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Efficacy and Safety Evaluation of Intravenous MiSaver Stem Cell Therapy in Recent Acute Myocardial Infarction: A Retrospective Phase IIa Study

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ABSTRACT

Background: Despite advancements in cardiovascular treatments, Acute Myocardial Infarction (AMI) remains a significant health challenge. We aimed to explore the potential of stem cell therapy to improve left ventricular function post-AMI through an open-label, dose-escalating trial. The study aimed to assess the safety and feasibility of intravenous infusion of MiSaver, a prefabricated product of ABO matched allogeneic umbilical cord blood stem cells (USC), in patients following recent AMI.

Methods: Participants were enrolled in cohorts of five, receiving escalating dosages of USC (0.5 × 10^7, 1.6 × 10^7, and 5.0 × 10^7 cells/kg). Infusions were administered 2-5 days post-AMI onset. Due to recruitment challenges during the COVID-19 pandemic, this retrospective analysis was conducted using completed low and middle dosage groups and a control group comprising 20 eligible participants meeting similar inclusion criteria.

Results: The primary analysis focused on safety and adverse events (AEs) over a 12-month observational period in the treatment group. The treatment was well-tolerated, with no AEs directly attributed to MiSaver. Initial analysis of 9 participants showed statistically significant improvements in Left Ventricular Ejection Fraction (LVEF) from baseline to 12 months post-treatment compared to the control group ($p<0.05$); however, significance was lost upon inclusion of participant 10. This participant drew attention to the analysis and exhibited unique characteristics, namely the highest Body Mass Index (BMI) and the youngest age among all participants.

Conclusion: This study suggests the potential of MiSaver in enhancing left ventricular function post-AMI. Notably, participants without morbid obesity showed significant recovery in LVEF, suggesting the exclusion of individuals with high BMI in future trials. Larger cohorts and controlled placebo studies are warranted to validate these findings and address trial limitations.

Keywords: Myocardial infarction; Coronary artery disease; Stem cells; MiSaver

INTRODUCTION

Cardiovascular diseases (CVDs) constitute a major global health challenge, responsible for a significant proportion of mortality worldwide, with myocardial infarction (MI) accounting for the majority of CVD-related deaths [1]. Despite advances in both pharmacological and nonpharmacological interventions, MI remains a leading cause of mortality and morbidity [2]. Therefore, there is a pressing need for innovative approaches to enhance cardiac function and recovery in patients post-MI.

Stem cell therapy has emerged as a promising avenue for cardiac regeneration and re-vascularization following AMI. Stem cells possess the ability to migrate, modulate the immune system, secrete trophic factors promoting angiogenesis, and differentiate into mature functioning cells such as cardiomyocytes and vascular endothelial cells [3-24]. However, while preclinical studies have shown encouraging

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results, clinical trials utilizing autologous stem cells have not consistently demonstrated significant benefits in terms of clinical outcomes or improvements in left ventricular function [13,21].

The challenges of obtaining stem cells from medically vulnerable patients post-AMI are compounded by the limitations associated with stem cells from older donors, which often exhibit reduced proliferative and differentiation potential compared to their younger counterparts [11,12]. To address this issue, we hypothesize that utilizing stem cells from sources with enhanced differentiation potential may lead to improved outcomes in left ventricular function post-AMI.

Lee's team transfused circulation derived CD34+ cells intracoronarily and found the clinical improvement correlates to the stem cells' cability of angiognesis [24]. We theorize using stem cells from sources of higher with improved differentiation potential will increase the left ventricular functional improvement.

In this study, we focus on umbilical cord blood-derived stem cells, which offer inherent advantages including established safety profiles in clinical use and immunological characteristics conducive to therapeutic applications [14-20] in myocardial infarction. Given the importance of Left Ventricular Ejection Fraction (LVEF) as a key indicator of heart function and its direct correlation with patient prognosis [22,23], our trial prioritizes safety evaluation while assessing the preliminary efficacy of MiSaver in enhancing LVEF recovery post-AMI.

METHODS

Study Design

We conducted an open-label, dose-escalating clinical trial at Chung Shan Medical University Hospital to evaluate the safety and preliminary efficacy of MiSaver stem cells in enhancing left ventricular function in patients with recent AMI. MiSaver comprised ABO matched allogeneic umbilical cord blood stem cells (USC) prefabricated into a standardized product. Institutional review board approval and regulatory authorization were obtained prior to the commencement of the trial.

Participants

Eligibility criteria ensured the safety and relevance of the results. Patients aged 20 to 80 years, diagnosed with AMI within 7 days, and exhibiting elevated cardiac enzymes and reduced LVEF were included. Hemodynamically stable patients, not requiring inotropic support, were eligible for enrollment. Exclusion criteria encompassed various medical conditions and circumstances incompatible with stem cell therapy.

Participants were enrolled in cohorts of five, each receiving escalating dosages (0.5×10^7, 1.6×10^7, and 5.0×10^7 cells/kg, respectively) of MiSaver stem cells *via* intravenous infusion 2 days-5 days post-AMI onset. Prior to stem cell therapy, all participants received standard treatment for AMI, including medication, percutaneous coronary intervention (PCI), and stent implantation.

Control Group

A retrospective control group comprising 20 eligible participants meeting similar inclusion criteria for recent AMI and reduced LVEF<45% served as a comparison for analysis with the treatment groups.

Stem Cells

USC were obtained from a GMP standard stem cell pharmaceutical company in Taiwan (HONYA Medical PTY LTD), under the name of MiSaver, based on blood type and the following specifications: (a) 200 million Total Nucleated Cell count (TNC) in a 13 ml solution, packaged in single-use 20 ml clear vials with coated stopper seals and flip-off caps; (b) viability greater than 80%; (c) negative results for bacterial and fungal cultures; (d) negative nucleic acid testing (NAT) for infectious diseases including HIV, hepatitis C virus, hepatitis B virus (HBV), as well as negative antibody testing for syphilis; and (e) negative results for endotoxin testing.

Administrations

MiSaver was thawed using a thermostat-controlled mini bath, drawn into a 20 ml syringe, and diluted with normal saline and intravenous infused following standard operating procedures.

Patients were premedicated with intravenous antihistamines (such as diphenhydramine) and corticosteroids (such as hydrocortisone) 30 minutes-60 minutes before the stem cell infusion. Any unused solution was discarded, and the total volume of injected solution was adjusted to accommodate the total daily fluid volume administered.

Safety Evaluation and Parameters

Patient safety was closely monitored during and post-infusion. Physiological parameters were continuously monitored, and laboratory tests were conducted to evaluate myocardial response and reaction after stem cell therapy.

Statistical Analysis

Quantitative data were reported as median (25th percentile-75th percentile), while qualitative data were presented as absolute frequencies and/or percentages. Fisher's exact test was used for testing differences between therapy groups for qualitative variables due to the small sample size. The non-normal distribution of quantitative variables was identified, and the Wilcoxon signed-rank test and Wilcoxon rank-sum test were used for within-group and between-group comparisons, respectively. The stepdown Bonferroni corrected p-value was calculated for multiple comparisons. Statistical significance was defined as a two-sided $p\text{-value}<0.05$. SAS 9.4 software was used for the analysis.

Endpoints

The primary objective of this study was to assess the safety of the treatment, including the incidence of study-related adverse events (AEs) and Graft-versus-host Disease (GVHD). Secondary endpoints included evaluating the change in LVEF using echocardiography in comparison to the control group.

RESULTS

Participants were enrolled in cohorts of five, receiving escalating dosages of USC (0.5 × 10^7, 1.6 × 10^7, and 5.0 × 10^7 cells/kg), with infusions administered 2 days-5 days post-AMI onset. Due to recruitment challenges during the COVID-19 pandemic, there was a maximum time interval of over 30 weeks between participants (Table 1). To address this, a preliminary efficacy evaluation was conducted as the phase IIa study, utilizing the completed low and middle dosage groups alongside a retrospective control group comprising 20 eligible participants meeting similar inclusion criteria for a preliminary efficacy analysis.

Table 1: Baseline characteristics of participants age, weight and MiSaver infusion time and dosages

Participant	Age (range)	Infusion, days post MI	Body weight range (kg)	MiSaver cell dose x107/kg	Time interval between previous participants (Months)
1	66-70	4	66-70	0.5	0
2	41-45	2	76-80	0.5	4
3	56-60	3	61-65	0.5	0.1
4	51-55	3	56-60	0.5	2.9
5	61-65	2	76-80	0.5	2
6	66-70	4	56-60	1.6	4.3
7	41-45	2	96-100	1.6	11.9
8	66-70	5	66-70	1.6	2.7
9	41-45	3	71-75	1.6	2.6
10	41-45	3	96-100	1.6	30
Median (range)	56.5 (41~70)	3 (2-4)	72.5 (57.5-88.2)	1.05 (0.5~1.6)	2.8 (1.05-8.1)

Baseline Characteristics

10 male adult patients aged 56.5 (44-68.5) were enrolled in the MiSaver study between January 2021 and March 2022. Most participants had risk factors for MI, including hypertension, hyperlipidemia and a history of smoking (Figure 1).

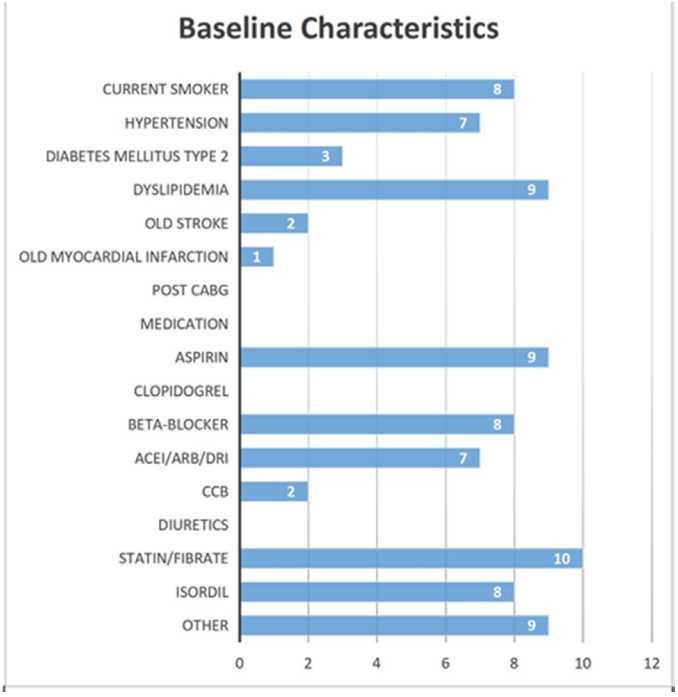

Figure 1: Baseline characteristics of participants

The control group consisted of participants meeting similar inclusion criteria, namely admission for AMI and LVEF<45%, who received standard intervention. Initially, 35 patients were identified based on the screening criteria. 10 were excluded due to a lack of follow-up echo LVEF results, and five were excluded because their follow-up echo occurred over 15 months or longer after the AMI. Thus, 20 patients were deemed eligible for retrospective inclusion in the control group from the trial hospital. Of the 20 patients in the control group, 17 were male and 3 were female, with a mean age of 57 (45.5-61). There were no significant differences in age between the two groups (P=0.116) (Figure 2).

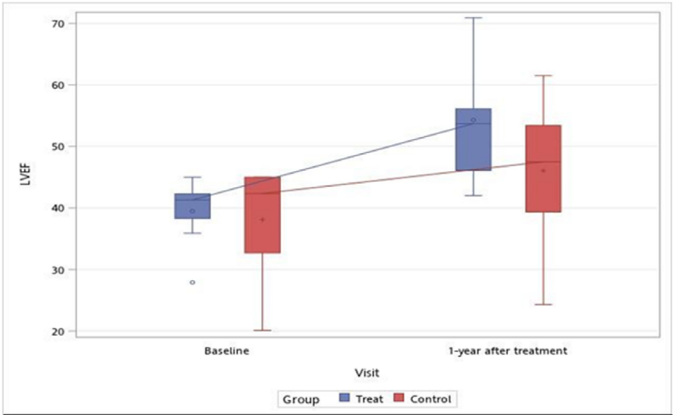

Figure 2: LVEF of Treatment group vs control, day 1 to 12 months

MiSaver Infusion

Baseline clinical laboratory tests, echocardiography, MRI, and 24-hour Holter EKG were obtained before the stem cell infusion. Participants received either a dose of 0.5 or 1.6 × 10^7/kg of ABO/Rh matched MiSaver stem cells intravenously within 2 days-5 days post-MI (Table 1).

Safety

Over the course of the 12-month follow-up period, no adverse events directly related to the study were observed. Furthermore, no signs or symptoms of Graft-versus-host Disease (GVHD) were reported. Participant 9 and 10 had COVID during the observation period and participant 10 reported

brief history of diarrhea which resolved spontaneously without medication just before the 12 months follow up. These events were considered unrelated to the investigational drug. Findings indicate that the treatment was well-tolerated and did not pose any significant safety concerns.

Recovery of LVEF on Echocardiogram

Due to the delayed enrolling of participant 10 caused by the COVID-19 pandemic, the initial analysis commenced upon completion of the 12-month observation period for the first 9 participants and was subsequently repeated upon completion of the observation period for the 10th participant.

The preliminary analysis compared all participants who received MiSaver treatment (low=5, middle=4; n=9) with the control group (C). There was no statistically significant difference in LVEF at admission between the treatment groups and the control group (Treat: 41.3 (38.3-42.3), C: 42.35 (32.7-45), p=0.6459); however, at the 12-month follow-up, LVEF of the treatment groups demonstrated a statistically significant improvement in LVEF compared to the control group, with measurements of 53.7% (46.1-56.1) versus 47.5% (39.35-53.4) respectively. (p=0.0455) (**Table 2**).

Upon completion of the follow-up for participant 10, both the low (L) and middle (M) dose treatment groups improved in LVEF compared to baseline (L: 42 [38.3-42.3], M: 40.65 [33.95-41.95]) at both 6 months (L: 49.6% [48.3-52.1], M: 53 [47.5-61.8]) and 12 months (L: 53% [46.1-68.6], M: 54.7 [48.15-55.9]); no statistically significant differences were noted between the two groups at baseline, 6 months, or 12 months (p=0.4567, 0.3886, or 0.5871, respectively) (**Figure 3**).

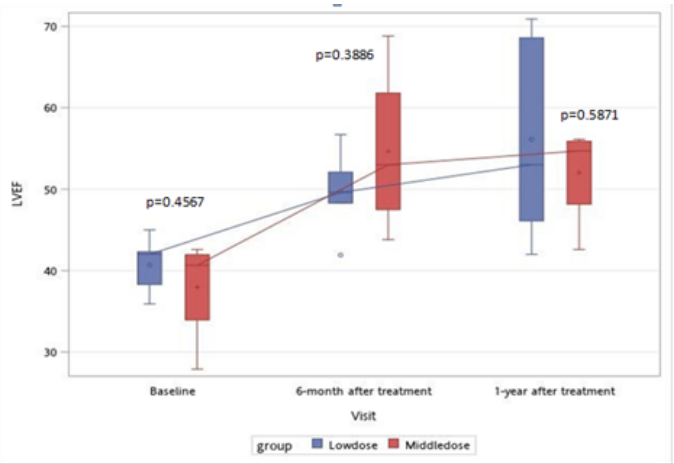

Figure 3, shows the mean LVEF values at baseline, 6 months, and 12 months for low (L) and middle (M) dosage groups. Both groups experienced an increase in LVEF from baseline (L: 42 (38.3-42.3), M: 40.65 (33.95-41.95)) to 6 months (L: 49.6% (48.3-52.1), M: 53 (47.5-61.8)) and to 12 months (L: 53% (46.1-68.6), M: 54.7 (48.15-55.9)). There was no statistical difference between the two groups at baseline, 6 months, or 12 months (p = 0.4567, 0.3886, or 0.5871, respectively).

Figure 3: LVEF of low vs middle dose group, day 1, month 6 and 12 months

The combined treatment groups (L and M dose groups) exhibited a statistically significant increase in LVEF from baseline 41.7 (38.3-42.6) to 6 months (50.4%) and a further improvement, although not statistically significant, to 53.4% (42.6-56.1) at 12 months. The combined treatment groups' improvement in LVEF from baseline to 12 months over the 12-month period; however, the statistical significance previously observed was lost, with updated p=0.1518 (**Table 2**).

Table 2: LVEF Control group vs participants 1-9 and Control group vs participants 1-10

	Control group	Treatment group (cases 1-9)	p value
Day-1	42.4 (32.7-45)	41.3 (38.3-42.3)	0.6459
12-month	47.5 (39.35-53.4)	53.7 (46.1-56.1)	0.0455
	Control group	Treatment group (cases 1-10)	p value
Day-1	42.4 (32.7-45.0)	41.7 (38.3-42.6)	0.8029
12-month	47.5 (39.4-53.4)	53.4 (44.8-56.1)	0.1518

DISCUSSION

Stem cell therapy has emerged as a promising avenue for cardiac regeneration and re-vascularization following AMI, however, numerous stem cell clinical trials, using autologous stem cells, have not found stem cell treatment beneficial [15,23]. Dr. Lee's team had found the quality of stem cells is an important correlation with the success of stem cell treatment. We theorize using stem cells of higher divisional and differentiation potential will make a positive impact on the treatment result.

UCB stem cells confer a number of advantages, particularly its low immunogenicity, which reflected by the high safety and no treatment related adverse events or signs or symptoms of GVHD were observed across all the participants in the 12 months observation period.

The treatment in the first 9 participants was found to have a statistical significance in the improvement on LVEF incidentally. However, upon completion of the 10th participant, this statistical significance was lost. This drew attention to the analysis of the particular participant. The particular participant showed no improvement in the recovery of the LVEF over the 12 months period. The participant was found to have the heaviest weight, highest BMI (36.7) and body surface area among all the participants. He was hypertensive, hyperlipidemic, a smoker and also the youngest amongst all the participants; these outstanding features drew attention due to unique characteristics.

At 6 months, low and middle dose groups LVEF have improved to 49.6% and 53% respectively, although not statistical significance, these difference is worth for further expanded study to study for whether different dosages have improved quicken onset of action potentials. The low dosage group improved further to 53% at 12 months, although not significant statistically, also deserves a focused study because most of LVEF improvement would have been completed within first 4 months and a further improvement of 3.4% if persistent may become significant when increased in number of treatment participants and warrants further placebo controlled researched and confirmation.

Based on the safety profile, preliminary efficacy, and ease of use of MiSaver stem cells, further larger-scale phase IIb/III clinical

trials are necessary to test their therapeutic effects in cardiomyopathic disorders. Establishing appropriate distribution facilities will ensure easy accessibility to MiSaver stem cells and facilitate testing of their efficacy.

CONCLUSION

The MiSaver Phase IIa study involved a relatively small number of participants and a retrospective control; however, it yielded valuable insights into both the safety and efficacy of MiSaver. Notably, the trial demonstrated statistically significant improvements in left ventricular ejection fraction (EF), indicating its potential as a therapeutic option. It is worth noting that the trial revealed challenges in treating morbidly obese participants, shedding light on patient demographics that may not be suitable candidates for this specific stem cell treatment. While the findings of this trial are promising, a larger clinical trial is warranted to further validate these results.

LIMITATIONS

This study has several limitations that may impact the interpretation of the results. Firstly, only male patients were enrolled in the study, despite both sexes being eligible to participate, potentially limiting the generalizability of the findings. Secondly, due to the COVID-19 pandemic during the trial period, only the low and middle dosages groups were statistically analysed with a retrospective control group. Thirdly, participants were subject to quarantine during the study period, which may have influenced the exact follow-up time or results. Future studies should aim to address these limitations to improve the generalizability and validity of the findings.

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CONFLICT OF INTEREST

J.L. is Director of HONYA Medical and sponsor of MiSaver. The remaining authors have no conflicts of interest to declare regarding the publication of the data and the manuscript.

CONTRIBUTORSHIP

K.U.: Conception and design, provision of study material or patients, data analysis and interpretation, manuscript writing, final approval of manuscript; C.T.,C.S. and Y.C.: Provision of study material or patients; J.L.: Conception and design, manuscript writing, collection and/or assembly of data, data analysis and interpretation.

ETHICAL APPROVAL

This clinical trial was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The dose escalating of MiSaver study received approval from the Institutional Review Board of Chung Shan Medical University Hospital, reference numbers CS19037. The additional efficacy analysis received approval from the Institutional Review Board of Chung Shan Medical University Hospital, reference numbers CS22019.

DATA SHARING STATEMENT

All data produced in the present study are available upon reasonable request to the authors.

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