REVIEW ARTICLE

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Safety and Efficacy of Mesenchymal Stem Cells in Burn Therapy: Systematic Review

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The experimental research on the use of mesenchymal stem cells (MSCs) for burn therapy has been published several times. However, current clinical procedure remains a challenging discussion. This systematic review assesses the safety and efficacy of administering mesenchymal stem cells (MSCs) to burns and determines the most effective source of MSCs for burn therapy. We reviewed several studies through PubMed, Google Scholar, Science Direct, and DOAJ online databases. PRISMA-P 2020 method was used based on inclusion and exclusion criteria that were re-selected through Joanna Briggs Institute (JBI) Critical Appraisal Tools. Results from 13 articles showed that MSCs are safe for burn therapy with minimal side effects/complications and have the potential to repair tissue and accelerate burn healing through several mechanisms. The treatment of MSCs in burns is influenced by donor characteristics and related to the severity and area of the burn. It can be concluded that the administration of MSCs is safe and effective in burn therapy.

Keywords*: burns, mesenchymal stem cells, therapeutic safety, therapeutic efficacy, wound healing*

Introduction

More than 30,000 new cases of burns are recorded worldwide, equivalent to about 11 million new burn cases annually and mostly occur in low- and middle-income countries, especially in Africa and Southeast Asia.[1] According to the World Health Organization (WHO) in 2019, the mortality rate of burn injury in Southeast Asia is 27% and almost 70% of them are women.[2] The 2018 National Basic Health Research Report notes that burns are one of the injury types in Indonesia, which mostly occur at the age of 25-34 years old. Burn cases mostly occur in women, with prevalence around 1.4%. Papua has the highest prevalence of burn injury (2.1%).[3] Burns are serious problems that require immediate medical attention.[4] There are several treatments that can be applied to repair burns, including natural remedies and commonly used therapeutic methods, such as skin grafting. However, these treatments do not provide significant results with long recovery time and have limitations in terms of donors and complications.[5,6] Therefore, stem cell therapy is considered as another alternative for healing burns.[7]

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Stem cell therapy has been widely used in basic research or for the development of new therapeutic strategies in clinical practice and can be considered as an alternative therapy for burn healing.[7,8] One of the most commonly used types of stem cells is mesenchymal stem cells (MSCs). MSCs are adult stem cells that can be isolated from various sources, such as adipose tissue, bone marrow, peripheral blood, and neonatal tissue.[9-11] MSCs are ideal for tissue regeneration because of their immunological properties, such as anti-inflammatory, immunoregulatory, and immunosuppressive abilities, which act as immunotolerant agents.[12] The expected outcomes of stem cell therapy in burn cases are skin regeneration, damaged tissue repair, and reduction of scar tissue formation.[13]

Various studies are still being developed to determine the role of stem cells in burn therapy. However, a comprehensive discussion of MSCs potency in burn therapy has not been widely discussed. Here we discussed comprehensively the potential of MSCs in burn therapy using systematic review. This research shows in detail about safety and efficacy of administering MSCs in burns and determines the most effective source of MSCs for burn therapy. This literature study is expected to be useful in providing information for better stem cell therapy in burn patients.

Methods

Eligibility Criteria and Search Strategy

This research was conducted by systematically reviewing some literatures through the online databases, *i.e.* PubMed, Google Scholar, Science Direct, and DOAJ using related keywords (Table 1). Literatures that discussed or related to the safety and efficacy of MSCs administration in burn therapy and published in the last 10 years were included. The research model or subject was not limited to human and animals, and the research subjects were not limited by age and sex. Meanwhile, literatures that were not published in English, review articles, and incomplete literatures (only showing abstract) were excluded.

Analysis and Study Selection

Literatures used for this research have gone through the study selection process based on the PRISMA 2020 flowchart (Figure 1) and re-selected through the Joanna Briggs Institute (JBI) Critical Appraisal Tools to assess the quality of literatures and obtain 13 literatures to be studied.[14] Six[15-20] and 7[21-27] literatures were considered to have medium (50-80% of the JBI criteria) and good quality (>80% of the JBI criteria), respectively.

Results and Discussion

Characteristics of Animal Models and Human Subjects

Based on the review results, most of the studies are conducted in animals[15-24], while only 3 studies are conducted in humans[25-27] (Table 2). In other words, studies to determine the role of MSCs in burn therapy are still being tested in animals rather than humans.[28] Animal models are cheaper and relatively easy to obtain. The use of animal models helps researchers to avoid research failures that may lead to complications, damage and other serious disturbances. Animal models have been known to have similar physiological processes compared to humans.[29]

Adult animal models are used in all animal research.[15-18,20-22,24] Meanwhile, in human research, the youngest age is 2 years old and the oldest is 58 years old.[25-27] According to the WHO, the majority of burn cases are found in children and working age.[30] The sex of the animal models and human subjects are dominated by male (Table 2).[15-21,24-27] Most animal studies use male animals to avoid variability as a result of periodic physiological changes due to the presence of reproductive hormones in female animals.[21] Recent data shows that women have a higher risk of burns than men. However, burns may also occur in men related to the risk of their work.[30]

The majority of burn cases are thermal injury caused by boiling water.[16-18,20,21,26] The minimum and maximum burn area in the studies are 0.5 cm^2 [24] and 9 cm^2 [18], respectively. The smallest total body surface area (TBSA) in these studies ranges from 3-5% TBSA[21] and the most extensive is ≥70% TBSA.[27] The burn degree is dominated by third-degree burns (full-thickness).[19-20,22,24-27] Thus, extensive and severe burns dominate in both animal studies and human research. Extensive and severe burns in mice models are comparable to third-degree burns in humans.[31]

Therapeutic Procedures

There are several factors that affect MSCs therapy. Researchers must pay attention to several important factors, such as stem cell source, therapeutic dose, route of administration, additional regimens, and administration time to obtain optimum results and evidences on stem cell therapy.[32]

Table 1. Literature search keywords.

Online Database	Keywords
PubMed and DOAJ	(burns OR burn injury OR burns trauma OR major burns) AND (mesenchymal stem cells OR mesenchymal stromal cells)
Google Scholar	allintitle: "burn" OR "burns" OR "burn injury" OR "burns trauma" OR "major burns" AND "stem cells" OR "stem cell" OR "stromal cells" OR "stromal cell"
Science Direct	Title, abstract or author: (burns OR burn injury OR burns trauma OR major burns) AND (mesenchymal stem cells OR mesenchymal stromal cells)

MSCs can be isolated from various sources, such as bone marrow[15-18,21,25-26], adipose tissue[17,22-24], umbilical cord[19,20,25], dental pulp[17], and umbilical cord lining membrane.[27] Each source of MSCs has its own advantages and disadvantages (Table 3). Bone marrow (BM)-MSCs are still used as the gold standard in several clinical trials and the main source of multipotent stem cells. The safety and effectiveness of BM-MSCs have been confirmed. However, invasive and painful procedure with a higher risk of infection is required to obtain BM-MSCs. Adipose-derived stem cells (ASCs) are often used as an alternative to BM-MSCs due to their convenience. The procedure to obtain ASCs is less invasive compared to BM-MSCs. ASCs can be used as a source of more practical autologous MSCs for tissue engineering compared to BM-MSCs.[33,34]

Umbilical cord (UC)-MSCs is a promising type of MSCs. Unlike BM-MSCs, procurement of UC-MSCs requires a non-invasive procedure, hence minimizes the risk of infection. In addition, UC-MSCs regeneration is faster with almost the same doubling time as BM-MSCs. Cord lining (CL)-MSCs is one of the UC-MSCs derivatives.[35,36] UC-MSCs do not cause an immune rejection response when administered allogeneically.[37] UC-MSCs are used more often than dental pulp stem cells (DPSCs), though dental pulp has been considered as an attractive source of MSCs due to its high cell content and relatively low invasive cell isolation procedure.[17,33,38-40] DPSCs are similar to ASCs in their immunomodulatory properties.[33]

There are 3 types of stem cell transplantation, *i.e.* allogeneic, autologous, and xenogeneic. Stem cells for

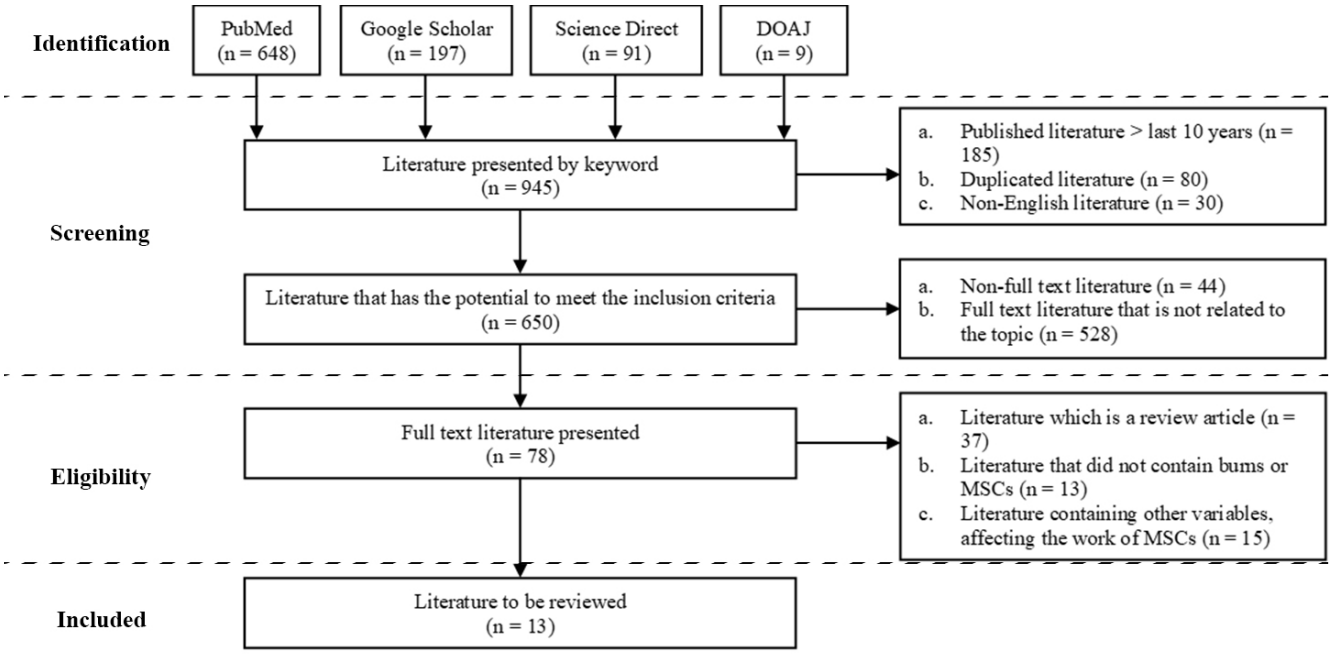

Figure 1. Study selection with PRISMA 2020 flowchart. Several studies were reviewed through PubMed, Google Scholar, Science Direct, and DOAJ online databases using the PRISMA-P 2020 method based on inclusion and exclusion criteria.

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Table 2. Characteristics of the selected literatures.

Subject or Animal Model (n)	Age	Sex	Burn Area, Mean (Range)	Burn Degree	Type of MSCs	Transplant Type	Dose (Cells)	Route of Administration	Administration Time	Outcome Index		Ref. No.
										Safety	Efficacy	
Sprague-Dawley rats (26)	Adult	M	1 cm^2	U	BM-MSCs	Allogeneic	1×10^6	Subcutaneous injection	30 minutes after burn	Mortality	Inflammatory response, repair area, apoptotic activity, angiogenesis activity.	15
Wistar rats (50)	Adult	M	U	U	BM-MSCs	Allogeneic	1×10^6	Subcutaneous injection	30 minutes after burn	Mortality, side effects.	Inflammatory response, repair area, apoptotic activity, necrosis activity, oxidative stress, angiogenesis activity, collagen and muscle activity.	16
Wistar rats (40)	Adult	M	U	U	BM-MSCs, ASCs, DPSCs	Allogeneic	1×10^6	Subcutaneous injection	30 minutes after burn	Mortality, side effects.	Inflammatory response, repair area, apoptotic activity, necrosis activity, oxidative stress, angiogenesis activity, collagen and muscle activity.	17
Wistar rats (32)	Adult	M	9 cm^2	IIB	BM-MSCs	Xenogeneic	U	Intraperitoneal injection	Every day for 14 days after burn	Mortality	Inflammatory response, repair area, angiogenesis activity, collagen and muscle activity, wound closure area, healing rate, healing time.	18
Sprague-Dawley rats (84)	U	M	1.77 cm^2	III	UC-MSCs	Xenogeneic	2×10^6	Intraperitoneal injection	24 hours after burn	Mortality	Inflammatory response, repair area, angiogenesis activity, wound closure area, healing rate, healing time.	19
Wistar rats (126)	6 weeks (adult)	M	30% TBSA	III	UC-MSCs	Xenogeneic	5×10^6	Intravenous injection	3 days after burn	Mortality, side effects.	Inflammatory response, angiogenesis activity, collagen and muscle activity, wound closure area, healing rate, healing time.	20
Mice (U)	8-10 weeks	M	3-5% TBSA	U	BM-MSCs	Xenogeneic	1×10^6	Subcutaneous injection	U	Mortality, side effects.	Angiogenesis activity, wound closure area, healing rate, healing time.	21
Athymic nude mice (24)	7-9 weeks	F	0.79% TBSA	III	ASCs	Xenogeneic	6.8×10^6	Subcutaneous injection	24 hours after burn	Mortality, side effects.	Repair area, angiogenesis activity, collagen and muscle activity, wound closure area, healing rate, healing time.	22
Sprague-Dawley rats (12)	U	U	1 cm^2	IIB	ASCs	Allogeneic	5×10^5	Intradermal injection	30 minutes after burn	Mortality, side effects.	Repair area, angiogenesis activity, wound closure area, healing rate, healing time.	23

Table 2. Characteristics of the selected literatures (cont.).

Subject or Animal Model (n)	Age	Sex	Burn Area, Mean (Range)	Burn Degree	Type of MSCs	Transplant Type	Dose (Cells)	Route of Administration	Administration Time	Outcome Index		Ref. No.
										Safety	Efficacy	
Wistar rats (20)	6-7 weeks	M	0.5 cm^2	III	ASCs	Autologous and Allogeneic	5×10^6	Subcutaneous injection	24 hours after burn	Mortality	Wound closure area, healing rate, healing time.	24
Patients (60)	20-27 years old	M and F	17% TBSA (12-22)	III	BM-MSCs	Autologous	1×10^5	Subcutaneous injection	2 days after surgical excision, repeated after 10 days	Mortality, side effects.	Wound closure area, healing rate.	25
	18-29 years old	M and F	15.95% TBSA (10-20)	III	UC-MSCs	Allogeneic		Topical and subcutaneous injection	Immediately given topically, followed by injection in 2 days after surgical excision			
Patients (5)	2 years old	M	55% TBSA	II and III	BM-MSCs	Allogeneic	$30/20/10/5\times10^6$	Injection	53 days after burn; repeated 2, 4, and 5 months later	Mortality, side effects.	Wound closure area, healing rate, healing time.	26
	4 years old	M	30% TBSA	II and III			$25/15\times10^6$		46 days after burn, repeated 10 weeks later			
	7 years old	M	15% TBSA	II			20×10^6		92 days after burn			
	10 years old	M	12% TBSA	III			10×10^6		42 days after burn			
	58 years old	M	45% TBSA	II and III			$30/30\times10^6$		19 days after burn, repeated 4 weeks later			
Patient (1)	20 years old	M	>70% TBSA	III	CL-MSCs	Allogeneic	3×10^6	Topical and subcutaneous injection	18 months after burn 1st: topical 2nd: subcutaneous injection	Mortality, side effects.	Wound closure area, healing rate, healing time.	27

U: Unclear, M: Male, F: Female, TBSA: Total body surface area, BM-MSCs: Bone marrow mesenchymal stem cells, ASCs: Adipose-derived stem cells, DPSCs: Dental pulp-derived mesenchymal stem cells, UC-MSCs: Umbilical cord mesenchymal stem cells, CL-MSCs: Cord lining mesenchymal stem cells.

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Table 3. Characteristics of MSCs from different sources in human body.[33,35]

Source	Advantages	Disadvantages
BM-MSCs	Relatively short culture time.	Invasive and painful procedure, higher risk of infection, influenced by donor characteristics (*e.g.* age), have a longer duplication period, higher risk of aging, limited number of cells.
ASCs	Less invasive than BM-MSCs, higher number of cells compared to BM-MSCs, expand effectively *in vitro* , higher differentiation potential, proliferate faster than BM-MSCs.	Influenced by donor characteristics (*e.g.* age), have a longer duplication period.
UC-MSCs and CL-MSCs	Non-invasive procedure, faster regeneration, lower risk of infection, donor abundance and availability, ease and reliability of sample collection, does not cause an immune rejection response when administered allogeneically since it has the low maturity level compared to other sources.	Similar duplication time as BM-MSCs.
DPSCs	High cell content, relatively low invasive cell isolation procedure, higher frequency of colony- forming cells compared to BM-MSCs.	The procurement can be difficult, influenced by ectomesenchymal and periodontal tissues.

allogeneic transplantation are obtained from other individuals within the same species.[37] Allogeneic MSCs are commonly used for MSCs therapy, although recent studies explain that there is a rejection from the recipient's immune response to allogeneic MSCs. This phenomenon may affect the efficacy of MSCs therapy.[41] Autologous transplantation uses the patient's own stem cells[42], while xenogeneic transplantation uses stem cells derived from non-human species.[43] Although research on the role of MSCs in burns commonly use animal models, this does not rule out the possibility that human MSCs can be studied in animal models. ASCs derived from humans may work effectively in animals. The regulation of human peroxisome proliferator activated receptor gamma (PPARγ) gene expression in animals indicates that human ASCs may survive in animals. Furthermore, an increase in fatty acid binding protein 4 (FABP4) indicates that human ASCs have a potential to initiate adipogenesis.[22] Autologous stem cells significantly accelerate wound healing compared to allogeneic stem cells.[24]

Question that often arises in stem cell research is how many doses are needed to achieve a good therapeutic response in degenerative diseases, such as burns, which are often associated with stem cell dosage to accelerate wound healing. The therapeutic dose obtained from 13 literatures varies from 1×10^5 [25] to 30×10^6 cells.[26] The dosage of MSCs transplanted in each patient varies depending on the area and degree of burn. Patients with larger burn areas need to apply repeatable injection with MSCs to the wound area at intervals of at least 1 month.[26]

Stem cells can be administered locally or systemically, either topically or by injection. In some cases, stem cell transplantation not only uses one method, but also can use 2 methods at once, such as the topical method followed by local injection in the burn area.[25,27] Most studies use local methods because of their convenience.[32]

Local injection method, dominated by subcutaneous injection, is used in 11 out of 13 selected studies.[15-17,19,21-27] Most studies use the intradermal injection method both in and around the wound area.[23,44] This method has been shown to improve wound healing, but its main therapeutic potential is still limited due to poor engraftment efficiency and cell retention at the wound site.[44]

Another method for systemically transplanting MSCs is intravenous injection. Transplantation of human UC-MSCs by intravenous injection effectively improves healing of severe burns in rats model.[20] However, MSCs transplantation by intravenous injection has a weakness. It has been reported that MSCs transplanted by intravenous injection do not go directly to the target tissue but migrate first to the lungs, so that MSCs are not detected in the wound area. In contrast, MSCs transplanted by local method go directly to the target tissue and are detected in the wound area. Local and systemic methods may improve wound healing at different times.[45] A study using severe burn rat model shows that the wound treated with intravenously injected MSCs requires a healing time of 74±4 days.[20] Meanwhile, wounds treated with MSCs using local injection methods (subcutaneous or intradermal) have a faster

healing time (15-25 days).[18,19,21,22,24] Topical transplantation method improves wound healing by reducing open wound area to half of the one third of initial wounds, whereas administration of MSCs using injection method followed by platelet-rich plasma (PRP) injection and autograft skin transplantation improves wound healing by 100%.[27]

Several additional regimens are used in the studies of MSCs. Most animal research (6 out of 13 literatures) use phosphate-buffered saline (PBS). PBS containing MSCs shows promising results in burn healing.[15-17,21-23] PBS is the most frequently used in research. PBS is the buffer solution that helps to maintain the pH and osmolarity. The ion concentration possessed by PBS corresponds to the human body (isotonic).[46] PRP can also be considered as another option to assist wound healing. PRP is a treatment modality that continues to develop and show promising results, especially in the field of dermatology.[47] PRP is an autologous serum containing high concentrations of platelets, leukocytes, and growth factors.[48] PRP helps the burn healing process in research subjects. Up to 100% wound area is healed in PRP treatment compared to non-PRP treatment.[26,27] Human MSCs and PRP may improve vascularization and cell differentiation, but do not accelerate the duration of epithelialization in burns. In addition, MSCs are better than PRP in increasing cell differentiation.[49]

The timing of MSCs transplantation is also an important factor that may determine the survival of stem cells in the wound bed. Inflammatory response activated in a burn wound might worse the damage cells and tissues.[32] The stasis zone is a vital area which has tissue hypoperfusion in the last 12-24 hours after injury. Without intervention, a coagulation zone will develop, and results in tissue necrosis. In other words, with intervention, the damaged zone will recover and form a hyperemia zone and even heal spontaneously.[6] Therefore, MSCs can be used for the restoration of the stasis zone by local (subcutaneous) injection right after burn (30 minutes after burn induction), which is beneficial for the survival of the stasis zone in acute burns and may reduce the progression of further burns.[15-17]

Safety of MSCs in Burn Therapy

Safety is an important factor that must be considered in providing MSCs therapy to burn patients. Complications that arise after treatment and mortality rate of patients are indicators to evaluate the safety of MSCs therapy. In all literatures, no mortality events occur in both animal models and human subjects when MSCs are transplanted in the burn area.

Side effects of MSCs for burn therapy in 13 selected literatures are shown in Figure 2. Histopathological side effects, such as epidermal injury, loose collagen matrix, severe edema, and extensive damage to the skin appendages, are lower in burn therapy using MSCs. Burn wounds treated with BM-MSCs, ASCs, and DPSCs show no notable differences.[17] In addition, there is an increase in epithelialization and desquamation of the eschar without severe infection.[20] MSCs applications for wound healing in burn patients are not commonly used. However, several case reports and clinical trials have demonstrated that MSCs are safe for burn therapy.[50] Major burn requires frequent operations, prolonged hospitalization, and intense rehabilitation. A decrease in the hospitalization time after treatment with BM-MSCs and UC-MSCs is reported in burn patients. The hospitalization time of patients treated with BM-MSCs (14.5±3.5 days) and UC-MSCs (15.6±3.86 days) is not significantly different. Early complications, such as infection, are more common in UC-MSCs therapy (70%), followed by late complications, such as hypopigmentation in BM-MSCs therapy (20%), and hyperpigmentation in UC-MSCs therapy (30%). Contracture scars occur in 2 patients treated with BM-MSCs (10%) and 2 patients treated with UC-MSCs (10%). Hypertrophic scars are more common in patients treated with UC-MSCs therapy (20%).[25] This suggests that most complications occur in UC-MSCs therapy.

A study which includes five human subjects (2, 4, 7, 10, and 58 years old) reports that there is a minimal skin discoloration in 4, 10, and 58-year-old patients. Hypertrophic scars or contractures are also not observed in these patients. Seven-year-old patient has good pigmentation and 58-years-old patient does not experience difficulty in movement in both upper limbs. Keloids are formed in 2-year-old patient.[26] This suggests that BM-MSCs and UC-MSCs effectively increase burn healing with minimal complications, which can reduce the formation of hypertrophic scar tissue with minimal discoloration.[25,26] No infection is observed in a third-degree burn patient 6 years with allogeneic CL-MSCs treatment. Six years after treatment, in follow-up, the patient's condition is greatly improved without hypertrophic scarring, keloids, and no wounds damage, and has a good functional range of motion. However, minimal hyperpigmentation is observed.[27]

Animal models of burn injury transplanted with human BM-MSCs are reported to experience an increase in body weight. These models can carry out normal activities and no tumor or pathological changes are found.[21] Minimal

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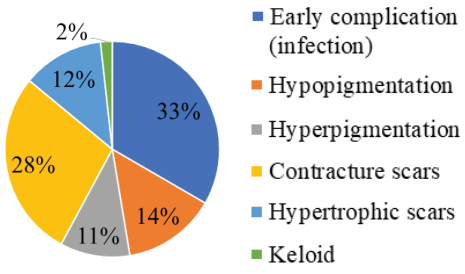

Figure 2. Side effects of MSCs in burn therapy.[16-17,20-23,25-27] MSCs are safe for burn therapy with minimal side effects and do not cause death.

scar tissue formation (about 2-3 mm) is observed and no complications are found in animal models transplanted with xenogeneic ASCs.[22] There is an increase in hair growth in the second week after xenogeneic ASCs transplantation, and no infection as well as systemic side effects are reported.[23] Therefore, it can be concluded that MSCs are safe to be used in burn therapy.

Efficacy of MSCs in Burn Therapy

Stem cells are very promising for cell therapy and tissue engineering, as well as pharmaceutical and biotechnology applications. Stem cells have the ability to self-renew and differentiate into specific cell types depending on the source.[51] MSCs have been extensively studied over the last 30 years due to their unique properties, broad clinical potential, and ability in tissue engineering developments.[52] MSCs are a type of stem cells that can be used as a therapy for treating degenerative diseases, including bone and cartilage reconstruction. MSCs are widely used for dermatology (plastic surgery and aesthetic medicine), cardiovascular, endocrine, and nervous system diseases, as well as cell transplantation and repair of damaged musculoskeletal tissue.[53] MSCs have a high proliferation level and differentiation capacity, and the ability to migrate to the site of damage.[54] An outline of the mechanism of efficacy of MSCs in burn therapy is shown in Figure 3.

MSCs play a role in tissue repair through their immunomodulatory properties by secreting paracrine factors, such as anti-inflammatory cytokines, chemokines, and growth factors into the injured area, thus induce neovascularization and stimulate cell proliferation.[55] This paracrine effect will also stimulate angiogenesis, prevent apoptosis, suppress inflammation, and modulate extracellular matrix dynamics.[56] The immunomodulatory properties of MSCs are caused by the low expression of major histocompatibility complex (MHC) molecules, both class I (MHC I) and II (MHC II) on the cell surface, making they difficult to recognize or even unrecognizable by antigen presenting cells (APC).[57] MSCs are usually administered allogeneically due to extensive burns with limited sources of autologous MSCs. In addition, the low expression of MHC I and II may inhibit T cell proliferation and will not cause an immune response.[26]

Transplantation of BM-MSCs leads to a decrease in pro-inflammatory cytokines, *i.e.* tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β and an increase in anti-inflammatory cytokines (IL-10).[16] UC-MSCs transplantation also shows similar results.[19] In addition, transplantation of UC-MSCs increases TNF-stimulated gene (TSG)-6 expression.[20] MSCs transplantation may also decrease the activity of myeloperoxidase, an inflammatory response marker, which indicates the accumulation of tissue neutrophils.[16,17] A study that compares myeloperoxidase activity in BM-MSCs, ASCs, DPSCs shows that myeloperoxidase in ASCs is decreased, which may be caused by CD44 activity in ASCs.[17] Transplantation of BM-MSCs decreases the number of neutrophils, lymphocytes, fibroblasts, and basal cells.[18]

UC-MSCs decrease the number of white blood cells and C-reactive protein (CRP) levels.[19] The decrease in cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA$^+$) is an indication of neutrophil infiltration and ED-1$^+$ is an indication of macrophage infiltration.[20] MSCs are effective in suppressing immunological activity in the injured area. Although immune system activity plays a role in inflammation, which is important in wound healing, hyperactive immune system will attack healthy cells and tissues and cause tissue or organ damage. Therefore, prolonged inflammatory reaction may limit the speed and quality of wound healing. Overstimulation of the immune system may be suppressed not only by anti-inflammatory cytokines, but also small amounts of pro-inflammatory cytokines produced by MSCs.[56]

The criteria for area of repair in animal models are assessed from the percentage of vital tissue and histopathological features. An animal study using BM-MSCs shows that the percentage of vital tissue from the burn stasis zone is notably higher in the MSCs group (83.6±4.9%) compared to the control group (62.6±8.3%).[15] Meanwhile, rat models of burn injury treated by BM-MSCs have 33.1%±7.58% of repaired area, with less epidermal desquamation, loose collagen matrix, tissue edema, hair

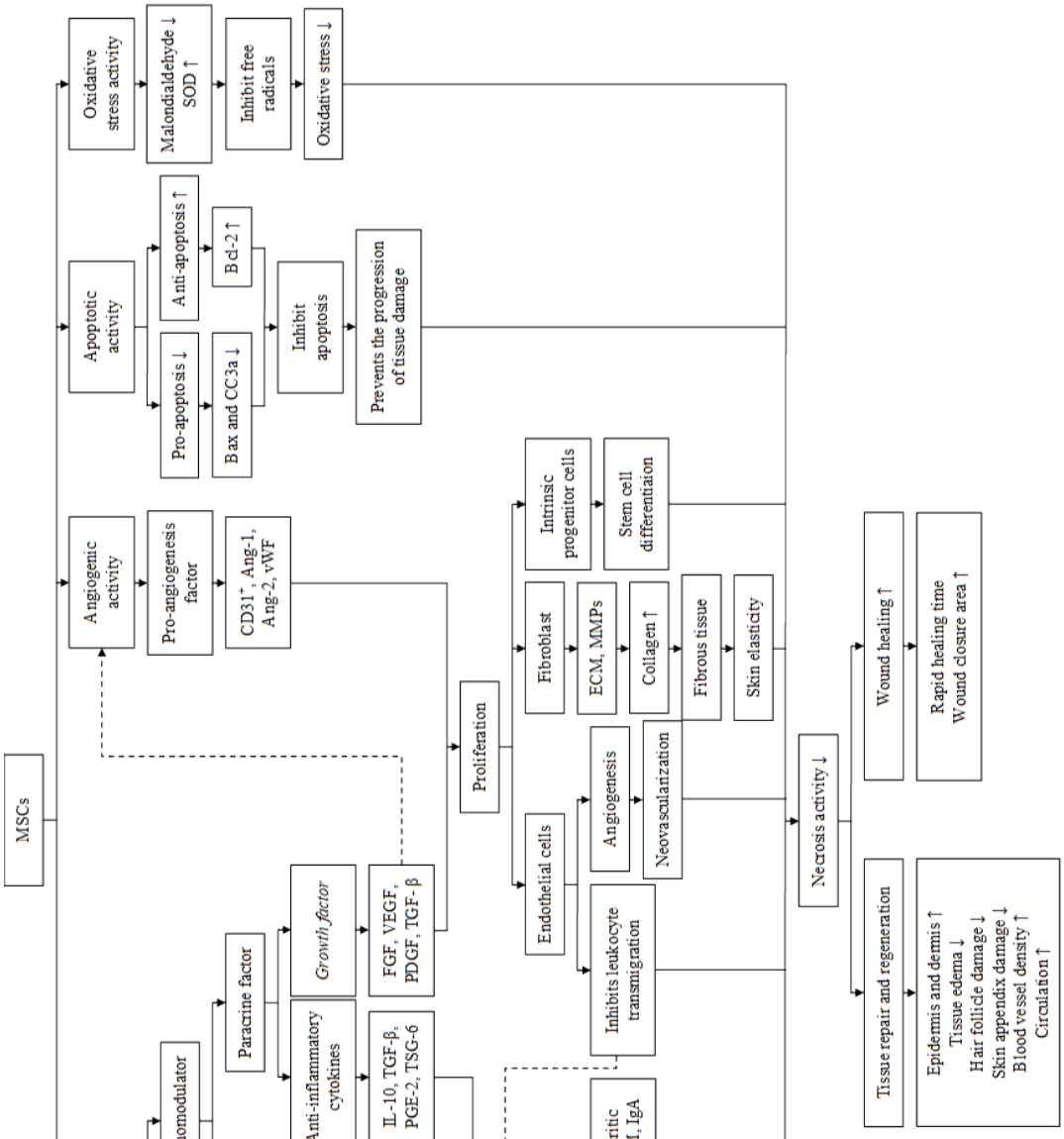

Figure 3. Mechanism of MSCs' efficacy in burn therapy.[55-62] Secretion of bioactive molecules from MSCs regulates immune system, angiogenesis, apoptosis, and oxidative stress. MSCs increase inflammation when the immune system is underactive and suppress inflammation when the immune system becomes overactive to avoid excessive self-attacks against healthy cells and tissues by suppressing leukocyte activity. They also have good immunomodulatory abilities. MSCs play a role in supporting angiogenesis mediated by the release of growth and pro-angiogenesis factors. They inhibit apoptosis by decreasing pro-apoptotic genes (Bcx and CC3a) and increasing anti-apoptotic genes (Bcl-2). MSCs inhibit oxidative stress by decreasing malondialdehyde level and increasing the production of antioxidant enzymes (SOD).

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follicle damage, and extensive damage to the skin appendix. However, there are no notable differences in collagen content between BM-MSCs treatment and control group.[16] Furthermore, a study which compares MSCs from BM-MSCs, ASCs, and DPSCs shows that all MSCs treatment recover histopathology of injured skin, but there are no notable differences between MSCs groups. This indicates that the benefits of MSCs are less dependent on the tissue source.[17]

Transplantation of human BM-MSCs[18] and UC-MSCs[19] improve histopathological features and increases the total vital tissue. In addition, human ASCs have an ability to migrate throughout the wound in animal models.[22] Transplantation of ASCs may increase the density of follicles in the injured area.[23] The improvement of this histopathological features indicates that MSCs contribute in increasing tissue perfusion as indicated by a decrease in tissue edema and damaged skin adnexal structures, suggesting that MSCs can act as a reservoir of keratinocytes to repair damaged skin tissues.[16]

Burn injury, especially in the stasis zone, causes apoptosis in the first 24-48 hours, which leads to tissue damage.[63] Therefore, decreasing apoptotic activity in the burn stasis zone may prevent more progressive tissue damage. BM-MSCs transplantation has been reported to decrease apoptotic activity. MSCs accelerate wound healing by interacting with ischemic microenvironments and regulating mediators that induce stem cells differentiation.[15] MSCs produce apoptosis inhibitor proteins to prevent cell death. BM-MSCs increase anti-apoptotic factor B cell lymphoma protein 2 (Bcl-2), as well as reduce pro-apoptotic factors Bcl-2-associated X (Bax) and cleaved caspase 3a (CC3a). Apoptotic cell numbers in BM-MSCs, ASCs, and DPSCs-treated burn injury rat models show no notable differences, suggesting that an anti-apoptotic mechanism may occur in various types of MSCs.[16,17]

Burn injury can also get worse, progressing to necrosis, if not treated properly.[6] There is an increase in high mobility group box protein 1 (HMGB1), a marker of cell necrosis, in the injured area.[16,17] Transplantation of MSCs reduces the area of necrosis in burns. However, there are no notable differences between BM-MSCs, ASCs, and DPSCs in reducing necrosis area.[17]

Apoptosis and necrosis in burns are also associated with oxidative stress. Oxidative stress is caused by the catabolism of phospholipids that produces malondialdehyde.[64] MSCs therapy shows promising results to downregulate oxidative stress in burns by inhibiting free radicals and stimulating endogenous antioxidant enzymes.[16,17] The degree of burn (%TBSA) is correlated with a decrease in antioxidants level. Therefore, other conservative therapy is needed to stimulate antioxidant substances.[64] BM-MSCs decrease malondialdehyde activity and increase superoxide dismutase (SOD) as an antioxidant enzyme. However, no notable differences in the decrease of malondialdehyde activity are observed between BM-MSCs, ASCs, and DPSCs.[16,17]

Angiogenesis is the process of forming new blood vessels from the branching of existing blood vessels. It is an important normal process during tissue repair and wound healing, and this process can be increased by the paracrine effect of MSCs that secrete several angiogenic factors.[60,61] BM-MSCs, ASCs, and DPSCs increase CD31 production on endothelial cells[16,17,21,22], but the best results were obtained in DPSCs.[17] MSCs increase pro-angiogenesis factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor (TGF)-β, and von Willebrand factor (vWF)[16,18,20,21], and produce proliferating cell nuclear antigen (PCNA).[23] BM-MSCs increase vascular density[18,21] and expression of both angiopoietin (Ang)-1 and Ang-2.[21] UC-MSCs increase the number of capillaries[19] as well as improve microvascular and microcirculation after 3 weeks of MSCs transplantation.[20]

Collagen is a substance found in the dermis produced by fibroblasts. Together with elastin fibers, collagen forms the structure of the skin and maintains skin elasticity.[55] BM-MSCs and UC-MSCs increase fibrous tissue which produces collagen[18,19] and degrade loose collagen matrix. No notable differences are observed in fibrous tissue and degradation of loose collagen matrix in burn wounds treated with ASCs and DPSCs.[17] Collagen is classified into several types. Type I collagen provides mechanical properties and is predominantly found in adult tendons and ligaments. This type of collagen combines with other molecules to form various tissue structures such as basement membranes, skin, and blood vessels.[65] Type II collagen consists of looser fibers which are the main component of cartilage and is related to joint cushioning.[66] Type III collagen plays a key role in the formation of the musculoskeletal system, blood vessels, and other organs.[67] Collagen types I and III are the main types of collagen in healthy skin. The ratio of collagen types I and III determines the progress of wound repair. In rat models of severe burn, accumulation of collagen types I and III are notably increased in the third week after UC-

MSCs administration. UC-MSCs increase the type I/III collagen ratio[20], while ASCs increase type I collagen, type III collagen, and the ratio of collagen type III/I. Type I collagen is generally more abundant in healthy skin compared to type III collagen. However, tissue repair in damaged skin depends on the deposition of type III collagen, so that the amount of type III collagen increases.[22]

The expected result of MSCs therapy for burns is recovery of burn wounds. Wound healing studies with animal models and human are intended to investigate the duration of burns recovery and whether the administration of MSCs on burns can heal 100% of the wound area. Intraperitoneal injection of human BM-MSCs to rat models of burn injury until the 14th day after burn induction improves wound healing with the observed final wound closure area being approximately 1 mm^2 on day 27.[18] The wound area that is injected subcutaneously with BM-MSCs is recovered approximately within 25 days.[21] In another study, subcutaneous injection of human UC-MSCs to rat models 24 hours after burn induction improves the percentage of healed wound area (approximately 97.2%) and healing time (29±2.8 days).[19] Meanwhile, intravenous injection of human UC-MSCs to rat models 3 days after burn induction improves wound healing within 74±4 days with 1% remaining wound area.[20]

Human ASCs which are injected subcutaneously in mice 24 hours after burn induction are able to completely cover the wound area at day 21. However, this result is not different from the control group.[22] Intradermal injection of ASCs in rats 30 minutes after burn induction improves burn healing by reducing the wound area within 4 weeks.[23] A study comparing subcutaneous injection of autologous and allogeneic ASCs in different areas, *i.e.* at the center of the wound and 0.5 cm from the wound margin 24 hours after burn induction demonstrates an increase in wound healing area with different healing rates within 15 days.[24]

Autologous ASCs injection at the wound center and a distance of 0.5 cm from the wound edge increase wound healing rate by 98.92±1.00% and 100±0.06%, respectively. Meanwhile, allogeneic ASCs injection at the wound center and a distance of 0.5 cm from the wound edge increase wound healing by 89.92±0.79% and 90.90±0.45%, respectively. These results are not different from the group that do not receive MSCs treatment. Therefore, ASCs therapy has efficacy in treating acute burns. In addition, autologous ASCs are better administered at a distance of 0.5 cm from the wound edge.[24]

A human research using autologous BM-MSCs and allogeneic UC-MSCs also reveals that MSCs therapy improves burn healing. BM-MSCs are injected after 2 days of surgical excision and 10 days after the first injection, while allogeneic UC-MSCs are administered topically after 2 days of surgical excision of injured tissues. The average burn area in patients transplanted with BM-MSCs and UC-MSCs are 17% and 15.95%, respectively.[25] In another study, allogeneic BM-MSCs are injected to burn patients who do not heal for more than 21 days with different ages (2, 4, 7, 10, and 58 years old) and burn degrees (second and third-degree), as well as time between injury and the first MSCs administration. The given MSCs doses depend on the severity of burns. BM-MSCs improve wound healing at different times in each patient. Burn wounds in 4, 7, 10, and 58-year-old patients are completely healed within 5 months, 4 months, 7 weeks, and 10 weeks, respectively. In addition, the area of open burn wound in a 2-year-old patient is reduced at least within 2 months.[26] These differences may be related to the size, depth, and damage to cells and burn tissue, which may affect the repair process in the skin.[68] Topical application followed by subcutaneous injection of allogeneic CL-MSCs 18 months after the injury improves burn healing by increasing wound closure area to half of the one third of initial wounds, within 3 weeks in a mid-twenties burn patient with extensive burns (70% TBSA or third-degree). CL-MSCs application, PRP injection, and skin autograft completely heal burn wounds within 4.5 months.[27]

Based on the above discussion, it can be concluded that MSCs improve burn wound healing. However, the wound healing time depends on the severity of the burn. This wound healing mechanism may be related to the paracrine effects produced by MSCs.

Conclusion

Mesenchymal stem cells (MSCs) are safe for burn therapy because they do not cause death as well as have minimal side effects and good efficacy. The lower the severity and the area of the burn, the better and the faster tissue repair and wound healing. The higher the degree of severity and the area of the burn, the higher the dose of MSCs given with the interval between the first and subsequent doses. Systemic transplantation improves tissue repair and wound healing better than topical application. Systemic (intravenous) injections require a longer healing time than

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local (subcutaneous or intradermal) injections. The sooner the MSCs transplantation is given, the better the tissue repair and wound healing. MSCs from different sources have their own advantages and disadvantages depend on their condition. Further holistic and comprehensive clinical trials of MSCs for burn therapy in humans are needed to investigate the differences between types of MSCs, hence the best source of MSCs can be used.

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