REVIEW

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Umbilical cord-derived mesenchymal stem cell for reducing neointimal hyperplasia: a literature review – exploring possible therapeutic use on arteriovenous fistula patient

Yopie Afriandi Habibie[1,2], Dessy Rakhmawati Emril[3*], Azharuddin[4], Dedy Syahrizal[5]

ABSTRACT

Umbilical cord mesenchymal stem cells have been shown to reduce neointimal hyperplasia in animal models. However, current studies about therapeutic use to reduce neointimal hyperplasia mainly utilized bone-marrow and adipose tissue-derived mesenchymal stem cells and lack of in vivo testing from umbilical cord mesenchymal stem cells. Herein, we explore the potential of the therapeutic use of umbilical cord-derived mesenchymal stem cells to reduce neointimal hyperplasia in patients with arteriovenous fistula. Studies were identified from Scopus, Pubmed, and Google Scholar published between 2000 and 2022. The inclusion criteria for the articles were: (1) written in English, (2) focused on the use of mesenchymal stem cells (MSCs) for the treatment of neointimal hyperplasia, and (3) animal-controlled studies. Exosome-derived from mesenchymal stem cell studies were excluded. A total of 9 articles were included. Overall, the available evidence suggests that UC-MSCs may be a promising therapeutic option for reducing neointimal hyperplasia in arteriovenous fistula (AVF) patients. However, more research is needed to confirm these findings and to determine the optimal dosing and administration for their use in clinical practice. Additionally, further studies are required to fully understand the standardization in isolating and characterizing UC-MSCs and their effects on neointimal hyperplasia.

Keywords: mesenchymal stem cell, neointimal hyperplasia, arteriovenous fistula.
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[1]Doctoral Student, Doctoral Study Program Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia;
[2]Division of Thoracic Cardiac and Vascular Surgery, Department of Surgery, Faculty of Medicine, Universitas Syiah Kuala, The Zainoel Abidin General Hospital, Banda Aceh, Indonesia;
[3]Division of Pain and Headache, Department of Neurology, Faculty of Medicine, Universitas Syiah Kuala, The Zainoel Abidin General Hospital, Banda Aceh, Indonesia;
[4]Division of Orthopedic and Traumatology, Department of Surgery, Faculty of Medicine, Universitas Syiah Kuala, The Zainoel Abidin General Hospital, Banda Aceh, Indonesia;
[5]Department of Biochemistry, Faculty of Medicine, Universitas Syiah Kuala, Banda Aceh, Indonesia;

*Corresponding author:
Dessy Rakhmawati Emril;
Division of Pain and Headache, Department of Neurology, Faculty of Medicine Universitas Syiah Kuala, The Zainoel Abidin General Hospital, Banda Aceh, Indonesia;
dessyemril@usk.ac.id

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INTRODUCTION

Umbilical cord-derived mesenchymal stem cells (UC-MSCs) have gained increasing attention in recent years due to their potential therapeutic applications in various medical conditions.[1] One area of particular interest is using UC-MSCs to reduce neointimal hyperplasia in arteriovenous fistula (AVF) patients. Neointimal hyperplasia is a common complication following AVF surgery. It is characterized by the thickening of the inner lining of blood vessels due to an abnormal proliferation of smooth muscle cells,[2,3] which can lead to stenosis or narrowing of the vessel lumen.[4] This can compromise blood flow and lead to the failure of the AVF.[5] The exact cause of neointimal hyperplasia in AVF patients is not fully understood,[6] but it is thought to be a result of a combination of inflammation and smooth muscle cell proliferation in response to the surgical injury.[3,7]

AVFs are surgically created connections between an artery and a vein, typically in the arm, that provide access for dialysis in patients with kidney failure.[8] But besides AVF's advanced patency compared to other techniques, about 60% of AVFs fail to mature because neointimal hyperplasia of the outflow vein induces venous stenosis.[4,5,9] In addition to these traditional treatment options, there has been increasing interest in the use of stem cells as a potential treatment for neointimal hyperplasia in AVF patients.[10–16] Mesenchymal stem cells (MSCs) have been shown to have potent anti-inflammatory and immunomodulatory properties,[17,18] and several studies have demonstrated their potential to reduce neointimal hyperplasia in animal models.[13,15,16]

Extracting stem cell populations from embryonic, fetal, and adult tissues is possible.[1] Because of their high self-renewal potential and pluripotency (ability to express into all germ layers), UC-MSCs stem cells are a leading candidate for tissue engineering both in vitro and in vivo.[1,18] Currently, multiple diseases are treated

with UC-MSCs. It possesses a variety of unique qualities that are essential for therapeutic applications.[1] Compared to bone marrow mesenchymal stem cells, UC-MSCs have a more similar gene expression profile to embryonic stem cells.[19,20] In addition, it is easier to collect a significant number of UC-MSCs after passages and extensive ex vivo expansion, which way more non-invasive and ethically acceptable.[1,21]

UC-MSCs have been shown to reduce neointimal hyperplasia in animal models of AVF. [22] However, current studies about therapeutic use to reduce neointimal hyperplasia mainly utilized bone-marrow and adipose tissue-derived mesenchymal stem cells and lack in vivo testing about umbilical cord-derived mesenchymal stem cells. Herein, we explore the potential of the therapeutic use of umbilical cord-derived mesenchymal stem cells to reduce neointimal hyperplasia in patients with arteriovenous fistula.

METHOD

Studies of mesenchymal stem cells for reducing neointimal hyperplasia in animal models were identified from Scopus, Pubmed, and Google Scholar published between 2000 and 2022. The search terms used were [<mesenchymal stem cell>] AND [<neointimal hyperplasia> OR <intimal hyperplasia>]. The inclusion criteria for the articles were: (1) written in English, (2) focused on the use of MSCs for the treatment of neointimal hyperplasia, and (3) animal-controlled studies. Exosome-derived from mesenchymal stem cell studies were excluded. We extracted data for characteristics, treatment, and outcomes to compare individual studies, as shown in the table below (Table 1). Electronic searching identified 115 publications, of which 9 articles were included in the review as they answered research questions related to the effect of MSCs in reducing neointimal hyperplasia using animal models.

RESULT

Bone-marrow derived mesenchymal stem cells (BM-MSCs)

Several studies have investigated the potential use of BM-MSCs in reducing neointimal hyperplasia. A total of $1x10^7$ BM-MSCs were injected into carotid-jugular vein ligation in a mice model. The results showed that infiltrating BM-MSCs could promote neointimal hyperplasia's vascular repair by effectively inhibiting tissue factors' thrombin. [23]

BM-MSCs have also been shown to have anti-inflammatory properties, which may contribute to their effectiveness in reducing neointimal hyperplasia. The exact amount of BM-MSCs ($1x10^7$ cells) also injected showed that Interleukin-1 receptor antagonist (IL-1Ra) originating from BM-derived cells helps to suppress arterial inflammation, resulting in decreased neointimal formation after injury.[24] In another study, BM-MSCs with $1x10^6$ cells injected has also shown that 28 days after administration, there was a significant reduction in neointimal hyperplasia – intima/media ratio was measured. This was attributed to the ability of BM-MSCs to reduce neointimal hyperplasia through decreased MCP-1 in mouse serum and inflammation of carotid arteries.[25] Other studies found that injecting $0.8x10^6$ BM-MSCs into the adventitial layer significantly reduced the intima/media ratio in the anastomosis site and the percentage of Ki67 + proliferating cells in arterial walls 14 days after treatment.[26]

Despite all successful results from other studies, research done by Feng et al. in a rat model found a counter effect where $1x10^4$ BM-MSCs were infused via percussion catheter into the carotid artery in percutaneous coronary intervention cases showed no significant difference between the treated and untreated group.[27]

Adipose-tissue derived mesenchymal stem cells (AT-MSCs)

In addition to AT-MSCs' potential to reduce neointimal hyperplasia, a study by Yang et al. in a rat model resulted in decreases in Mcp-1 gene expression, accompanied by a reduction in venous neointimal hyperplasia.[28] With the same technique, research done by Ni et al. was. Injected $1mm^3$ and found a significantly reduced neointimal hyperplasia in consequences of Matrix Gla Protein (MGP) promoted the differentiation of AT-MSCs toward smooth muscle cells through BMP2/SMAD-mediated signaling pathway.[29]

Umbilical-cord derived mesenchymal stem cells (UC-MSCs)

UC-MSCs have shown promise in treating neointimal hyperplasia in several preclinical studies. A study by Zhu et al. demonstrated that UC-MSCs were injected into a vein grafted in a rat model and showed endothelial regeneration was significantly enhanced, likely due to both direct engraftment and paracrine actions of UC-MSCs. The inflammatory response was inhibited, intimal cell proliferation was reduced, and neointimal hyperplasia was diminished in vein grafts.[22] In another study, a mixture of 7×10^6 human UC-MSCs and fibrin matrix was injected into the adventitia layer into a rabbit model, resulting in a significantly reduced intima/media ratio in the group treated with UC-MSCs compared with the non-treated group. UC-MSCs reduce the formation of intimal hyperplasia through rapid re-endothelialization.[30]

DISCUSSION

Mesenchymal stem cells (MSCs) are a potential candidate for novel therapeutic concepts promoting cell therapy.[31,32] The first source of MSCs to be reported was BM-MSCs. However, due to the highly invasive donation process, BM-MSCs may be counterproductive for therapeutic use. [31] In addition, the number and differentiation potential of MSCs decreases with age.[32] MSCs have shown remarkable tissue repair and regeneration capacity through transdifferentiation into tissue-specific cell types and paracrine secretion of key wound healing cytokines.[33–35] Therefore, the use of MSCs is being considered as a potential therapeutic option to repair injured arteries.[36]

UC-MSC can be obtained from the amniotic membrane, umbilical cord lining, Wharton's jelly, and intervascular and perivascular areas.[37,38] The majority of the studies employ UC MSCs from Wharton's Jelly,[38] a gelatinous tissue surrounding the umbilical vessels.[39] UC-MSCs directly from uncontaminated Wharton's jelly offer the best clinical utility due to their unique beneficial properties.[40] In contrast to bone marrow stem cells, UC-MSCs have a painless collection procedure, a low risk of infection, non-tumorigenicity, multipotency, low immunogenicity,

Table 1. **In vivo studies evaluating mesenchymal stem cells to reduce neointimal hyperplasia based on published articles.**

Author, Year	Type of MSCs	Study design	Intervention		Outcome (intima/media ratio)			Ref
			Administration	Dose	Experiment	Control	p-value	
Chen, et al (2006)	Bone-marrow	Animal model: mice Control: yes Blinded: yes	Local injection to tail vein, carotid artery	$1x10^7$ cells	CD34+ cells from α-TFPI-Tg: 0.18 ± 1.6 CD34+ cells from α-Hir-Tg: 0.3 ± 0.03 (after 28 days)	2.68 ± 0/17 (after 28 days)	p<0.0001	[23]
Shoji, et al (2011)	Bone-marrow	Animal model: mice Control: yes Blinded: N/A	Injection into cardiac left ventricle	$1x10^6$ cells	0.149 ± 0.006 (after 28 days)	0.423 ± 0.48 (after 28 days)	p<0.05	[25]
Feng, et al (2014)	Bone-marrow	Animal model: rat Control: yes Blinded: N/A	Infused via percusion catheter into carotid artery	$1x10^4$ cells	no significant differences	no significant differences	p>0.05	[27]
Isoda, et al (2014)	Bone-marrow	Animal model: mice Control: yes Blinded: N/A	IV injection	$1x10^7$ cells	1.9 ± 0.1 (after 14 days)	3.5 ± 0.5 (after 14 days)	p<0.01	[24]
Iso, et al (2018)	Bone-marrow	Animal model: rat Control: yes Blinded: N/A	Local injection to adventitial layer	0.8×10^6 cells (control) $3x10^6$ cells (experiment)	0.5 ± 0.1 (after 14 days)	0.9 ± 0.1 (after 14 days)	p<0.05	[26]
Yang, et al (2016)	Adipose-tissue	Animal model: mice Control: yes Blinded: N/A	Local injection to adventitial layer	2.5×10^5 cells	3.06 (After day 21)	4.25 (After day 21)	p<0.0001	[28]
Ni, et al (2022)	Adipose-tissue	Animal model: mice Control: yes Blinded: N/A	Local injection to adventitial layer	1 mm^3	1.0 ± 0.1 (After 28 days)	2.1 ± 0.1 (After 28 days)	p<0.0001	[29]
Kim, et al (2014)	Umbilical-cord	Animal model: rabbit Control: yes Blinded: N/A	Local injection to adventitia layer	7×10^6 cells (Mixture of umbilical cord mesenchymal stem cells and fibrin matrix).	0.44 ± 0.002 (after 28 days)	0.98 ± 0.21 (after 28 days)	p<0.05	[30]
Zhu, et al (2010)	Umbilical-cord	Animal model: mice Control: yes Blinded: N/A	Local injection into vein-grafted injury	N/A	0.2 (after 14 days)	0.8 (after 14 days)	p<0.01	[22]

and faster self-renewal properties.[38,41] In addition to its outstanding advantages, UC-MSCs have shown the potency to differentiate into a variety of cells of three germ layers, synthesize and secrete a series of trophic factors and cytokines, support the expansion and function of other cells, migrate to pathological areas, and be efficiently transfected with conventional methods.[41]

Most of the studies we found conditioned the animal model using a conjugate carotid/jugular vein, which is quite similar to arteriovenous fistula surgery. In addition, our results showed that MSCs are a potential cell-based therapy for reducing neointimal hyperplasia in arteriovenous fistula patients. Even though MSCs from different tissues have similar levels of surface antigen expression, immunosuppressive activity, and differentiation ability,[32] currently, there is a lack of in vivo studies demonstrating the reduction of neointimal hyperplasia with UC-MCSs, and further investigation is needed.

Although the current studies of UC-MSCs showed different mechanisms of reducing neointimal hyperplasia, they have shown promise in the treatment of neointimal hyperplasia through enhanced endothelial regeneration, probably due to both direct engraftment and paracrine actions of UC-MSCs, inhibiting inflammatory response, decreasing intimal cell proliferation, and reducing neointimal hyperplasia in vein grafts.[22] In another study, UC-MSCs reduced the formation of intimal hyperplasia through a rapid re-endothelialization process.[30]

From our results, it is shown that local injection into the injured vessel produces the desired effect.[22,23,26,28–30] The potential benefit of local injection of MSCs at the site of injury might not necessarily imply differentiation into regenerative tissue type but rather the local production of growth factors or other factors or physical properties.[42] Moreover, intravenous (IV) and systemic delivery of MSCs to animal models from studies that we found showed that it was cultivated to the desired effect to reduce the intima/media ratio.[14,24] Evidence is accumulating to show that MSCs are capable of homing to injured tissues following intravenous administration and systemic administration in adults.[42] However, studies by Feng et al. showed no significant difference in intima/media ratio when MSCs were infused into the carotid artery.[27] It requires further investigation of the protocol they were using.

Despite the promising results of these studies, several limitations still need to be addressed to fully understand the potential of UC-MSCs as a therapeutic option for reducing neointimal hyperplasia in AVF patients. One limitation is the lack of large, randomized, controlled trials investigating the use of UC-MSCs in this setting. Most of the studies were conducted in animal models using BM-MSCs and AT-MSCs.[22,30]

Another limitation is the need for more standardization in isolating and characterizing UC-MSCs. The process of isolating UC-MSCs from umbilical cord tissue can vary among different laboratories, leading to differences in the purity and potency of the cells.[22–30,43,44] Based on the literature reviewed above, there is no consensus on the optimal method for characterizing UC-MSCs, making it difficult to compare the results of different studies. Most protocols for primary cell culture isolation from Wharton's jelly include three steps: 1) Extraction of epithelial, vascular, and perivascular tissues; 2) Enzymatic digestion with trypsin, collagenases I, II, or IV, dispase, protease, and hyaluronidase. 3) Transfer into the culture medium.[37]

It is worth noting that inconsistent findings have been observed in MSCs.[27] For instance, according to one study, MSCs may increase neointimal hyperplasia by over-repairing the vessel in vivo.[45-47] Other studies reported the unexpected observation that MSCs aggravated the vascular postangioplasty vascular remolding and restenosis in a hyperlipidemia rat model,[48] it differentiates not into an endothelial progenitor cell, which increased intima-media ratio. All this failure might be due to animal models and protocols for preparing and expanding the MSCs in culture.[25]

CONCLUSION

The evidence suggests that UC-MSCs may be a promising therapeutic option for reducing neointimal hyperplasia in AVF patients. However, more research is needed to confirm these findings and to determine the optimal dosing and administration for their use in clinical practice. Additionally, further studies are required to fully understand the standardization in isolating and characterizing UC-MSCs and their effects on neointimal hyperplasia.

AUTHOR CONTRIBUTION

All authors have contributed to this research process, including conception, design, collection and assembly of data, analysis and interpretation of the data, drafting of the article, and critical revision of this manuscript.

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CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

Not applicable.

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