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Comparison of Intravenous and Topical Injection Administration Mesenchymal Stem Cell Secretome to Restrain Gastrointestinal Anastomosis Leakage: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Intestinal anastomosis is one of the most commonly performed gastrointestinal surgical procedures, especially in emergencies and is commonly performed in elective procedures when resection is performed for benign or malignant lesions of the gastrointestinal tract. One of the important postoperative complications that causes significant morbidity and adversely affects the length of hospital stay is anastomotic leak after gastrointestinal anastomosis. Recently, developments in regenerative medicine applied to gastrointestinal anastomoses show promise for improving anastomotic healing. Recent studies have demonstrated that stem cell-derived secretomes can potentially enhance anastomized tissue regeneration without the safety and ethical limitations of stem cell transplantation. A study showed that the MSC secretome significantly promoted cell proliferation and survival in a dose-dependent manner and resulted in the controlled release of growth factors. Mesenchymal stem cell (MSC)-derived secretomes have controlled delivery of bioactive factors, and have potential in improving healing of intestinal anastomoses. In this review, we discuss the comparison of the therapeutic effects of the MSC secretome given by topical injection and the MSC secretome injected intravenously in terms of healing and anastomotic resistance.

Keywords: Mesenchymal stem cells; mesenchymal stem cells secretome; intestinal anastomosis leakage; anastomotic resistance.

1. INTRODUCTION

Gastrointestinal (GI) system anastomosis is an artificial connection procedure after a resection of all or part of the digestive organs (Lai et al., 2022). Anastomotic leak is a serious clinical problem and is caused by infiltration of intestinal contents into the abdominal cavity due to failure of healing of the anastomosis after intestinal resection and anastomosis procedures. This complication can easily cause abdominal infections and lead to sepsis, which is one of the main causes of death (Khan et al., 2012). Several studies have reported that the incidence of anastomotic leak complications after gastroesophageal procedures is 7–12%, and after colorectal procedures is around 3–19% (Wang et al., 2022; Rose et al., 2015). Estimated to be at least one million patients worldwide suffer from associated anastomotic leaks complications after surgery every year (Reischl et al., 2021). The improved surgical techniques for gastrointestinal operations, improvement of surgical instruments, and accumulation of experience in perioperative management in recent years, incidence and anastomotic leak mortality has been reduced (Kiran et al., 2015). However, research shows that there is more to it than that half of the patients do not benefit from this intervention (Wang et al., 2022; Ntampakis et al., 2023; Li et al., 2024; Gregoire et al., 2016). Therefore, surgical healing is poor anastomosis has become a difficult problem to solve in clinical practice.

2. MESENCHYMAL STEM CELLS SECRETOME CHARACTERISTICS

MSCs produce and secrete a wide variety of bioactive molecules. MSCs are also referred to as “trophic factories”. And the secretome is a combination of all trophic factors or molecules secreted by these cells into the extracellular space. Mesenchymal Stem Cells secretome have the ability to produce a variety of autocrine and paracrine factors including cytokines, extracellular matrix (ECM) proteases, chemokines and growth factors, thus allowing the possibility of being used as a potential source of cell-free based therapy. In addition, MSC secretome also contain exosomes and extracellular vesicles (Sentoso et al., 2024). Exosomes can contain lipids, miRNAs, long noncoding RNAs that regulate various related signaling inflammation pathways. Identification and characterization of all forming biomolecules secretome is difficult to achieve, but can improve understanding of the profile of secreted factors and provides information about its regulation, function, and clinical applications. The MSCs can influence surrounding cells and regulate various biological processes (Sentoso et al., 2024; Arifka et al., 2022; Seo et al., 2023).

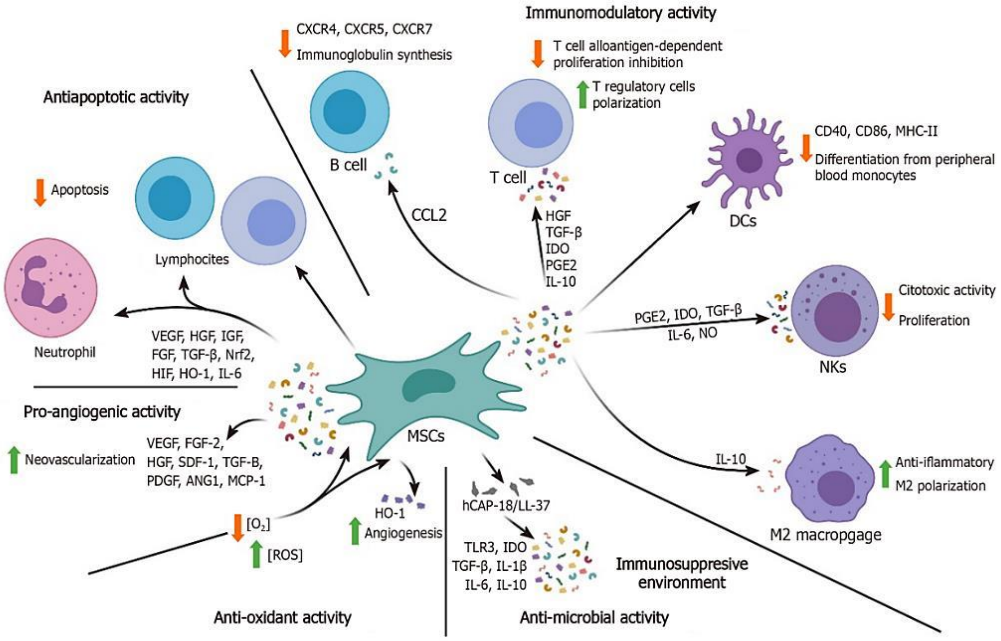

Fig. 1. Potency of various soluble factors secreted by mesenchymal stem cells (Sentoso et al., 2024)

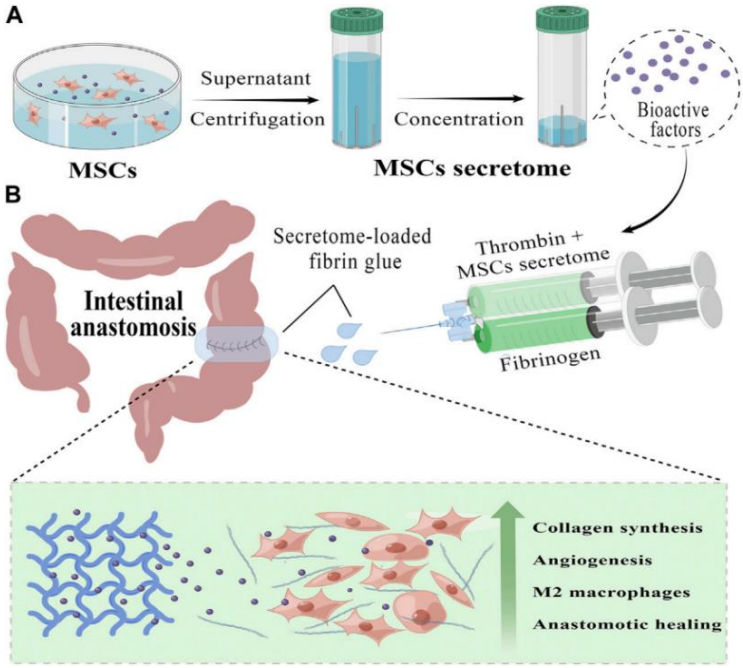

Fig. 2. The fiibrin glue containing the MSC secretome is prepared for application (by Fig. draw). (A) The secretome is collected from human umbilical cord mesenchymal stem cells (hucMSCs) with conditioned medium and then in a protein ultrafiltration bath concentrates it into different secretome concentrates, which contain various bioactive factors that promote tissue repair. (B) The fibrin glue patch (Secretome/FG) is formed quickly using an easy-to-use injection mixture containing MSC secretome that tightly covers the post-resection intestinal anastomosis. Secretome/FG releases bioactive factors slowly to increase collagen synthesis and angiogenesis, regulate M2 macrophage polarization, and ultimately promote healing of ischemic intestinal anastomosis (Yu et al., 2023)

3. POTENTIAL OF MESENCHYMAL STEM CELLS SECRETOME IN REGENERATION OF GASTROINTESTINAL ANASTOMOSIS

The MSC secretome in vitro significantly promotes cell proliferation cell survival in a dose-dependent manner and resulting in controlled release growth factors. A study in mice treated with surgical anastomosis experimentally found that the secretome of MSCs provides increased anastomotic blast pressure, increased granulation tissue collagen formation and deposition, and significantly improves anastomosis healing. The MSC secretome causes accelerated cell proliferation, angiogenesis, and polarization of M2 macrophages at the site of surgical anastomosis by releasing bioactive factors also have the effect of reducing inflammatory reactions and cell apoptosis at the anastomosis site (Yu et al., 2023; Damayanti et al., 2021; Golubinskaya et al., 2020).

4. COMPARATIVE EFFECT OF MESENCHYMAL STEM CELL SECRETOME REGENERATION THERAPY ADMINISTERED BY INTRAVENOUS AND TOPICAL INJECTION

The secretome of mesenchymal stem cells can be applied to their delivery routes local injections and cell sheets followed by biosuture (SC-coated suture) or purely topical. To see potential strengths and weaknesses in terms of delivery, a review still needs to be carried out. There is marked heterogeneity across studies in this regard, making comparisons difficult. So it is necessary to standardize the isolation process and clinical application (Trébol et al., 2022).

Topical administration has the disadvantages of poor control over the actual SC dose administered and very high interindividual variability. Systemic administration (IV) has a real homing problem. Many studies describe high SC homing to the injury focus but other studies describe very low homing [87]. Directing all administered SC to the injury site, avoiding placement into other organs, appears to be very difficult to achieve (Trébol et al., 2022).

Other potential approaches are combining SC with biomaterials or adding SC to mechanical anastomosis devices (i.e. in staple line reinforcement). Another important issue is the survival of the SC in the anastomosis area. Studies analyzing whether cells with different SC markers were present were able to detect them. However, there are conflicting findings in similar areas such as fecal incontinence, with some studies unable to find cells with SC markers (Trébol et al., 2022).

There are still many questions regarding the mechanism of action of SC. We will focus on MSC. It is possible that other SCs, such as myogenic SCs, have a greater role based on differentiation, but MSCs probably base their function mainly on their immunomodulatory, anti-inflammatory and angiogenic abilities, reducing fibrosis and stimulating resident progenitor cells as mentioned in all studies which is included. . The immunomodulatory capabilities of MSCs are based on the inhibition of T cell and B cell proliferation as well as the maturation of dendritic cells and on the secretion of a large number of cytokines (Trébol et al., 2022)..

5. CLINICAL AND EXPERIMENTAL TRIALS

Eighteen preclinical studies and three review papers were identified; there are no published clinical studies or registered clinical trials. Colon and colorectal anastomoses are the most frequently examined (ten studies) and rats (12 studies) are the mostly employed animals followed by pigs (Kamarajah et al., 2020). Three anastomotic models have been described: conventional (4 studies), high risk of AL (Zhang & Che, 2021) and insufficient (Rahbari et al., 2010); gastric perforation models either included (2 studies) or did not include repair. Most analyzed SCs were Mesenchymal (16 studies); cell transplant was autologous in 8 studies, allogeneic in 7 and xenogeneic in 2 (human); SCs dosage ranged from 5×10^5 to 1×10^7 and delivery routes were mainly local injections (Hammond et al., 2014) and cell sheets (Kamarajah et al., 2020) followed by biosutures (sutures coated by SCs) or purely topical (2 studies each one). Random assignation of treatments was applied only in 3 publications and blinded evaluations were scarce.

Regarding outcome measures, the evaluation period most often carried out is the first period weeks (9 studies) or during the first month. All studies were evaluated morphologically abdominal cavity and/or digestive anastomosis or suture, and eleven of 17 analyze the strength

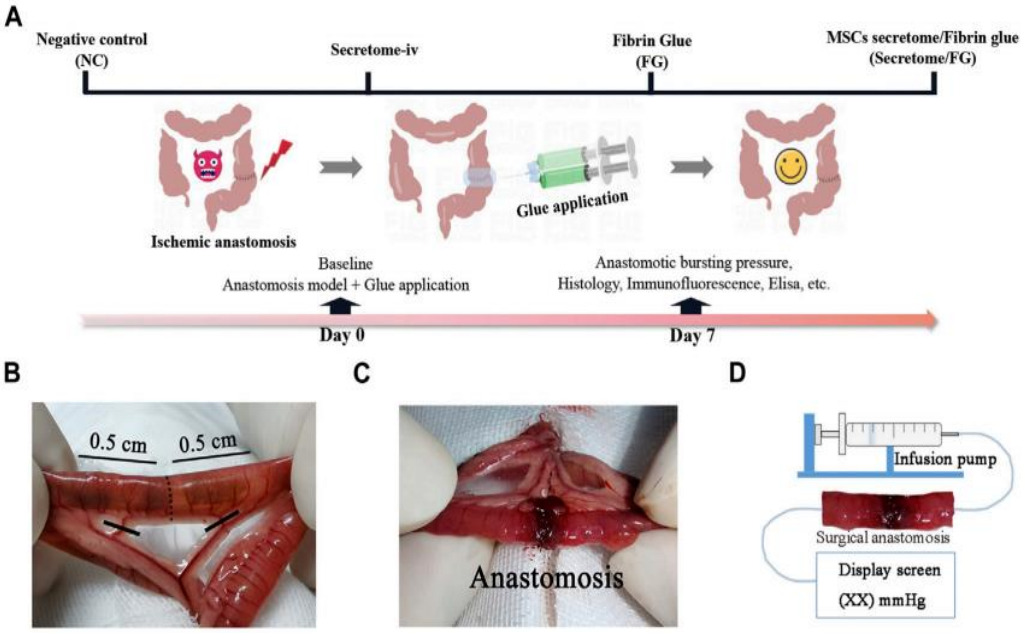

Fig. 3. (A) In a mouse model that was treated with intestinal resection surgery, and given fibrin glue containing MSC (Secretome/FG) secrets, it had an effect on increasing the healing of intestinal anastomoses. This research was conducted for 7 days with a group scheme and experimental design for animal research. (B, C) To induce ischemia in the intestinal anastomosis, vessel ligation is performed. (D) Maximum pressure measured with a pressure transducer is used to detect anastomotic burst pressure during continuous air intake into a closed isolated bowel containing a surgical anastomosis (Sentoso et al., 2024)

of the anastomosis or suture by evaluation of rupture pressure.

All investigations confirmed safety and the absence of relevant side effects attributed to SC. What needs to be emphasized is the relatively low rate of severe complications and mortality (Trébol et al., 2022).

In general, the morphology is good, especially the histology, almost all studies, functional (8 positive studies and 3 without effect) and even clinical results has been observed and some data suggests regeneration. Clinically, five studies reported a significantly lower incidence of AL, five fewer adhesions, four fewer abscesses and the death rate is reduced by one. Eight studies analyzed SC labeling and confirmed it SC survival in these potentially septic areas. As a potential weakness, animal models need to be improved to make them better comparable, and the SC isolation process needs to be standardized (Trébol et al., 2022).

In 2017, Van de Putte et al published an evaluation of allogeneic subcutaneous ASCs on colonic anastomoses after high-dose irradiation in rats. Thirty-two SD males received 27 Gy irradiation of the colorectal region. Four weeks later, the damaged zone was identified, the colon was cut just above it and end-to-end anastomosis was performed with interrupted 6/0 polydioxanone stitches leaving knots outside. Three experimental groups were defined: G1, control/sham (n = 4), anastomosis after sham irradiation; G2, phosphate-buffered saline (PBS) (n = 10), irradiation, anastomosis and PBS injections; and G3, ASCs (n = 10): irradiation, 5 × 106 intravenous (IV) ASCs 1 wk before anastomosis, intraoperative injection of 5 × 106 ASCs around anastomosis and two other IV doses on PO days 10 and 20. In G2 and G3, 3 animals died postoperatively. 18F-fluorodeoxyglucose PET scans were taken just before surgery (4 wk) and PET and colonoscopy were performed at 8 wk when animals were sacrificed to obtain samples for histology. With colonoscopy, G2 anastomoses presented large amounts of necrotic tissue and fibrin, which were less frequent in G3; bleeding appeared in 0% G1, 57% G2 and 14% G3 animals (no P value provided). Regarding histology, the ulcerated area was statistically smaller in G3 compared to

G2 (P < 0.05). For PET scans, isolated anastomoses (G1) did not generate a significant activity change; irradiation increased it 65%; and IV ASCs prior to anastomoses reduced activity by 21%, making it similar to G1. While G2 had greater values than G1 (P = 0.03), there was no difference between G2 and G3 at 8 wk. At 8 wk, G3 had the highest percentage of M2 macrophages compared with G2 and G1 (no p value provided) and the G3 vessel number was significantly increased (P = 0.007) compared with G2, reaching a value even higher than that of G1. The authors proposed that the observed benefits are probably due to the stimulation of endogenous cells (Trébol et al., 2022).

In 2012, Yoo et al. modelled ischemic colonic anastomosis by ligating remote marginal vessels from the anastomotic site. Blood flow was monitored by Doppler flowmetry until the blood flow near the anastomosis reduced to <50% of normal. A total of 60 male Sprague Dawley (SD) rats were divided into 2 groups: G1, without treatment; G2, 1×106 MSCs coated with fibrinogen and thrombin were locally injected around the anastomosis. Body weight, infection, AL, mortality, adhesion, ileus, anastomotic fibrosis, ABP, histology features, and microvascular regeneration were assessed on PO d 7. No significant differences in lesion infection, AL, death rate, adhesions, or ulcer size were found (Yoo et al., 2012).

6. CONCLUSION

Several strategies have been developed to prevent gastrointestinal tract anastomotic leaks in recent decades, including perioperative drug administration and interoperative local strengthening strategies. However, perioperative medications have limited side effects, while the effectiveness of local strengthening strategies to prevent anastomotic leakage has not been confirmed. Ischemia is considered one of the most important risk factors for anastomotic leakage and studies have also shown that ADMSCs through increased expression of VEGF promote angiogenesis. Currently, ADMSCs have been applied to prevent leakage of anastomoses of the gastrointestinal system, including colon, stomach, small intestine, and biliary anastomoses in animal model studies. The effectiveness of ADMSCs in preventing anastomotic leakage has been proven by several studies, while the results of different studies are inconsistent and another limitation is that ADMSCs have not been studied in humans. In the future, more pre-clinical studies are needed to verify the effectiveness of ADMSCs in the prevention of anastomotic leakage of the gastrointestinal system.

7. FUTURE DIRECTION

Limited experimental research and the absence of clinical research regarding the comparative effect of mesenchymal stem cell secretome regeneration therapy given by topical and intravenous injections is a challenge for researchers in the future. The author hopes that this review can be used as a basis for future experimental research and can be developed into clinical research and can be applied clinically.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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