Regenerative Therapy 27 (2024) 445–454

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Interceed combined with bone marrow mesenchymal stem cells improves endometrial receptivity of intrauterine adhesion

Yuan Yang [a, b, 1, *], Yidan Wang [b, 1], Yi Huang [a], Ji Song [a], Xiaoling Ma [a]

[a] Reproductive Medicine Center, The First Hospital of Lanzhou University, Lanzhou 730000, China
[b] The First Clinical Medical College, Lanzhou University, Lanzhou 730000, China

ARTICLE INFO

Article history:
Received 4 February 2024
Received in revised form
21 March 2024
Accepted 11 April 2024

Keywords:
BMSCs
Interceed
Intrauterine adhesion
Endometrial receptivity

ABSTRACT

Background: This study aimed to investigate the impact of intrauterine adhesions (IUA) therapy and endometrial receptivity by implanting autologous bone marrow mesenchymal stem cells (BMSCs) into the Interceed and subsequently placing them in the uterine cavity of rats.

Methods: Fifty rats were divided into 5 groups according to the random number table method (10 rats in each group). Following the development of the IUA model through mechanical injury, the animals were categorized into different treatment groups: the IUA model (intrauterine perfusion of saline), Interceed therapy (intrauterine placement of Interceed), BMSCs therapy (intrauterine perfusion of BMSCs), BMSCs + Interceed therapy (intrauterine placement of BMSCs + Interceed), and a control group (intrauterine perfusion of saline). The Hematoxylin-eosin (HE) staining technique was employed to identify and assess the pathological alterations in the endometrium. Additionally, it facilitated the quantification of endometrial glands and the determination of endometrial thickness. Masson staining was used to detect fibrosis in rat uterus. The number of microvascular density (MVD) was detected by immunohistochemistry (IHC). Real-time quantitative reverse transcription polymerase chain reaction (qRT-PCR) and Western blot were used to detect the levels of leukemia inhibitory factor (LIF), integrin αvβ3, and vascular endothelial growth factor (VEGF) in uterine tissue. Male and female rats were combined in cages for reproductive and conception evaluation.

Results: In comparison to the control, the number of endometrial glands in the IUA model was significantly reduced, and the degree of endometrial thinning and fibrosis was significantly increased ($p < 0.05$). Compared with the IUA model, the number of endometrial glands did not exhibit any significant alterations in endometrial thickness and MVD number. The expressions of LIF, integrin αvβ3, and VEGF in the uterine tissue were not significantly improved with Interceed therapy, resulting in no significant improvement in the pregnancy rate ($p > 0.05$). The number of endometrial glands, endometrial thickness, and MVD in the BMSCs therapy group were significantly increased. Moreover, the expressions of LIF, integrin αvβ3, and VEGF in uterine tissue exhibited a significant increase, leading to a comparatively higher pregnancy rate ($p < 0.05$). In the BMSCs + Interceed therapy group, the number of endometrial glands, endometrial thickness, and MVD were significantly increased, and the expressions of LIF, integrin αvβ3, and VEGF in uterine tissue were significantly increased as well, along with a corresponding rise in the pregnancy rate ($p < 0.05$).

Conclusion: The intrauterine placement of Interceed combined with BMSCs in IUA rats can thicken the damaged endometrium, increase the number of glands, promote endometrial angiogenesis, improve endometrial receptivity, and increase the rate of pregnancy in IUA rats.

Abbreviations: **IUA**, intrauterine adhesions; **BMSCs**, bone marrow mesenchymal stem cells; **LIF**, leukemia inhibitory facto; **VEGF**, vascular endothelial growth factor; **MVD**, microvascular density; **IVF-ET**, embryo transfer; **TCRA**, Hysteroscopic transcervical resection of adhesion; **FDA**, Food and Drug Administration.

* Corresponding author.
E-mail address: yangyuan0302@163.com (Y. Yang).

Peer review under responsibility of the Japanese Society for Regenerative Medicine.

[1] Contributed equally.

https://doi.org/10.1016/j.reth.2024.04.007

Contents

1. Introduction

Intrauterine adhesion (IUA) is a common gynecological disease with an incidence rate of about 1.5% [1]. Various factors, such as induced abortion, spontaneous abortion, mechanical trauma, and bacterial infection, can result in damage to the endometrium, leading to partial or complete adhesion of the uterine cavity. This adhesion subsequently causes narrowing or complete obliteration of the uterine cavity, resulting in menstrual disorders, dysmenorrhea, amenorrhea, recurrent miscarriages, and infertility [2–5]. Hysteroscopic transcervical resection of adhesion (TCRA) is considered the primary treatment option for IUA [6]. However, it is important to note that the recurrence rate associated with this procedure is rather high. Studies have shown that recurrence rates range from 3.1% to 23.5%, with moderate adhesions exhibiting a recurrence rate of around 20% and severe adhesions having a recurrence rate that can reach up to 50% [7–9]. For several years, a combined therapeutic approach has been employed to mitigate the risk of post-operative recurrence. This approach involves the installation of an intrauterine device following TCRA, along with an administration of a high dose of estrogen and progesterone, which facilitates endometrial healing [10,11]. This treatment has a significant effect on patients with mild to moderate IUA but does not exhibit any improvement in patients with severe IUA. Furthermore, the extensive region of endometrial damage and the resultant exposed post-surgical wound offer challenges in restoring the endometrial regenerative capacity despite the surgical restoration of uterine cavity shape.

The IUA patients undergoing *in vitro* fertilization and embryo transfer (IVF-ET) sometimes encounter difficulty when high-quality frozen embryos are available, but due to inadequate monitoring of the endometrial status, their transfer is hindered. The thickness of the endometrium may be the key to a successful pregnancy. Current studies believe that the endometrial thickness should reach at least 6–8 mm [12] before embryo implantation can be completed. However, the most difficult problems in the treatment of IUA patients are the recurrence of adhesion and the regeneration of the endometrium. Therefore, “separation of adhesion, prevention of re-adhesion, and promotion of endometrial regeneration” is the key to the treatment of IUA patients who underwent IVF-ET and whose embryos have been frozen. Firstly, a physical barrier is placed to block the separated endometrial wound and to reduce the recurrence of adhesion. Furthermore, it is imperative to facilitate the regeneration and restoration of the endometrium at the injured location to prevent adhesion formation and achieve an optimal endometrial thickness suitable for embryo implantation. This approach aims at solving the reduced endometrial receptibility resulting from IUA.

Interceed is a sterile woven fabric made from regenerated cellulose that has been authorized by the Food and Drug Administration (FDA) to prevent post-operative adhesion. It has demonstrated favorable outcomes against the post-operative anti-adhesion of the pelvic and abdominal cavity [13], middle ear [14], tendon [15], and other parts of the body. Current studies suggest that the Interceed membrane effectively prevents the readhesion of TCRA but does not promote the regeneration of functional endometrium.

Bone marrow mesenchymal stem cells (BMSCs) are a kind of non-hematopoietic adult stem cells that originate from the mesoderm germ layer. These cells possess the capacity for multi-differentiation and immunological regulation. They are easy to expand and culture *in vitro* and are widely used in the repair of liver, nerve, cardiac muscle, skin, and gastrointestinal cells [16,17]. A plethora of studies have demonstrated that BMSCs possess the capability to facilitate endometrial and vascular neogenesis, thereby facilitating endometrial repair. Previous research has

indicated that the administration of BMSCs *via* the tail vein in Sprague-Dawley (SD) rats can induce their migration to the uterus and promote intimal hyperplasia. However, it is worth noting that the homing efficiency of BMSCs is quite low (around 20%) [18]. Nagoni et al. [19] performed curettage on a patient with infertility caused by IUA and transplanted autologous bone marrow into the uterine cavity while applying estrogen treatment. After the above treatment, the thickness of the uterine endometrium increased to 8 mm, and the patient conceived successfully *via* IVF. In the aforementioned research, it was shown that BMSCs were excessively activated and unable to sustainably promote the enhancement of the internal environment within the uterine cavity.

The current study aimed to shed light on the therapeutic effect of Interceed combined with BMSCs transplantation on the glands, endometrial thickness, and microvascular density (MVD) of IUA-damaged endometrium and to assess its effect on endometrial receptivity as well. The findings of this research may offer a novel perspective on IUA therapy, therefore establishing a foundation for clinical interventions.

2. Materials and methods

2.1. Animals

In this investigation, a total of fifty sexually mature female SD rats of specific-pathogen-free (SPF)-grade were selected. These rats weighed between 220 and 240 g and were not mated before the experiment. The rats were purchased from the Lanzhou University Animal Center and raised in the GLP animal room of Lanzhou University. Fifty rats were divided into 5 groups according to the random number table method (10 rats in each group). The IUA model was established by mechanical injury. The rats were administered anesthesia using a pentobarbital sodium at a dosage of 30 mg/kg. A longitudinal incision was performed along the midline of the abdomen, followed by a longitudinal incision of approximately 3 mm in the lower third of the uterus. The uterine cavity was scratched with a curettage until the endometrium became red, swollen, and rough. Four rats were randomly chosen for the pathological evaluation of uterine tissue seven days following the modeling process. The presence of evident pathological alterations in the uterine tissue of these rats was deemed a successful outcome of the modeling procedure. After the completion of modeling, the rats were divided into five groups according to the treatment method (10 rats in each group): Control (intrauterine perfusion of saline), IUA model (intrauterine perfusion of saline), Interceed therapy (intrauterine placement of Interceed), BMSCs therapy (intrauterine perfusion of BMSCs), and BMSCs + Interceed therapy (intrauterine placement of BMSCs+Interceed). The endometrial thickness, number of endometrial glands, and MVD in tissue sections were collected at four-time points (7, 14, 21, and 28 days) throughout regular feeding.

2.2. Isolation, culture, and identification of bone marrow mesenchymal stem cells

BMSCs were isolated from the tibia and femur of 3-week-old female rats by whole bone marrow culture method. Bone marrow cells were collected under complete sterile conditions and were treated with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. The low-glucose Dulbecco's Modified Eagle Medium (DMEM) media was used to incubate cells at a temperature of 37 °C in an atmosphere containing 5% CO_2. The cell culture medium was replaced every two days, and the cells were observed for growth and fusion until reaching a confluence of 90%. Subsequently, the cells were detached and subcultured using trypsin and were utilized for experimentation after undergoing three successive passages. The isolated BMSCs were subsequently transplanted back into the same mouse in subsequent experiments. All items were acquired from Procell Life Science & Technology Co., Ltd., Wuhan, China. After appropriate centrifugation, 1×10^5–10^8 single cells were resuspended in an adequate amount of flow staining buffer and supplemented with 5 μl Anti-Mouse CD45/CD29/CD44/CD34 (Lianhe Biologic Co., LTD., Hangzhou, China), resulting in a final reaction volume of 100 μl. The mixture was thoroughly shaken and incubated at room temperature for 15 min, protected from light. Each tube was then supplemented with 1–2 ml of flow stain buffer, followed by centrifugation at 300×*g* for 5–10 min. The supernatant was discarded, and the pellet was resuspended in 500 μl of flow stain buffer. Finally, the verification of BMSCs was performed using flow cytometry.

2.3. PKH26 fluorescent dye was used to label bone marrow mesenchymal stem cells

BMSCs, labeled with PKH26 (Sigma Aldrich, USA) at different concentrations (100 μL, 200 μL, and 300 μL), were planted on the Interceed membrane. The proliferation and migration of BMSCs on the Interceed membrane were observed under a fluorescence microscope to determine the optimal cell concentration of BMSCs.

2.4. Hematoxylin-eosin (HE) staining

The rat uterine tissue was fixed with 4% paraformaldehyde (coolaber, Beijing, China) for 24 h and then embedded in paraffin. Following the paraffin micrograph sectioning procedure, the tissue was subjected to hematoxylin and eosin (HE) staining. Subsequently, the endometrium was examined using a microscope, and five areas were selected at random for the quantification of endometrial glands and the measurement of endometrial thickness.

2.5. Masson staining

Rat endometrial tissues were fixed, as mentioned before. The sections were dewaxed into distilled water. A Masson staining kit (coolaber, Beijing, China) was used for staining the sections, and images were taken under an inverted light microscope. Analysis was performed using ImageJ software, and the percentage of blue staining indicated the degree of endometrial fibrosis.

2.6. Immunohistochemical

Tissue samples were fixed with paraformaldehyde for 24 h, embedded in paraffin, sectioned, and deparaffinized with xylene, followed by hydration. The antigen retrieval was done by adding citrate buffer at high pressure, and the endogenous peroxidase was removed by letting it stand with 3% hydrogen peroxide for 10 min. MVD was calculated by CD31(Sanying Biotechnology Co., LTD., Wuhan, China) staining to evaluate endometrial injury and blood supply.

2.7. Real-time polymerase chain reaction

Total RNA was extracted from the uterine tissue and reverse transcribed into cDNA (TIANGEN, Beijing, China). Gradient PCR was utilized to assess the mRNA expression levels of leukemia inhibitory factor (LIF), integrin αvβ3, and vascular endothelial growth

factor (VEGF) in rat uterine tissue. The sequences of primers used for real-time quantitative PCR (qRT-PCR) are LIF: F: TCAACTGGCTCAACTCAACG, R: ACCATCCGATACAGCTCGAC; Integrin αvβ3: F: AAGAGCCAGAGTGTCCCAAG, R: AGTTTCCAGATGAGCAGGGC; VEGF: F: TTGCTGCTCTACCTCCAC, R: AATGCTTTCTCCGCTCTG; GAPDH: F: TGGTGAAGGTCGGTGTGAAC, R: GACTGTGCCGTTGAACTTGC. The relative mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method with GAPDH as an internal reference.

2.8. Western blot analysis

Proteins were extracted from rat endometrial tissue using radioimmunoprecipitation assay buffer (RIPA buffer; coolaber, Beijing, China). The quantification of the extracted protein content was performed using the Bicinchoninic acid (BCA) Protein Assay kit (coolaber, Beijing, China). Subsequently, the protein was denatured by the addition of a loading buffer and subjected to boiling at 100 °C for 15 min. After separation using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE), it was transferred to the polyvinylidene fluoride (PVDF) membrane. The samples were blocked using skim milk with a concentration of 5% for 1 h. The antibodies (Wuhan Sunying Biotechnology Co., LTD., China) used were anti-LIF (diluted at 1:1000), anti-integrin αvβ3 (diluted at 1:1000), anti-VEGF (diluted at 1:1000), and anti-β-actin (diluted at 1:5000), and were incubated at 4 °C overnight. The secondary antibody (diluted at 1:10000) was incubated for 1 h at room temperature, and an ECL chemiluminescence kit was used for visualization and color development. The gel imaging system was used for imaging and analysis, while the Image J software was used for quantitative analysis.

2.9. Reproductive assessment

After the intervention was completed, the four groups of female rats were mated with male rats, and subsequently, the female rats were isolated for 15 days. The number of gestational sacs in the uterine horn of female rats was recorded.

2.10. Statistical analysis

The data were analyzed using SPSS 26.0 software, and GraphPad Prism 8.0 was utilized to generate histograms. The results were presented as mean ± SD. Statistical analysis included a two-tailed unpaired T-test for comparing the two groups and one-way analysis of variance (ANOVA) for group comparisons. A significance level of $P < 0.05$ was considered statistically significant.

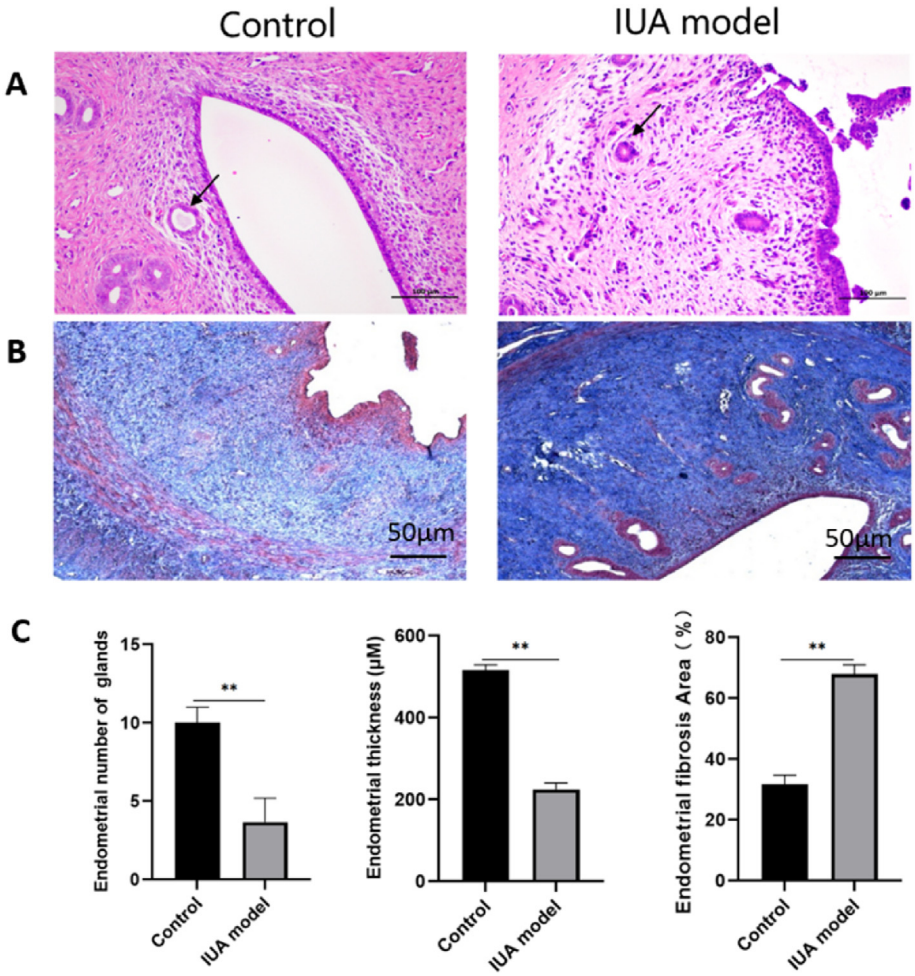

Fig. 1. Establishment of the rat IUA model. A. Uteri of normal and model rats stained with HE on day 7 after injury (arrows indicate endometrial glands). B. Uteri of normal and model rats stained by Masson on day 7 after injury. C. Statistical results of endometrial gland number, endometrial thickness, and endometrial fibrosis in normal rats and model rats, $^{**}p < 0.01$.

3. Results

3.1. Evaluation of the IUA model in rats

The results of HE and Masson staining revealed that the endometrium of rats in the control group exhibited intact morphology, evenly distributed glands, and normal cellular structure, with the absence of significant fibrosis and pathological alterations. Compared to the control group, the IUA model exhibited a significantly reduced endometrial thickness, a notable decrease in glandular count, and an evident increase in the extent of endometrial fibrosis ($p < 0.05$) (Fig. 1).

3.2. Isolation, culture, and identification of BMSCs

The results of flow cytometry revealed that the surface markers CD29 (98.84%) and CD44 (99.93%) were positively expressed in BMSCs. Moreover, the BMSCs exhibited negative expression for CD34 (0.40%) and CD45 (0.22%), which are the hematopoietic stem cell markers. These findings suggest that the isolation and identification of BMSCs was achieved. Under a fluorescence microscope, the proliferation and migration of BMSCs on the Interceed membrane were examined after they were labeled with the fluorescent dye PKH26. It was observed that the 200 μL concentration of BMSCs exhibited the highest migratory and proliferative activity on the Interceed (Fig. 2).

3.3. IUA rats, Interceed membrane joint BMSCs can promote the number and thickness of endometrial glands

The findings of the HE staining showed that Interceed treatment did not significantly alter the number of endometrial glands or the thickness of the endometrium when compared to the IUA model group ($p > 0.05$). In the BMSCs treatment group, the number of endometrial glands and endometrial thickness increased significantly with the increase in intervention time ($p < 0.05$). In the treatment group receiving Interceed + BMSCs, there was a substantial increase in the number of endometrial glands and endometrial thickness. This increase was observed to be most significant among all intervention groups, and it also increased significantly with the increase in intervention time ($p < 0.05$; Fig. 3).

3.4. In IUA rats, Interceed combined with BMSCs can promote endometrial angiogenesis

Immunohistochemical results showed that compared with the IUA model, the number of endometrial MVDs in the Interceed therapy did not change significantly ($p > 0.05$). However, the number of endometrial MVDs increased in the BMSCs therapy, and it increased with the increase in intervention time ($p < 0.05$). In the Interceed + BMSCs therapy, there was a statistically significant increase seen in the number of endometrial MVDs. This rise was particularly evident among all intervention groups, and it increased with the increase in intervention time ($p < 0.05$; Fig. 4).

3.5. In IUA rats, Interceed membrane combined with BMSCs improved endometrial receptivity

The results obtained from qRT-PCR and Western blot analyses revealed no significant alterations in the mRNA and protein expressions of LIF, integrin αvβ3, and VEGF following the Interceed therapy when compared to the IUA model group ($p > 0.05$). During the BMSCs treatment, there was an increase in the relative expressions of LIF, integrin αvβ3, and VEGF mRNA and

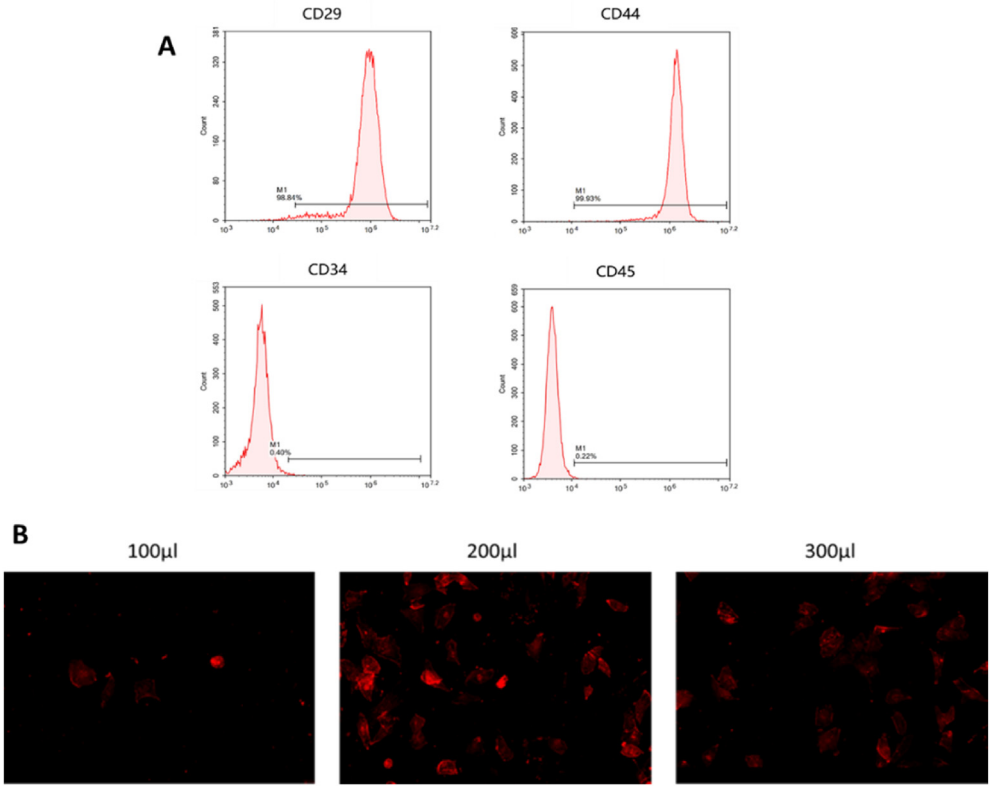

Fig. 2. Isolation, culture, and identification of BMSCs. A. Flow cytometric detection of cell surface markers, showing CD29, CD44, CD34, and CD45 expression levels. B. The proliferation and migration of BMSCs with different concentrations on the Interceed were observed under a fluorescence microscope, and the highest proliferation and migration activity of BMSCs was observed at a concentration of 200 μL.

protein, and it increased with the increase in intervention time ($p < 0.05$). In the Interceed + BMSCs therapy group, the mRNA and protein relative expressions of LIF, integrin αvβ3, and VEGF in endometrium were significantly increased. This increase was most significant among all intervention groups. Moreover, it also increased with the increase in intervention time ($p < 0.05$; Fig. 5).

3.6. In IUA rats, Interceed membrane combined with BMSCs can change the pregnancy outcome of rats

Compared with the IUA model, there was no significant change in the number of gestational sacs in the Interceed therapy ($p > 0.05$). However, the number of uterine gestational sacs increased in the BMSCs therapy group ($p < 0.05$). Moreover, in the Interceed + BMSCs group, the number of uterine gestational sacs increased significantly ($p < 0.05$; Fig. 6).

4. Discussion

IUA can arise as a consequence of several factors, including mechanical trauma, abortion, infection, and other sources of injury to the basal layer of the endometrium. Partial or complete occlusion of the uterine cavity or cervical canal leads to morphological deformities or even obliteration of the uterine cavity [20]. This study is the first in which Interceed, in conjunction with BMSCs, was introduced into the uterine cavity of rats with IUA. The objective was to examine its impact on endometrial glands, thickness, vasculature, and receptivity. The implementation of mechanical damage effectively developed a female rat model of IUA. During the

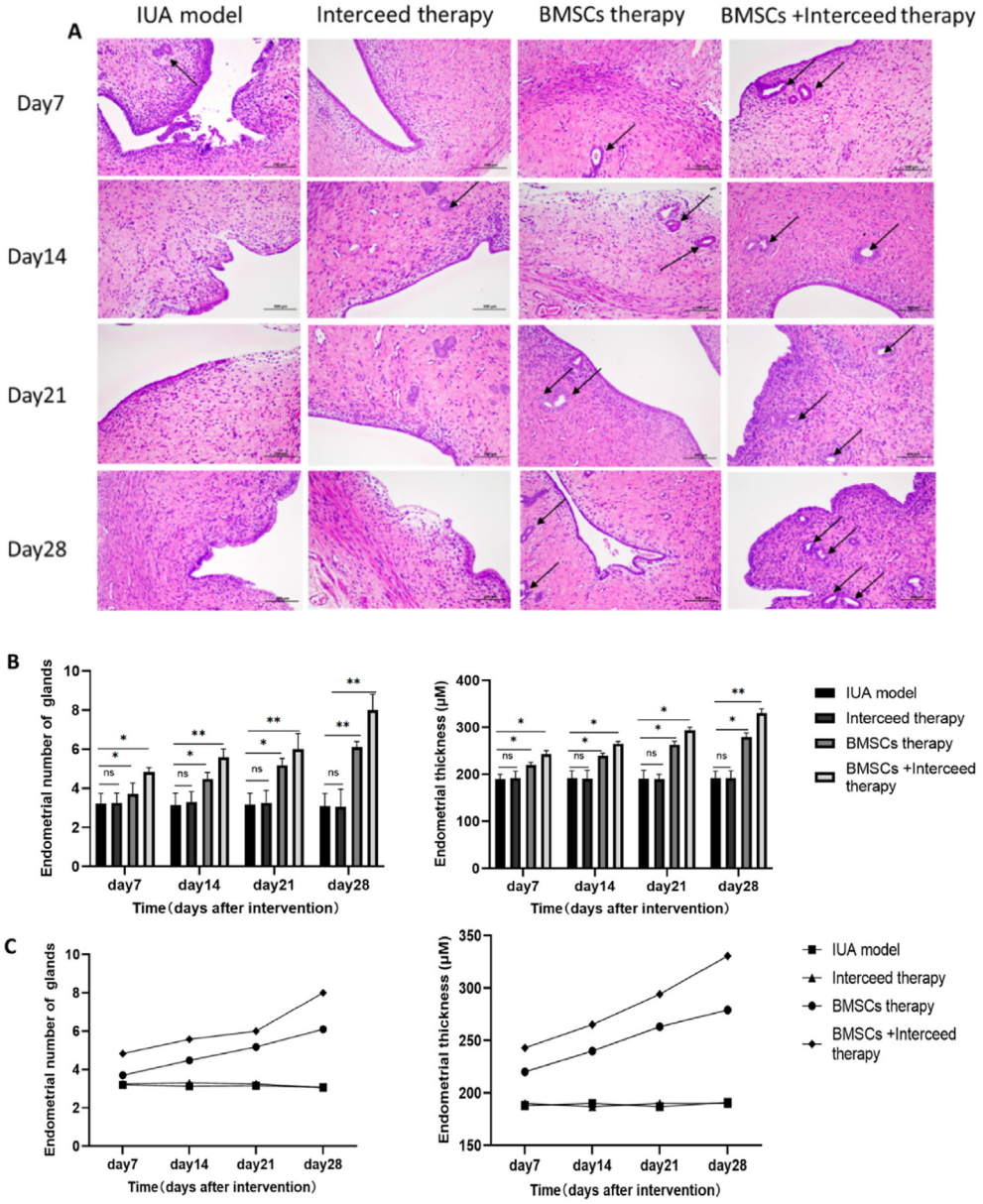

Fig. 3. Interceed combined with BMSCs improves endometrial gland and thickness. A. HE staining was performed on uterine tissue samples from rats in each group at 7, 14, 21, and 28 days post-intervention. (arrow indicates endometrial glands) B. The post-intervention quantification of endometrial glands in each experimental group at various time points, along with the assessment of endometrial thickness. C. The number of endometrial glands and the thickness of the endometrium in each group at different time points after intervention, *p < 0.05, **$p < 0.01$.

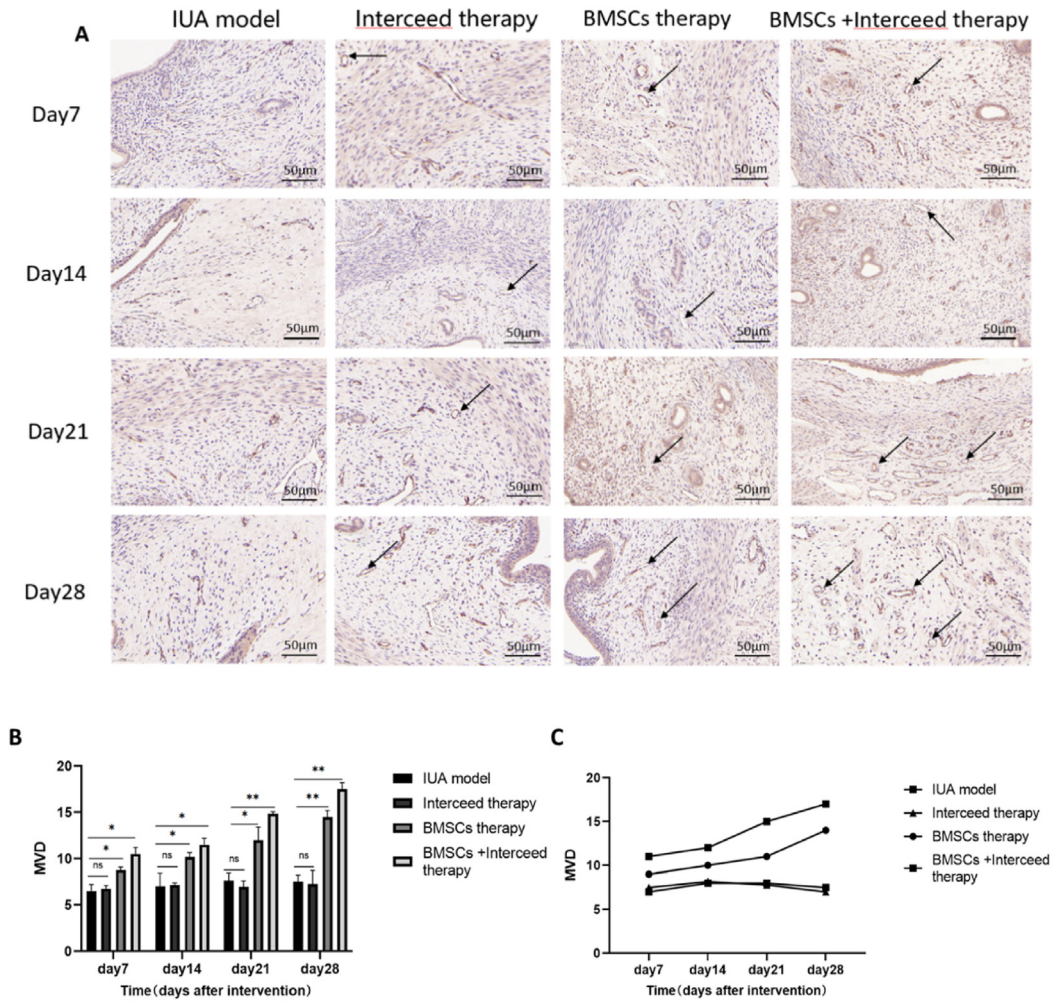

Fig. 4. Interceed combined with BMSCs promotes endometrial angiogenesis. A. Immunohistochemical staining of uterine tissue on the 7th, 14th, 21st, and 28th day after intervention (arrow shows endometrial MVD) B. and C. Statistical results of endometrial MVD number in each group at different time points after the intervention, $*p < 0.05$, $**p < 0.01$.

occurrence of IUA, it was shown that the rat uterine cavity exhibited adhesion, resulting in a reduction in endometrial thickness, a drop in glandular count, an increase in fibrosis, and a decline in fertility. There was a substantial increase observed in the number of endometrial glands, endometrial thickness, and MVD in rats that received treatment with Interceed in combination with BMSCs following IUA. The expression levels of LIF, integrin αvβ, and VEGF in the endometrium exhibited a significant increase, leading to a substantial improvement in the uterine pregnancy rate.

The Interceed is a physical barrier that attaches to the injury site and separates the potential adhesion surface until mesoderatization occurs again, thereby reducing the formation of adhesions. The efficacy of Interceed in preventing post-operative adhesions has been well established. A. Temiz et al. [15] established a rat tendon repair model and confirmed that Interceed could significantly reduce the formation of peritendinous adhesion after tendon repair in rats. The initial investigation conducted by Jang et al. [14] examined the safety and efficacy of Interceed in the prevention of mucosal adhesion following middle ear surgery. In gastrointestinal surgery [21], Interceed has also been widely used for post-operative anti-adhesion. Additionally, several studies have also demonstrated that the appropriate utilization of Interceed has the potential to mitigate the development of adhesions after abdominal and pelvic surgical procedures, including laparoscopic myomectomy and laparoscopic lobectomy. Moreover, the application of Interceed is effective in the prevention of adhesion formation [22]. The current study suggests that Interceed can effectively prevent the readhesion of TCRA, but cannot effectively promote endometrial regeneration. The results of this study demonstrated that the intrauterine placement of Interceed in IUA rats did not significantly alter the number of endometrial glands, endometrial thickness, or MVD. Additionally, there were no significant changes observed in the expressions of LIF, integrin αvβ3, and VEGF in the endometrial tissue. These findings are consistent with previous studies.

BMSCs are adult stem cells that possess remarkable attributes such as high proliferative capacity and multi-differentiation potential. These cells originate from the mesoderm and are distinct from hematopoietic stem cells. BMSCs can move to the site of injury inside the uterine cavity and facilitate the regeneration of both the endometrium and the blood vessels. Thereby facilitating the restoration of the endometrium. Research findings indicate that the administration of BMSCs *via* the rat's tail vein can facilitate their migration to the uterus and induce intimal hyperplasia. However, the homing efficiency of BMSCs is quite low, around 20% [18]. In a study conducted by Nagori et al. [19], a patient with severe IUA showed a progressive improvement in endometrial thickness and vascular density following the administration of autologous bone marrow stem cells by vaginal injection. Ultimately, the patient achieved successful pregnancy and delivery. Santamaria et al. [23] employed a combination of BMSCs and hormone replacement

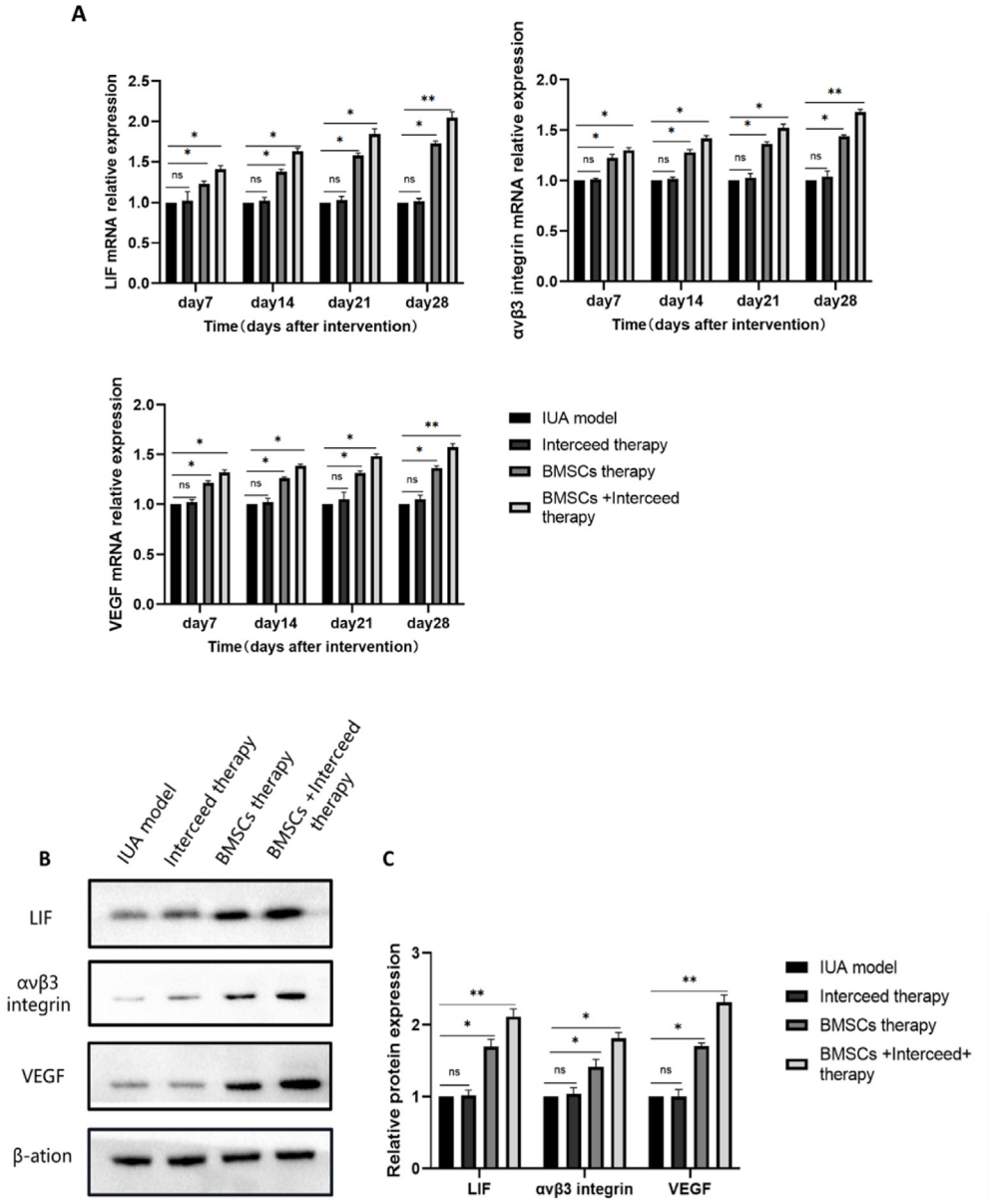

Fig. 5. Interceed membrane combined with BMSCs improves endometrial receptivity. A. Statistical results of LIF, integrin αvβ3, and VEGF mRNA relative expression in endometrial tissue of rats in each group at 7, 14, 21, and 28 days after the intervention. B. The relative expression of LIF, integrin αvβ3, and VEGF protein in endometrial tissue of rats in each group after 28 days of the intervention. C. The relative expression of LIF, integrin αvβ3, and VEGF protein in endometrial tissue of rats in each group after 28 days of intervention showed statistically significant results ($*p < 0.05$, $**p < 0.01$).

therapy for the treatment of IUA over 2 months. The administration resulted in an increase in endometrial thickness among the IUA patients, accompanied by enhanced endometrial vascular density within the initial 3-month duration. Moreover, an increase in the duration of the menstrual cycle was noted, followed by a subsequent return to baseline levels during 6 months. In the aforementioned research, it was shown that BMSCs exhibited transitory stimulation and were unable to sustain continuous stimulation of the internal environment within the uterine cavity. The findings of this study indicate that there was a substantial increase in the number of endometrial glands, endometrial thickness, and MVD in rats that received injections of BMSCs, as compared to both the IUA model group and the Interceed group. Similarly, the expressions of LIF, integrin αvβ3, and VEGF were also significantly increased in endometrial tissue. Notably, the effect of BMSC on endometrial regeneration was more significant over time.

Previous studies have found that BMSCs can be used in combination with other biological materials to exert better therapeutic effects. The findings of this study demonstrated that intrauterine placement of Interceed combined with BMSCs could significantly improve the number of endometrial glands, intimal thickness, and intimal MVD in rats, and the effect was more pronounced with the passage of treatment time. LIF and integrin αvβ3 have been recognized as markers of endometrial receptivity, and their changes in expression levels during the menstrual cycle support their decisive role in the normal implantation process [24]. VEGF has predominant expression throughout the menstrual and proliferative stages of the menstrual cycle. Its expression is intimately associated with the maintenance and development of microvessels, as well as the regeneration of endometrial tissue [25]. In this study, The intrauterine placement of Interceed combined with BMSCs significantly enhanced the expression levels of LIF, integrin αvβ3,

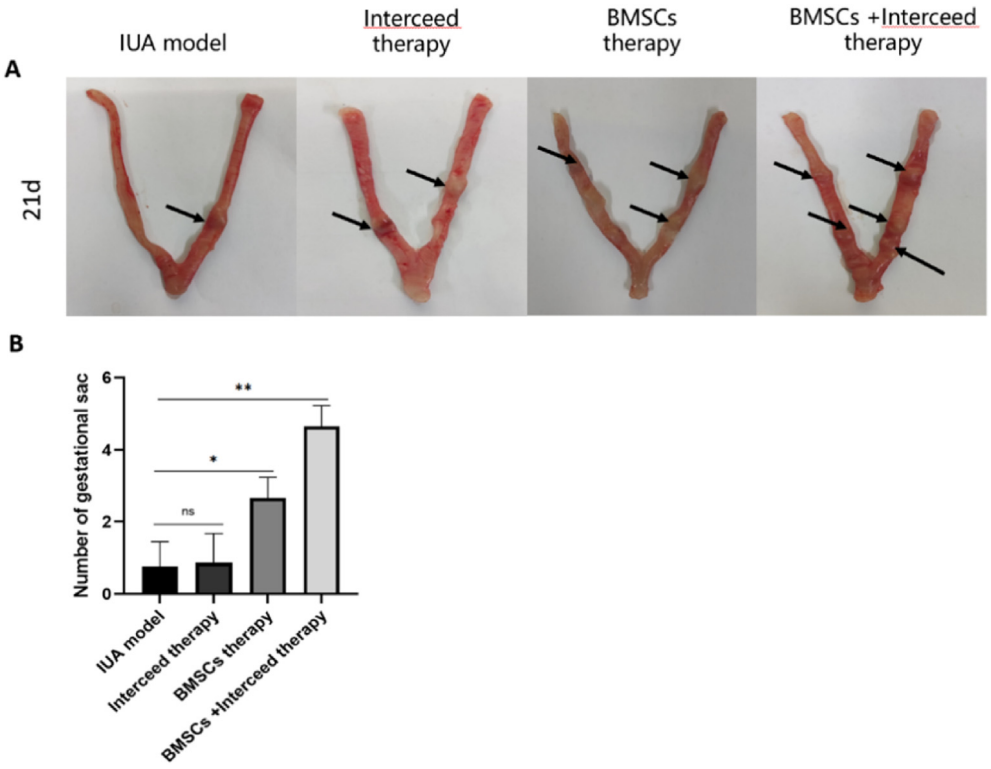

Fig. 6. Interceed membranes combined with BMSCs can alter pregnancy outcomes in rats A. Images showing the samples of rat gestational sac in the uterus of each treatment group. B. Statistical results of the number of rat uterus gestational sacs in each group $*p < 0.05$, $**p < 0.01$.

and VEGF in the endometrium, as well as improved the pregnancy rate compared to other treatment groups.

5. Conclusion

The findings of this study demonstrate that the intrauterine transplantation of Interceed, in combination with BMSCs, in rats with IUA, leads to an augmentation in the thickness of the impaired endometrium, an increase in glandular structures, the promotion of angiogenesis within the endometrium, an enhancement in endometrial receptivity, which facilitates pregnancy in rats with IUA. This study presents a novel approach for addressing endometrial repair in individuals diagnosed with IUA, providing a dependable therapeutic alternative for the clinical treatment of IUA.

Ethical approval

The study protocol for this retrospective cohort study was approved by The First Hospital of Lanzhou University Research Ethics Committee (ldyyshll2021-100).

Funding

The study was supported by the Regional Scientists Fund of the National. Natural Science Foundation of China (No. 82260305). Natural Science Foundation of Gansu Province (No. 22JR5RA607). Gansu Provincial Health Commission (No. GSWSKY2022-60). Lanzhou Science and Technology Bureau talent Project (2021-RC-133).

Data availability statement

Not applicable.

Declaration of competing interest

In our manuscript “Interceed combined with bone marrow mesenchymal stem cells improves endometrial receptivity of intrauterine adhesion”, there is no conflict of interest.

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