. Efficacy of MSCs/MSCs + fibrin glue vs. contreol treatment (saline solution or fibrin glue) for pCD. B. Efficacy of MSCs vs. saline solution for pCD. C. Efficacy of MSCs for pCD evaluated by MRI. D. Long-term effectiveness of MSCs for pCD. E. Different sources of MSCs for the treatment of pCD. F. Pooled OR of adverse events.