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A case series on safety and tolerability of human umbilical cord-derived mesenchymal stem cells on patients in Malaysia

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Abstract

Umbilical cord-derived mesenchymal stem cells for regenerative therapy are a promising treatment option for chronic illnesses. Umbilical cord-derived mesenchymal stem cells offer several advantages over other sources, which makes them an attractive option in tissue repair and regeneration. This clinical study describes a 1-year follow-up on the safety and tolerance of umbilical cord-derived mesenchymal stem cell therapy on nine patients in Malaysia. Patients were assessed for adverse effects, and liver function tests were carried out on both pre- and post-treatments. Umbilical cord-derived mesenchymal stem cells' effectiveness and safety were assessed by follow-up evaluations. All nine patients responded positively towards umbilical cord-derived mesenchymal stem cell therapy, without any adverse effects. After umbilical cord-derived mesenchymal stem cell therapy, a significant improvement was observed in liver functioning test outcomes, as haematological parameters and tumour markers were stable. The present study concludes that umbilical cord-derived mesenchymal stem cell therapy is well tolerated by Malaysian patients; however, further clinical screening must be done over a large number of patients population.

Keywords

Umbilical cord-derived, liver, regeneration, chronic diseases, mesenchymal stem cells, regenerative therapy

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Introduction

Evidence suggests that chronic disease treatment with regenerative therapy (RT), which involves the replacement or regeneration of non-functional or damaged tissue is a promising method. There are several approaches for regenerative medicine, including stem cell therapy and platelet-rich plasma.[1] Among these, mesenchymal stem cells (MSCs) have been extensively studied and applied, attributed to their ease of extraction from a wide range of tissue sources such as bone marrow, adipose tissue, synovium and umbilical cord.[2] MSCs are known for their unique properties, such as their ability to differentiate into different cell types and their immunomodulatory and anti-inflammatory effects.[3] This versatility renders MSCs an attractive option for tissue repair and regeneration. MSCs have been explored as a potential treatment for a wide range of acute and chronic illnesses.[4] In Malaysia, regenerative medicine therapy is rapidly and constantly developing, with various ongoing clinical trials in a wide range of fields, including oncology, orthopaedics and

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anti-ageing.[5] Liver dysfunction is a chronic condition of increasing concern worldwide, with numerous causes ranging from viral hepatitis to alcohol abuse and non-alcoholic fatty liver disease. Despite advances in medical care and management, liver disease remains a significant cause of morbidity and mortality, especially in middle- and lower-income countries, with transplantation as the only definitive cure. As the demand for liver transplantation continues to grow, the need for more innovative therapies has become increasingly urgent. In rat models, the transplantation of human umbilical cord mesenchymal stem cells (UC-MSCs) has been shown to enhance liver function, reduce fibrosis and damage and facilitate liver regeneration.[6] The transfusion of UC-MSCs in human patients with acute-on-chronic liver failure resulted in a significant improvement in survival rates and a reduction in end-stage liver disease scores.[7] We present the clinical case series per the CARE (consensus-based clinical case reporting) checklist, describing the real-world outcomes and tolerance of nine patients in Malaysia, who received MSC therapy at ALPS Medical Centre for RT.[8] The present study aimed to highlight the safety record of MSCs used in this case as a therapeutic option, provide insights into this approach's potential benefits and limitations and support the development of future experimental protocols for this innovative therapy.

Case description

The present clinical study was registered with the National Medical Research Register (NMRR) (NMRR ID-23-01459-CMH). Data were extracted following the ethical principles of the Declaration of Helsinki and Malaysian Good Clinical Practice.[9] The study involved nine non-consecutive patients who received MSC therapy, at ALPS Medical Centre. To establish the effectiveness and safety of UC-MSCs (MyCelest) therapy, a clinical investigation was done in the years 2020 and 2022. The patients' data was traced from the database and selected based on specific inclusion and exclusion criteria.

In the present study, the inclusion criteria involved individuals aged 18 years or older who had received MSC therapy at ALPS Medical Centre and were willing to provide informed consent for data publication. The exclusion criteria were individuals who received any other MSC therapy or MSC products, individuals with known allergies or hypersensitivities to any component of MSC therapy, individuals with a history of cancer or other severe medical conditions and individuals who were pregnant or breastfeeding. As per the standard of care, each patient underwent a thorough evaluation before the initiation of MSC treatment, including a detailed medical history review, physical examination and laboratory testing. The medical history review was conducted to assess the overall health status of each patient and to identify any contraindications to MSC therapy. During the physical examination, doctors assessed general health and well-being, including vital signs and the presence of any acute exacerbations of their medical conditions. To establish the initial health status of patients and keep track of their progress following MSC infusion, laboratory tests (e.g., full blood count, white cell differentiation, diabetic screening, lipid profiling, liver function profile, renal function, gout screening, sexually transmitted diseases, hepatitis B, hepatitis C screening, cancer and urinalysis) were conducted before the MSC infusion. Based on the results of the initial evaluation, if patients were deemed eligible for MSC therapy, they were then scheduled for an appointment to receive a dose of the MyCelest MSC infusion. Throughout the infusion and treatment process, all subjects were closely monitored to ensure their safety and well-being.

This case series comprised nine patients with a wide age range, spanning from 37 to 81 years, inclusive of five males and four females. These individuals underwent UC-MSC therapy to address a spectrum of health conditions including diabetes, osteoporosis, chronic kidney disease, erectile dysfunction, anti-ageing, strokes and cardiovascular diseases.

The subjects' current health statuses are reviewed, ensuring that they do not exhibit any contraindications for MSC infusion. A pre-MSC infusion phase involves the administration of 350 mL of normal saline accompanied by 50 mL of Myers[10] cocktail for 1 h, as per the written prescription by the attending physician. Following the infusion, a vigilant monitoring process is implemented to detect and address any potential acute hypersensitivity reactions before the patients are discharged from daycare. Patients are advised to promptly communicate any new symptoms such as fever, vomiting, insomnia, redness or pain at the injection site, rash, or shortness of breath to the medical team at ALPS Medical Centre. After the procedure, follow-up visits are scheduled 2 weeks post-infusion, primarily for a thorough physical examination. Additionally, laboratory tests are conducted after 30 days to objectively evaluate blood parameters, ensuring a comprehensive review of tolerability and potential effects stemming from the UC-MSC therapy.

Case series

Case 1: The first case, an 81-year-old female patient with a medical history notable for cardiovascular disease and hypertension, presented for examination. The patient's vital signs included a blood pressure (BP) reading of 120/67 mmHg and a pulse rate (PR) of 128/min. Given her pre-existing cardiovascular condition, the patient underwent a thorough physical examination and blood tests, following which she received UC-MSCs therapy. Continuous monitoring was implemented, and subsequent blood analyses were conducted to assess the safety profile of the administered UC-MSCs.

Case 2: A 70-year-old male, previously diagnosed with diabetes, was scheduled for UC-MSC therapy. The patient's vital signs revealed a BP of 127/85 mmHg, a PR of 70/min and an oxygen saturation SpO_2 of 99%. Additionally, his fasting blood glucose level was recorded at 7.5 mmol/L. Routine blood analysis during the follow-up indicated no safety concerns, and the patient reported an enhancement in well-being post-UC-MSC therapy.

Case 3: A 73-year-old female, with a history of stroke, was scheduled for UC-MSC therapy. Vital signs assessment indicated a BP of 134/82 mmHg, a PR of 84/min and SpO_2 of 96%. A pre-procedure blood analysis was conducted to evaluate the safety of stem cell administration. Following the procedure, the patient reported no safety concerns during subsequent follow-ups and exhibited notable improvements in motor skills and cognitive function.

Case 4: A 63-year-old female sought UC-MSC therapy for anti-ageing purposes. Vital signs assessment revealed a BP of 125/80 mmHg and a PR of 72 beats/min. A baseline blood analysis was performed to establish a safety reference point for comparison with post-UC-MSC administration. The patient reported no safety concerns post-therapy.

Case 5: A 50-year-old male patient who was previously diagnosed with erectile dysfunction, presented with vital signs indicating a BP of 150/84 mmHg, a PR of 89 beats/min and a SpO_2 of 95%. At post-treatment, the patient reported enhanced erectile function and overall sexual well-being. Subsequent follow-ups revealed no safety concerns related to UC-MSC therapy.

Case 6: A 59-year-old female who was previously diagnosed with osteoporosis was scheduled to undergo UC-MSC therapy. Her vital examination exhibited signs including a BP of 127/74 mmHg, a PR of 54 beats/min and SpO_2 of 98%. The patient outcome post-treatment shows increased bone density. Subsequent follow-ups confirmed the absence of safety concerns associated with UC-MSC therapy.

Case 7: A 53-year-old male who was diagnosed with chronic kidney disease presented with vital signs showing a BP of 120/85 mmHg, a PR of 82 beats/min and SpO_2 of 98%. Pre-treatment and post-treatment blood analysis was conducted. The outcome indicated improved kidney function and subsequent follow-ups revealed no safety concerns related to UC-MSC therapy.

Case 8: A 44-year-old male who was diagnosed with erectile dysfunction displayed vital signs, including a BP of 112/74 mmHg, a PR of 69 beats/min and a SpO_2 of 97%. Post-treatment outcomes revealed enhanced erectile function and overall sexual well-being. Follow-up examinations confirmed the absence of safety concerns associated with UC-MSC therapy.

Case 9: A 37-year-old female is scheduled to undergo stem cell therapy to counter anti-ageing due to potential health problems. The patient's vital signs indicate a BP of 101/71 mmHg, PR of 78 beats/min and SpO_2 of 97%. The patient reported no pain post-treatment. Subsequent follow-ups revealed no safety concerns associated with UC-MSC therapy.

Preparation and infusion of UC-MSCs

Local regulations permit only the use of umbilical cord stem cells and haematopoietic stem cells for transplantations to patients. Hence, we have chosen to use UC-MSCs in this clinical case series. The umbilical cord samples were obtained from mothers after the delivery of full-term healthy babies. The mothers provided informed consent to donate the samples. The samples were then thoroughly screened for infectious diseases such as HIV, hepatitis B and C, syphilis and cytomegalovirus. Throughout the whole process, the cell products were handled according to current good manufacturing practice principles. MSCs were isolated from umbilical cord tissues using the tissue culture method. Following isolation, the MSCs were grown in a specific medium containing DMEM HG, Glutamax, Elite-Gro Adv, Antibiotic-Antimycotic (Thermo Fishers Scientific) and Elite-Gro Advance (ELITE Cell). The culture media were adjusted to maintain undifferentiated cells, which is crucial for their potential as a form of treatment. Cells were cultured from Passage 0 (P0) to Passage 5 (P5) and were maintained and grown in 5% CO_2 at 37 °C. The passaging of the cells involved trypsinisation using TrypLe 10× and Dulbecco's Phosphate Buffer Saline and centrifugation. Each passage involved cryopreservation, a commercial cryoprotectant and a slow-freezing method with an alcohol bath. MSCs were harvested and prepared for infusion once they had reached a sufficient number. This required the cells to be processed into a concentrated solution suitable for injection after eliminating any remaining growth media. Throughout the procedure, quality control methods were used, such as checking for sterility, viability, endotoxins and cell immunophenotyping as well as ensuring the absence of mycoplasma infections. Several assays and microscopy methods were used to assess the growth, vitality and quality of the cells during the culture time. The morphology and confluency of the cells were observed using 10x and 4x microscopic methods, respectively. The morphology of the cells chosen for the final product appeared to be spindle-shaped, and the confluency was 80%–90% upon harvesting. For each passage of cells, immunophenotyping was conducted to ensure that CD90, CD73 and CD105 markers were greater than 95% (BD C6plus flow cytometer). The negative markers (CD34, CD11b, CD19, CD45 and HLA-DR) were fewer than 2%, which was per the International Society for Cellular Therapy (ISCT) guidelines.[11] The microbiology tests, sterility of the cells (no growth), mycoplasma (qPCR method; detection limit ND $<$ 100 copies) and bacteria endotoxin (Limulus

Amebocyte Lysate kit, ND < 0.25) were also checked at an independent accredited laboratory. The finished cell product was then packaged in normal saline as per the recommended dosage and transported under a controlled temperature range from 2 to 8 °C in a vaccine carrier box to the Medical Centre.

Outcome, safety and tolerability measures

As the present study was intended to report the wellness and regenerative effects of UC-MSCs, this study was focused on the laboratory indicators of tolerability, along with the patient-reported factors. Since liver enzymes are the common indicators for liver functioning, liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) that were used to assess liver function. The pre-MSC infusion standard laboratory tests included a haematology panel (full blood count, including white cell differential count), glucose and lipid profile, liver function profile, renal function profile (including electrolytes), tumour markers, hepatitis screening and urinalysis for all patients. After the infusion of stem cells, the above laboratory tests were performed 30 days later. The tolerability of UC-MSCs was assessed based on the physical assessments, patient-reported symptoms and post-infusion blood tests to compare the findings with the pre-infusion states.

Across these cases, gross notable improvements were observed post-therapy. These collective outcomes suggest the potential efficacy and versatility of UC-MSC therapy across a wide range of medical conditions, although larger-scale studies are necessary to confirm and establish standardised protocols.

The results obtained from the experimental protocol of the present study were analysed using SPSS version 26 (IBM SPSS, Chicago, IL, USA). This clinical case study involved nine different individuals with a mean age of 58.8 years (SD = 4.8 years), including five females and four males, who received MSC therapy between 2020 and 2022 (Table 1). All nine patients were able to tolerate the infusion well, with vital signs remaining stable throughout the monitoring period. Monitoring was carried out pre-infusion, throughout the infusion period and after discharge from the daycare. The characteristics of the subjects are summarised in Table 1.

Baseline (pre-infusion) routine laboratory assessments were carried out for all nine patients. The basic haematologic profile, including white cell counts, haemoglobin levels, haematocrit (HCT), mean corpuscular volume (MCV) and platelet counts were assessed. There was no significant change ($p = 0.31$) in haemoglobin level, with a mean of 14.4 g/dL (95% confidence interval: 13.2–5.6) pre-MSC infusion and 14.2 g/dL post-MSC therapy. The differential eosinophil count remained within normal ranges for all patients and did not significantly change ($p = 0.08$) between the baseline and post-MSC therapy. The parameters are presented in Table 2. As part of the assessment of tolerability, we also monitored the serum albumin-to-globulin ratio (A/G ratio) of patients as a marker of inflammation. The association between the A/G ratio and inflammatory processes for various conditions has been described in the literature.[12] The A/G ratio of all patients remained similar, both at the baseline (mean = 1.7) and at post-MSC (mean = 1.7) assessments, which suggested that there was no significant increase ($p = 0.68$) in inflammatory activity in the patients. The tumour markers were also monitored in the patients at the baseline and post-MSC therapy. At the baseline, the mean carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP) and carbohydrate antigen 19-9 (CA19-9) were within the normal range; post-MSC therapy assessments showed no significant change in these tumour markers ($p = 0.89$). Similar findings were observed in a study on Wharton's jelly MSCs from a COVID-19-treated patient at a 1-year follow-up.[13]

Table 1. Subject characteristics for the study.

Case number	Gender	Age	Dose of MSC* (million)	Body weight (kg)
Case 1 (3)	Female	81	50	55
Case 2 (6)	Male	70	100	85
Case 3 (9)	Female	73	50	52
Case 4 (10)	Female	63	50	57
Case 5 (13)	Male	50	100	100
Case 6 (15)	Male	59	50	56
Case 7 (18)	Male	53	50	61
Case 8 (19)	Male	44	50	63
Case 9 (20)	Female	37	50	55

MSCs: mesenchymal stem cells.
*UC-MSC therapy dosage was given based on the body weight and severity of the patient's condition.

Six patients (cases 1, 2, 6, 7, 8 and 9) who had undergone pre-infusion laboratory assessments were notable for having either single or multiple raised liver enzyme readings; their liver function indicators are shown in Table 3, along with the levels out of the normal range. All six of these patients had undergone testing for hepatitis B surface antigens and anti-HCV antibodies, which were found to be negative. None of the patients had any acute symptoms of infection, such as fever and did not have physical signs of chronic liver disease upon physical examination.

Discussion

The search in the PubMed database with the keywords 'Umbilical cord AND Stem AND Cells AND safety[ti] AND Malaysia' resulted in only one clinical study (phase I) that tested the safety of umbilical cord stem cells in humans in Malaysia.[14] Additionally, another preclinical study reported that MSC toxicological data essential for the clinical application of these cells are limited.[15] However, regenerative medicine has become increasingly

Table 2. Baseline and post-MSC therapy assessments.

Parameter (unit)	Normal range	Baseline ($n=9$)	Post-MSC therapy ($n=9$)	p-Value*
White blood cells (WBC) ($\times 10^9$/L)	4–11	6.0 (4.6–7.3)	5.5 (4.7–6.3)	0.31
Haemoglobin (g/dL)	11.5–16.5	14.4 (13.2–15.6)	14.2 (13.2–15.3)	0.61
HCT (%)	37–47	42.6 (39.1–46.2)	42.8 (39.0–46.5)	0.73
MCV (fL)	76–96	90.0 (88.5–91.5)	90.6 (88.7–92.5)	0.73
Platelet ($\times 10^9$/L)	150–400	244.2 (204.9–283.6)	240.7 (200.1–281.2)	0.48
Eosinophil differential count	1%–6%	2.9 (1.7–4.0)	3.9 (3.2–4.6)	0.08
A/G ratio	0.9–1.8	1.7 (1.5–1.8)	1.7 (1.5–1.8)	0.68
Total cholesterol (mmol/L)	<5.2	6.3 (4.9–7.7)	6.1 (4.7–7.5)	0.81
Creatinine (μmol/L)	44–80	79.0 (58.2–99.8)	69.8 (54.4–85.6)	0.05
ALP (U/L)	35–104	84.8 (67.5–102.0)	72.3 (61.3–83.4)	0.12
AST (U/L)	<32	26.8 (17.5–36.1)	21.3 (17.7–25.0)	0.16
ALT (U/L)	<33	35.3 (18.0–52.7)	23.0 (17.5–28.5)	0.04
GGT (U/L)	<40	87.2 (1.0–173.5)	40.6 (12.4–68.7)	0.01
CEA (ng/mL)	<5	2.5 (1.1–3.8)	2.6 (1.8–3.4)	0.73
AFP (IU/mL)	<15	2.3 (1.3–3.2)	2.2 (1.2–3.1)	0.37
CA19-9 (U/mL)	<37	12.8 (5.3–20.3)	12.2 (6.1–18.3)	0.89

AFP: alpha-fetoprotein; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; GGT: gamma-glutamyl transferase; HCT: haematocrit; MCV: mean corpuscular volume; MSCs: mesenchymal stem cells. *Values are presented as mean and 95% confidence interval. Wilcoxon signed-rank test was used for paired samples. p-Values set in boldface indicate statistical significance.

Table 3. Baseline and post-MSC therapy liver enzyme levels.

Parameter (unit)	Normal range	Baseline ($n=6$)	Post-MSC ($n=6$)
ALP (U/L)	35–104		
Case 1		88	89
Case 2		87	80
Case 6		125	87
Case 7		85	75
Case 8		60	45
Case 9		114	61
AST (U/L)	<32		
Case 1		12	15
Case 2		37	30
Case 6		53	21
Case 7		20	18
Case 8		27	23
Case 9		19	18
ALT (U/L)	<33		
Case 1		19	12
Case 2		36	37
Case 6		91	28
Case 7		26	24
Case 8		44	21
Case 9		20	16
GGT (U/L)	<40		
Case 1		85	44
Case 2		44	29
Case 6		379	134
Case 7		65	42
Case 8		88	34
Case 9		25	14

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; MSCs: mesenchymal stem cells.

popular in Malaysia in recent years. Many researchers are investigating the potential of using it in clinical settings as an alternative to traditional treatments.

This clinical case series provided supporting information on the outcomes and tolerability of MSC therapy of patients at ALPS Medical Centre who received UC-MSCs. Stem cell therapy using umbilical cord mesenchymal cells has been tested for rheumatoid arthritis, COVID-19 and type 2 diabetes.[16–18] The results have shown that this treatment option is both safe and practical. Based on the primary objectives of this study, we assessed the tolerability as not causing increased inflammation, hypersensitivity reactions and tumour-marker activity. To measure this objective, the A/G ratio was assessed as a proxy laboratory indicator of inflammation, and the differential eosinophil count was assessed as a marker of hypersensitivity reactions. A comparison of the baseline and post-MSC values demonstrated that the markers of inflammation (A/G ratio) and hypersensitivity reactions (differential eosinophil count) did not significantly change between the baseline and post-MSC therapy. MSCs possess the ability to decrease inflammation through a variety of mechanisms.[19] The patients did not report any fevers, vomiting, insomnia cutaneous eruptions, or swellings. These findings suggest that UC-MSC therapy did not result in increased inflammatory activity or hypersensitivity reactions. Other available parameters were assessed, such as the haematologic profile and tumour markers; these also did not demonstrate any significant changes, suggesting that UC-MSCs did not have unintended actions during the assessment period. Similarly, the safety of UC-MSCs has been well demonstrated in several clinical studies.[20]

Conclusion

Based on the findings of the present study, it can be concluded that UC-MSCs exhibit good safety and tolerability in patients in Malaysia, with no significant increase in inflammation, hypersensitivity reactions, or tumour-marker activity during the monitoring period. The results of the present study support the safety of UC-MSCs; however, the current investigation recommends further studies on the UC-MSC product to evaluate its efficacy in improving liver functions.

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Author contributions

S.K.T., K.X.D. and X.L.Z. contributed to Conceptualisation; S.K.T., B.Y., N.K.F. and M.R. contributed to methodology; I.K. contributed to formal analysis; S.K.T., B.Y. contributed to investigation; S.K.T. contributed to resources; I.K., K.M.L., N.K.F. contributed to data curation; M.R. and S.K.T. contributed to writing original draft preparation; S.K.T., M.R., I.K., K.M.L., J.W.K., N.K.F. and X.L.Z. contributed to writing review and editing; S.K.T. and K.X.D. contributed to supervision; S.K.T. contributed to funding acquisition.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declaration of conflicting interests

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Ethical approval

This case series was registered and approved by the National Medical Research Register (NMRR) (NMRR ID-23-01459-CMH), Ministry of Health Malaysia. Data were extracted in accordance with the ethical principles of the Declaration of Helsinki and Malaysian Good Clinical Practice.

Informed consent

Written informed consent was obtained from all nine patients for publication of this case report.

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