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CASE REPORT

Effect of Umbilical Cord-Mesenchymal Stem Cells (UC-MSCs) Derived Secretome Combined with UC-MSCs in Anterior Cruciate Ligament Tear: A Case Report

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ABSTRACT

Introduction: Anterior cruciate ligament **(**ACL) tears are common among athletes and active individu. Up to date, treatment for a Grade 3 ACL tear (compleat torn) is usually surgery. However, expert is starting to look for other options such as using stem cells and their derivatives (secretome) as an option instead of going under the knife.

Case: We reported a man in his 30s who played futsal recreationally. He experiences compleat ACL tear. He experienced considerable pain (Numeric Pain Rating Scale [NPRS] score of 7) and his knee felt like it was giving way. An MRI confirm a grade 3 ACL tear, but he refused surgery.

Intervention: We gave him a shot of 1.5 mL of UC-MSCs derived secretome around his knee. Then, a few months later, we injected his knee joint with 1×10^7 UC-MSCs mixed in 3 mL saline and 1.5 mL secretome. He also undertook rehabilitative exercises at home to help his knee get better.

Result: After six months, his pain level went way down (from a 7 to 0), he was back to playing sports, and his knee felt much better. A follow-up MRI showed that the tear had healed. The treatment didn't cause any serious adverse effects.

Conclusion: This case suggests that UC-MSCs and its derivative, secretome, could be a good non-surgical way to fix ACL tears. However, further in deep studies is needed to confirm the effectiveness and safety of UC-MSCs and its derivative, secretome.

Keywords: ACL tear; UC-MSCs; secretome; pain

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INTRODUCTION

The knee joint is supported by 11 ligaments for its stability. One of those ligaments is the anterior cruciate ligament (ACL).[1] This ligament is frequently injured during sports, which can result in a tear. Patients with a greater body mass index (BMI) also have a higher prevalence of ACL tears.[2] Symptoms of ACL include significant discomfort, knee joint swelling, and, in more severe cases, instability of foothold. This condition could leave an impact on the patient's quality of life and, in the long run, can ultimately result in osteoarthritis and functional limitations.[2,3] Although magnetic resonance imaging (MRI) is the gold standard for identifying ACL tears, physical examinations, including the anterior drawer and Lachman tests, are also used.[1,3]

The grade or severity of the tear in millimeters (mm) might determine the course of treatment. While bracing and rehabilitation can be used to conservatively manage grade 1 (3–5 mm) and grade 2 (5–10 mm) tears, surgery remains the standard for managing grade 3 (>10 mm) ACL tears. However, long-term results from these conservative approaches might not be sufficient for total relief, especially with grade 3 tears.[2,3]

Hence, experts are now beginning to investigate stem cell therapies and stem cell-conditioned media (secretome) as non-operative options for treating ACL rupture. Recent research indicates that it has produced positive effects. Studies on both humans and animals have shown that both stem cells and secretomes promote tendon and ligament regeneration through paracrine pathways.[4–6] Umbilical cord-mesenchymal stem cells (UC-MSCs) are one type of stem cell that has demonstrated the most potential for the healing of tendons and ligaments. A study is comparing MSCs from bone marrow (BM), umbilical cord blood (UCB), and umbilical cord tissue (UC). It found that UC-MSCs are particularly excellent at differentiating into tendon-like cells and creating structured tendon-like matrices while under tension. Histologically, UC-MSCs outperform BM-MSCs and UCB-MSCs in promoting the regeneration of full-thickness tendon defects.[7] Other than that, studies suggest that the biological processes and regenerative effects of MSCs predominantly originate from paracrine factors secreted by MSCs, which are known as secretomes.[4–6] It functions by reducing inflammation and modulating the immune response. It has also shown the ability to promote cellular proliferation, migration, and differentiation. All of those abilities are critical for tissue repair and regeneration.[11,9] The secretome contains soluble proteins, lipids, cytokines, nucleic acids, extracellular vesicles, and growth factors (transforming growth factor (TGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF)).[4–6]

We describe a case of grade 3 ACL injuries treated with UC-MSCs and UC-MSC-derived secretome. We asked the patient to use his case in this report. He agreed and signed the informed consent. Moreover, data on the patient will be kept confidential and used for research purposes only. Up to date, surgery is still the best option for treating grade 3 ACL injuries, but it has drawbacks, including prolonged recovery periods, severe pain and swelling, and possible long-term functional restrictions, which can lower the patient's quality of life.[10] For patients who refuse surgery, the use of UC-MSCs and UC-MSC-derived secretome can offer a promising alternative.

PRESENTATION / CASE DESCRIPTION

Patient Presentation

We present a case of a recreational futsal player in his 30s who, during a futsal match, felt a "popping" feeling in his right knee. He experienced knee pain and instability after the injury, making it difficult for him to run, walk, and carry out daily tasks. When the patient visited the clinic two weeks after the incident, he reported that he had episodes of his knee "giving way" when bearing his body weight, which made it difficult for him to carry out everyday tasks. It was suggested that the patient get a knee MRI and come back for additional assessment and care.

Physical Examination

Upon physical examination, the legs showed a slight outward bowing (genu varum), where the left knee angled at a 6-degree angle and the right knee at a 4-degree angle. The right knee was found to be red, swollen, and tender. Lachman tests were performed on the patient. The result is positive, which suggests an ACL tear. When the physician attempts to flex or extend the knee, it causes severe pain; hence, the patient's Numerical Pain Rating Scale (NPRS) score was 7. The right knee patella was observed lower compared to the left knee patella. Since the patient was unable to flex the right knee past 100 degrees, the

range of motion was measured between 0 and 100 degrees. In addition, the patient was overweight.

Imaging

An MRI performed eight weeks post-injury revealed a complete ACL tear (grade 3) in the right knee, along with tears in both the medial and lateral menisci (Figures 1a and 1b). It also showed patellofemoral disorder, characterized by patella baja, but the posterior cruciate ligament (PCL) is observed as stable.

Figure 1: Sagittal MRI images of the right knee before intra-articular UC-MSCs and secretome therapy

a) Baseline MRI showing a complete anterior cruciate ligament (ACL) tear (grade 3); the blue arrow indicates disrupted ACL fibres.

b) Stable posterior cruciate ligament (PCL) at baseline.

Treatment

The patient was recommended to undergo surgery and then followed by temporary wheelchair use for post-surgery recovery, alongside discontinuing futsal. However, the patient declined surgical intervention and opted to explore alternative treatment. Thus, we proposed regenerative medicine using UC-MSCs along with UC-MSC-derived secretome. The UC-MSCs and UC-MSC-derived secretome used in this case are manufactured by PT. Bifarma Adiluhung, a facility accredited for Good Manufacturing Practices (GMP) by the Indonesian Food and Drug Authority (Certificate Number: PW S.01.04.1.3.333.09.21-0082). Additionally, the Indonesian Ministry of Health has granted this institution operational authority to process stem cells (No: 81202131002260001).

Secretome Preparation

The UC-MSCs were isolated and cultured in flasks with growth medium until they reached 70–80% confluence. The UC-MSCs were then subcultured and conditioned in a hypoxic environment with oxygen reduced to 5%. After the growth medium was removed and the cells were washed, a collection medium without supplementation was added. The cells were incubated at 37°C under 5% CO_2 and 5% O_2. Afterward, the secretome was then harvested from the medium. It is then filtered using 0.45 and 0.22 micrometer (μm) membrane filters to remove debris and protein aggregates. The final product was stored at temperatures below −180°C until further testing or application. As per the manufacturer's protocol, the levels of growth factors, cytokines, and proteins were quantified using Enzyme-Linked Immunosorbent Assay (ELISA). The secretome was prepared in a sterile solution, free from antibiotics, preservatives, and phenol red. Each tube contained 1.5 mL of 100% pure secretome, with no synthetic serum or additional growth factors. As part of the quality control process, keratinocyte growth factor (KGF) was used as a marker for the secretome batch.

Stem Cells Preparation

The mesenchymal stem cells used in this case report were derived from a human umbilical cord obtained from a donor who underwent a cesarean section. The donor was rigorously screened and tested for infectious diseases, including HIV, Hepatitis B, Hepatitis C, Syphilis, and CMV IgM. In addition, karyotyping was performed to ensure donor eligibility.

The umbilical cord was processed at the Regenic Laboratory, PT. Bifarma Adiluhung in Jakarta, Indonesia. The MSCs were isolated using

Alpha MEM (+ GlutaMAX), supplemented with human serum, growth factors, vitamins, and 1% antibiotic-antimycotic. The cells were expanded up to passage 7 in Alpha MEM (+ GlutaMAX) with human platelet lysate. To confirm the identity of the MSCs, flow cytometric analysis was performed, verifying the presence of surface markers CD105, CD73, and CD90 (>95%) and the absence of CD45, CD34, CD14, CD19, and HLA-DR (<2%). Additionally, the cells were tested for their differentiation capacity into adipogenic, osteogenic, and chondrogenic lineages.

Injection Method

At the second visit, ten weeks post-injury, 1.5 mL of secretome was injected intramuscularly around the patient's right knee. Secretome injections were administered using the Trigger Point Injection (TPI) technique. It targets two regions with distinct myofascial trigger points (MTrPs). They are the pes anserine band muscles (sartorius, gracilis, and semitendinosus tendons) and the iliotibial band. A 22-gauge needle was inserted at a 30° angle, delivering 0.2 to 0.5 mL of secretome solution per injection site. In parallel, the patient engaged in a structured rehabilitation program, including daily home exercises. By the third visit, four months post-injury, the patient reported pain reduction (NPRS 5) but persistent instability, especially during stair climbing and pivoting movements. At that time, a second, intra-articular injection was administered: 1×10^7 UC-MSCs suspended in 3 mL saline, followed by 1.5 mL of secretome.

Rehabilitation

The patient underwent individualized Muscle Energy Technique (MET) rehabilitation through sport-specific conditioning, which included daily 30-minute home exercises to strengthen the thigh muscles and reduce stress on the ACL and meniscus during healing. The patient also used a 0.5 cm silicon-based lateral wedge insole to address the genu varum posture.

Outcome and Follow Up

Pain and Functional Outcome

The patient showed progressive improvement. By six months post-injury, he reported NPRS pain scores of 0, with restoration of basic activities including walking, standing, and light activity. Occasional mild discomfort was noted during more intense activity.

Structural Outcome

The TPI procedure, used in this case, can induce muscle relaxation, which helped realign the patella and fix the patella baja. A follow-up MRI at six months post-injury demonstrated notable structural healing: the ACL appeared elongated but continuous (Figure 2a), and patella positioning had improved, with resolution of patella baja. The PCL remained stable (Figure 2b). Meniscal tears were still evident, likely contributing to intermittent discomfort during intense activity.

By eight months post injury, the patient had returned to recreational futsal. Even though the patient reported occasional pain, there were no more instability episodes.

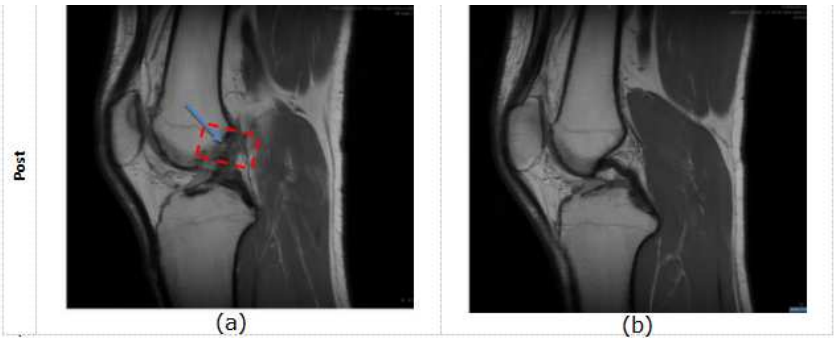

Figure 2: Sagittal MRI images of the right knee after intra-articular UC-MSCs and secretome therapy

a) Follow-up MRI at six months post-treatment showing elongated but continuous ACL fibres; the blue arrow indicates reconnection of the ligament.

b) No significant change in PCL morphology compared to baseline.

Complication and Adverse Events

Throughout the treatment and follow-up period, the patient did not experience any significant adverse events. Mild discomfort at the injection site was reported initially, but this was self-limiting and did not require analgesics.

DISCUSSION AND CONCLUSION

A recreational futsal player in his 30s felt a "popping" feeling in his right knee during a futsal match. He complains of pain and instability in his right knee as well as episodes of his knee "giving way" when bearing his body weight, which makes it difficult for him to carry out daily tasks. On the first visit, 2 weeks after the injury, a physical examination conducted on the patient revealed that the right knee was red, swollen, and tender. The Lachman test result is positive, and pain (NPRS 7) was experienced when attempting to flex or extend the knee. The patient was unable to flex the right knee past 100 degrees. The right knee patella appears lower than usual compared to the opposite side. The patient was overweight. From this history, the symptoms experienced by the patient and the positive result from the Lachman test all suggested an ACL tear.[1,3] Other than those who are active in sports, the prevalence of ACL tears is also high in those with higher BMI.[2] Results from the patient's MRI confirmed a complete ACL tear (grade 3) in the right knee, along with tears in both the medial and lateral menisci.

Currently, the standard of care for a Grade 3 ACL tear is ACL reconstruction through surgery,[11,12] but it can cause several complications, such as postoperative muscular weakness, arthrofibrosis, and the potential development of early osteoarthritis.[2,3,10] The patient declined to undergo surgery. Thus, we proposed regenerative medicine using UC-MSCs along with UC-MSC-derived secretome. At the second visit, 10 weeks post-injury, 1.5 mL of secretome was injected intramuscularly around the patient's right knee. Recent advances in regenerative medicine, particularly the use of stem cells and their derivatives (secretome), have shown considerable promise for tissue regeneration. Among stem cell types, MSCs, especially UC-MSCs, have been widely studied due to their multipotency. It has been shown to be superior to BM-MSCs and UCB-MSCs in tissue regeneration, especially tendon tissue.[7] For instance, Kanye et al. (2007) used model rats with partial ACL tears. Kanye reported that rats injected intra-articularly with BM-MSCs had improved their histological and biomechanical outcomes compared to placebo.[13] Similarly, Sun et al. (2021) demonstrated the positive result of injections of secretome from BM-MSC after ACL reconstruction. It shows that secretomes promote activity of myofibroblasts, which eventually enhances graft-bone integration.[14] As noticed, most studies are animal or preclinical studies, while human studies on secretome for ACL treatment specifically focus on ACL graft augmentation rather than purely non-operative treatment.[15] However, promising positive results are generated from these studies.

At the second visit, the secretome was injected using the TPI technique. This technique has been demonstrated to alleviate myofascial pain syndrome (MPS), which can develop secondarily in patients with ACL tears.[16] TPI likely contributed to muscle relaxation, pain relief, and realignment of the patella. In this patient, the right patella was observed realigning to the right position as soon as the area was injected. While the exact mechanism remains unclear, these effects are consistent with previous findings in pain management and rehabilitation.[17] In parallel, the patient engaged in a MET rehabilitation with a sport-specific conditioning program, including daily home exercises. MET rehabilitation has been shown to improve muscle strength and speed up recovery in knee injuries, further complementing the regenerative effects of regenerative therapies.[18]

By the third visit, 4 months post-injury, the patient reported pain reduction (NPRS 7 to 5) but persistent instability. Hence, a second, intra-articular injection of UC-MSCs followed by secretome was injected. On the fourth visit, 6 months post-injury, the patient reported NPRS pain scores of 0, with minimum limitation. By 8 months post injury, the patient had returned to recreational futsal. In this case, pain score reduction can be seen from 4 months post injury and reaches 0 at 6 months post injury. An animal study has demonstrated that a single secretome injection can provide long-lasting pain relief by reducing neuroinflammation in the peripheral and central nervous systems.[19,20] While a previous study on knee osteoarthritis found that secretome injections showed improvement in pain (measured in VAS) and function scores (measured with WOMAC and KOOS) over 3-6 months compared to hyaluronic acid injections.[21] Hence, these findings are in line with the suggestion that both MSCs and their secretome have a positive effect on enhancing ligament and tendon healing. Both have potential as adjuncts to conventional ACL treatments.

Most research on regenerative medicine focused only on the effects of stem cells or secretome

alone. Majority comes from animal studies or pre-clinical trial and there is a notable lack of direct human clinical studies on secretome as a non-operative therapy for ACL tears. However, UC-MSCs and secretome shows promise in reducing pain, functional recovery and healing in preclinical and some clinical contexts.[15,21,22] Despite the promising early results from this case, UC-MSC-derived secretome in ACL injury treatment is still not standardized, and treatment protocols vary widely across clinicians. Additionally, while secretome and MSC therapies appear safe, side effects such as mild swelling and discomfort at the injection site have been reported in some studies.[6] In this case, the patient experienced only mild discomfort, which was self-limiting, suggesting that this treatment could be a viable alternative to surgery for certain ACL injuries.

CONCLUSION

The use of stem cells and secretome therapies holds peerless promise for ACL repair. This case report suggesting that secretome and UC-MSCs therapies can be a viable option for enhancing healing, reducing pain, and improving recovery times for patients with severe ACL injuries. The combined application of UC-MSCs and secretome in the treatment of grade 3 ACL tears remains an area requiring further exploration. Further well-designed human clinical trials are needed for conclusive evidence on healing duration, pain relief, and recovery time in ACL tears treated non-operatively with secretome.

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