International Journal of Research in Medical Sciences
Kumar M et al. Int J Res Med Sci. 2026 Jun;14(6):2677-2684
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20261726

Review Article

Cell therapies for hematopoietic failure in trauma hemorrhagic shock

Manoj Kumar[1]*, Niharika[2], Arun Kumar[3], Nipun Agarwal[4], Kavneet Khanna[5], Sanjeev Bhoi[2]

[1]Department of Microbiology, Sukh Sagar Medical College and Hospital, Jabalpur, MP, India
[2]Department of Emergency Medicine, JPN Apex Trauma Centre, AIIMS, New Delhi, India
[3]Department of Zoology, Kirori Mal College, University of Delhi, Delhi, India
[4]Department of Respiratory Medicine, Sukh Sagar Medical College and Hospital, Jabalpur, MP, India
[5]Department of Dentistry, Sukh Sagar Medical College and Hospital, Jabalpur, MP, India

Received: 31 March 2026
Revised: 07 May 2026
Accepted: 13 May 2026

***Correspondence:**
Dr. Manoj Kumar,
E-mail: manojssmc@gmail.com

ABSTRACT

Traumatic hemorrhagic shock (T/HS) is clinically associated with hematopoietic failure (HF). HF in T/HS patients is characterized by an increase in the levels of norepinephrine, cytokines, granulocyte-colony stimulating factor and peripheral blood hematopoietic progenitor cells, as well as a decrease in the expression of erythropoietin receptors. Reducing cytokines, vascular dysfunction, tissue damage, apoptosis and HF may be possible with cell-based therapy. Regulatory T cells, mesenchymal stem cells, bone marrow mononuclear cells and induced pluripotent stem cell-derived hematopoietic progenitor cells are all cell-based treatments that have shown promise in improving the prognosis of patients with T/HS by ameliorating bone marrow malfunction or HF. Here, we discuss the latest cell-based therapy approaches for treating HF in T/HS patients.

Keywords: Cell therapy, Hematopoietic failure, Traumatic hemorrhagic shock

INTRODUCTION

The most common cause of mortality after trauma is HS. About half of all deaths may be attributed to HS. There are around 60,000 annual fatalities in the United States. An estimated 1.9 million people die each year throughout the world.[1,2] Trauma associated hemorrhagic shock accounts for 30–40% of deaths of the patients brought to the emergency room do not survive the first 24 hours.[3] Hypoxia-ischemia is a condition in which oxygen and nutrients are not delivered to tissues as well as it also leads to cellular malfunction. Insufficient oxygen needs of individual cells rise to meet the demands of the shock.[2] Patients suffering from T/HS and multi-organ failure (MOF) had a better chance of survival when they were challenged MOF. The development of MOF after severe trauma is one of the leading causes of morbidity and mortality, where immunological dysfunction plays a central role.[4] One of the causes of this is associated with the suppression of hematopoietic progenitor cells (HPCs). Erythropoiesis controls HPCs, bone marrow (BM) stromal cells and their surrounding environment. High levels of cytokines in the peripheral blood after T/HS are linked to hematopoietic failure (HF).[5-7] Overproduction of catecholamine, in turn connected to the stress-induced release of cytokines, is linked to the release of HPCs from the bone marrow (BM) into the peripheral circulation.[6,8] Increasing evidence suggests that in T/HS patients, increased granulocyte colony stimulating factor (G-CSF) is also linked to the mobilization of HPCs from the BM into peripheral circulation. Patients with severe trauma and neutropenia had comparable outcomes. Mobilization of HPCs from the bone marrow into the peripheral circulation is strongly stimulated by G-CSF.[9,10] The research team has previously shown that a decrease in the expression of erythropoietin receptors (EpoR) is linked to HF in individuals who have undergone T/HS. Erythropoietin

receptor (Epo-R) expression is notably elevated on HPCs (colony-forming unit-erythroid (CFU-E) and burst-forming unit-erythroid (BFU-E)). Epo-EpoR signaling is crucial for survival because it increases HPCs proliferation and differentiation through the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway. Apoptosis in neuronal and erythroid progenitor cells is also inhibited by EpoR signaling.[11]

Anemia caused by HF increases a patient's vulnerability to infection, sepsis, multiple organ failure and a bad prognosis in HS patients. Cell-based treatments (CBT) and molecular basis of HF and effective treatments for it remains poorly understood in T/HS patients. A lot of progress has been made in the last decade in treating individuals who have suffered with severe trauma or trauma induced hemorrhagic shock. Surgical intervention open or in laparoscopic surgery, controlled bleeding during through vessel ligation, suturing and electrocautery. Topical hemostatic agents are useful adjuncts to surgical hemostasis for controlling non-specific bleeding.[12] Fluid blood and its components can also stop hemorrhage. Early use of blood and its component can help to preserve oxygen delivery and coagulation parameters. However, excessive blood transfusion carries the added risk of transfusion reactions, infections and several metabolic complications in massive transfusion. Which exacerbate injury-induced immune suppression, are costly, carry the risk of infectious disease transmission and have been associated with a worsening of organ failure. Hence, the prophylactic use of blood products is not warranted.[3,13] However, excess fluid also causes problems with the immune system. More progress is needed in the management of HF in HS patients.[1]

Emerging medical research is mostly focused on CBT. Similar to other approaches, CBT has the potential to inspire new scientific discoveries and advance technology. Except for hematopoietic stem cell (HSC) transplantation, which is already well established for the treatment of blood-related illnesses, CBT accounts for the vast majority of current clinical trials. Sub-acute and long-term therapy of severe injury, trauma and shock are areas where CBT shows tremendous potential. Mesenchymal stem cells, bone marrow mononuclear cells, induced pluripotent stem cell-derived hematopoietic progenitor cells and regulatory T cells are all examples of cell-based therapy that have been shown to decrease HF and improve outcomes for T/HS patients.[14,15]

TRAUMA-RELATED HEMORRHAGIC SHOCK AND HEMATOPOIETIC FAILURE

Following hemorrhagic shock, anemia is linked to a number of causes. These include peripheral blood HPCs, granulocyte colony-stimulating factor, catecholamines, increased cytokines (Tumor necrosis factor (TNF) and Interleukin (IL-6)) and reduced expression of EPO-R, which is also linked to HPCs suppression (Figure 1). As a result of HPCs apoptosis, there is a risk of infection, sepsis and MOF, as well as chronic anemia associated with HF.[1]

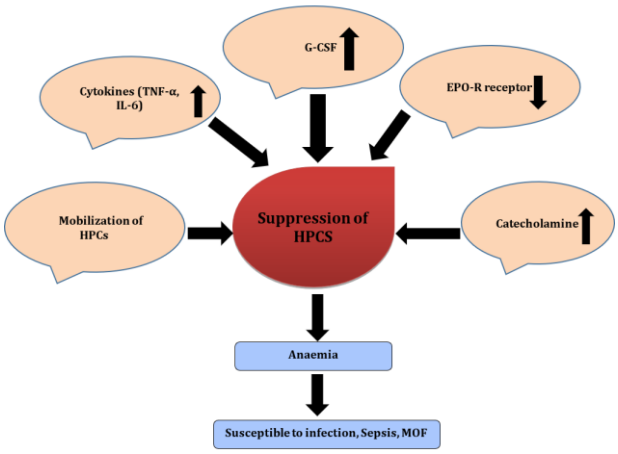

Figure 1: Diagrammatic representation of suppression of HPCs.

HEMATOPOIETIC INSUFFICIENCY AND CYTOKINES

The inflammatory response to HS causes changes in the concentrations of certain cytokines in the surrounding environment. It is believed that immunological dysfunction, leading to MOF and mortality, is caused in part by a balance of pro-inflammatory and anti-inflammatory cytokines. In both the innate and adaptive immune systems, cytokines are tiny protein molecules that play an important role as effectors during times of inflammation. They function by sending signals to target cells. Sepsis and late-onset multiorgan failure (MOF) result from a patient's increased vulnerability to infection brought on by an unbalance between early SIRS (systemic inflammatory response syndrome) and late compensatory anti-inflammatory response (CARS).[16] Systemic inflammation or infection creates enormous essential for mature myeloid cells, such as neutrophils and monocytes, which is termed emergency myelopoiesis. During emergency myelopoiesis (Figure 2), hematopoietic stem/progenitor cell (HSPC) populations elevated and undergo sustained pro-granulocyte proliferation. Murine models have demonstrated that HSPC populations can double following sepsis and remain elevated for over one week after the insult.[17,18,34,35]

High cytokine levels can cause hematopoietic progenitor Cells (HPCs) to self-destruct via a process known as apoptosis. There is an inverse relationship between IL-6, TNF- and HPC suppression in T/HS patients. When TNF- levels rise, it binds to its receptor on HPCs. It is believed, however, that a larger number of signalling pathways contribute to erythropoiesis dysfunction. In the aftermath of severe trauma, IL-1, IL-6, IL-8 and TGF- inhibit erythroid progenitor cell development. Recent research has linked apoptosis in HPCs to the cytokines tumor necrosis factor alpha and interferon beta. The combined

effects of these two cytokines were more suppressive than the effects of either (Interferon) IFN- or TNF-alpha one in cultures. Survival, proliferation, differentiation, maturation and functional binding to their receptors on HSCs are all regulated by cytokines.

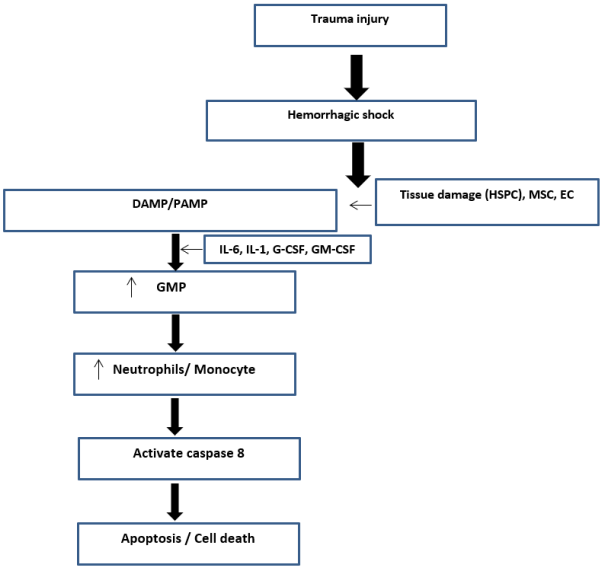

Figure 2: Emergency myelopoiesis following trauma hemorrhagic shock.[1,34]

GMP: Granulocyte-monocyte progenitors, IL-1: interleukin 1, IL-6: interleukin 6, IFN-γ: interferon γ, GM-CSF: granulo-monocyte colony-stimulating factor, G-CSF: granulocyte colony-stimulating factor, M-CSF: monocyte colony-stimulating factor. PAMPs: Pathogen-associated molecular patterns, DAMPs: damage-associated molecular patterns, HSPC: hematopoietic stem and progenitor cells,MSC: mesenchymal stromal cells, EC: endothelial cells.

Many cytokines have many, overlapping roles. Depending on the cytokine, it may operate on cells of a specific lineage or influence the cells across numerous lineages. Nonetheless, a combination of cytokines is necessary for a few cell types since their effect will only be maximized by working together. Cytokines regulate both rapid and steady growth of hematopoietic stem cells. IL-1, IL-10, TGF (Transforming growth factor), SCF (stem cell factor), High mobility group box1 (HMGB-1) and B-cell lymphoma-extra-large (Bcl-Xl) are examples of proteins. Although alterations in the cytokine profile are linked to bone marrow failure after trauma, their interplay is poorly understood due to its complexity. After an injury, cytokines such as Bcl-xL, IL-10, SCF and IL-1 encourage the differentiation of HPCs. Both transforming growth factor 1 and hepatocyte growth factor 1 are inflammatory and suppress the production of blood cells. These follows that proinflammatory cytokines would be increased and pro-hematopoietic cytokines would be downregulated in a post-traumatic hypercatecholamine state. HSCs have 13 and 5 V proteins that bind to their receptors. Proinflammatory and ani-inflammatory cytokines associated with overlapping roles. Depending on the cytokine, it may operate on cells of a specific lineage or it may influence cells across numerous lineages. However, numerous cytokines working together are necessary for the proper functioning of some cell types.

Emergency and routine hematopoietic cell growths are both regulated by cytokines. IL-1, IL-10, transforming growth factor (TGF), SCF, HMGB-1 and Bcl-Xl are examples of proteins. Despite the fact that the alterations in the cytokine profile are linked to bone marrow failure after trauma, their interplay is poorly understood because of its complexity. Several cytokines, including Bcl-xL, IL-10, SCF and IL-1, have a role in promoting HPC differentiation in the wake of injury. Both transforming growth factor-1 and hepatocyte growth factor-1 are inflammatory and suppress the production of blood cells. It follows that proinflammatory cytokines would be increased and hematopoietic cytokines would be downregulated in a post-traumatic hypercatecholamine state, which bind to their receptors on HSCs. Many cytokines have many overlapping roles. Depending on the cytokine, it may operate on cells of a specific lineage or it may influence cells across numerous lineages. However, numerous cytokines working together are necessary for the proper functioning of some cell types. Emergency and routine hematopoietic cell growth are both regulated by cytokines. IL-1, IL-10, TGF, SCF, HMGB-1 and Bcl-Xl are examples of proteins. Despite the fact that alterations in the cytokine profile are linked to bone marrow failure after trauma, their interplay is poorly understood because of its complexity. Several cytokines, including Bcl-xL, IL-10, SCF and IL-1 have a role in promoting HPC differentiation in the wake of injury. Both transforming growth factor 1 and hepatocyte growth factor 1 are inflammatory and suppress the production of blood cells. It follows that proinflammatory cytokines would be increased and prohematopoietic cytokines would be downregulated in a post-traumatic hypercatecholamine state.[7,19]

IMPAIRED HEMATOPOIETIC FUNCTION AND CATECHOLAMINE RELEASE

T/HS-induced stress increases norepinephrine levels in the blood, which in turn stimulates the bone marrow to release HPCs. Due to an overabundance of inflammatory cytokines, catecholamine levels, including chemokine receptor 4 (CXCR4) and stromal cell derived factor1 (SDF-1) remain elevated. They are associated with chronic anemia by suppressing BM, HPCs and then mobilizing them into circulation. SDF-1's involvement in directing HPCs from the bone marrow to the wounded tissue, where they may speed healing, has just recently been documented.[1,20] The adrenal glands secrete catecholamines such as dopamine, epinephrine (adrenaline) and norepinephrine. Physical or mental stress causes the release of these hormones. These hormonal compounds are metabolized and excreted in the urine in various forms. When we're under mental or physical pressure, our body secretes chemicals called catecholamines.[20]

INDUCTION/CONSCRIPTION OF BLOOD-FORMING PRECURSORS

T/HS raises HPCs in the bloodstream, as discussed before. Furthermore, in comparison to survivors, non-survivors had significantly higher levels of circulatory HPCs (Table 1).[21] After damage and T/HS, Badami et al, claims that HPCs will mobilize, leading to BM failure.[6] By growing blood cells on methylcellulose medium, Livingston et al, discovered that seriously damaged patients had much more HPC development compared to healthy controls (Table 2) (1526 vs. 31, p 0. 05). However, no association between peripheral HPC concentrations and health outcomes was found in this investigation.[3] Injured tissue may benefit from HPCs being mobilized from the bone marrow (BM), where they can aid in wound healing and immune response maintenance. However, excessive mobilization can cause problems in the BM. [21]

HEMATOPOIETIC PROGENITOR CELL MOBILIZATION THROUGH GRANULOCYTE-COLONY-STIMULATING FACTOR

Humans have used G-CSF, a hematopoietic cytokine and robust stem cell mobilization agent, in both experimental and therapeutic settings. The active proliferation of endothelial cells and the development of vascular structures were induced by G-CSF in an animal model. This suggests that G-CSF may have the ability to boost endothelial cells' angiogenic properties. G-CSF has been shown to have tissue-protective effects via two mechanisms: by boosting the host's immune system, anti-inflammatory response and protecting cells from apoptosis. Many studies have shown that G-CSF speed up the healing process and encourages tissue regeneration after trauma. G-CSF injections after resuscitation sped up the wound-healing process by boosting angiogenesis and early anti-apoptotic capabilities. The ability of Human Umbilical Vein Endothelial Cells (HUVECs) to resist apoptosis, as well as their ability to migrate and form tubes, were all improved by G-CSF in vitro tests. However, high levels of G-CSF are linked to the release of HPCs from the bone marrow into the bloodstream.[22,23]

Previous research (Table 1, 3) demonstrated that in T/HS, granulocyte-colony stimulating factor (G-CSF) was significantly higher than in the control group.[10] It is the most potent activator of hematopoietic mobilization and this effect was demonstrated in patients with severe trauma and neutropenia. Both HS and LC/HS patients exhibit elevated amounts of G-CSF in their plasma and peripheral blood HPCs.[10,24] In addition, patients with severe injuries, burns or infections have been shown to have increased amounts of G-CSF.[10]

REDUCING EXPRESSION OF THE ERYTHROPOIETIN RECEPTOR

Kidneys generate a cytokine called erythropoietin (EPO), which binds to the erythropoietin receptor (EpoR) and sends a signal to the CFU-E cells via the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways.[9] EPO-induced activation of STATs is mainly involved (STAT-5) in cell survival via up-regulation of the expression of antiapopototic factors.[3] Their ability to maintain viability and multiplicity depends on Epo-EpoR signalling. Recent work from our lab has shown that individuals with T/HS have abnormally high Epo levels in their blood. There is no increase in RBC production after T/HS, despite high Epo levels. We have discovered that the expression of EpoR on BM cells was significantly lower in the T/HS group compared to the control group (Table 1).[11] A recent study found that blunted EPO contributes to anemia in critically ill patients. In order to protect tissues, EPO uses a receptor (tissue-protective receptor) that is pharmacologically separated from the conventional EPO receptor, which is responsible for mediating erythropoiesis. In addition, apoptosis in neuronal and erythroid progenitor cells is inhibited by EpoR signaling.[1,25]

HEMATOPOIETIC INSUFFICIENCY AND CELL-BASED TREATMENT

Bone marrow malfunction and hematopoietic failure in HS after injury are examples of how cell-based treatments have shown recent promise in the trauma system (Figure 3). In addition, previous studies have shown that stem cells can heal spinal cord injuries, traumatic brain injuries, organ injuries and extremity injuries, including those caused by orthopaedic trauma, burns and severe limb ischemia. However, further investigation is needed in this area.

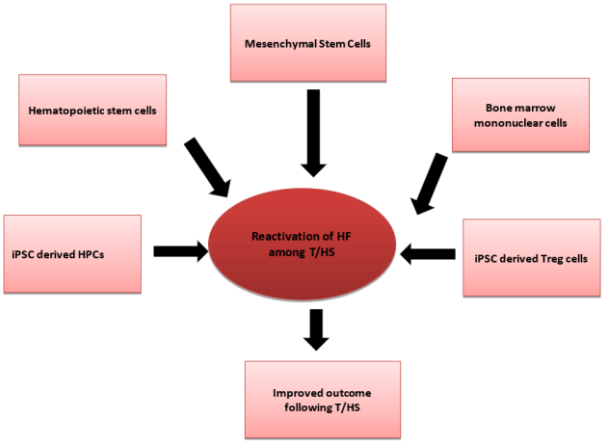

Figure 3: Diagrammatic representation of cell based therapy for the reactivation of HPCs.

HEMATOPOIETIC STEM CELLS

HSC transplantation has been used as a treatment for BM failure, immune system diseases and hemoglobinopathies.[20] Renal repair and regeneration were shown to be aided by hematopoietic stem cells and hematopoietic progenitor cells in an animal model of

ischemia-reperfusion damage conducted by Li et al. By stimulating new blood vessel growth, human CD34+ cells and HSCs-HPCs aided in healing bone and brain damage. Patients suffering from haematological failure following T/HS may benefit from HSC transplantation as a potential treatment option.[26]

Table 1: Peripheral blood HPCs, G-CSF and erythropoietin receptor among T/HS.

Variable	Kumar et al[1,3,4]			
	T/HS	Control	Outcome	
			Survival	Death
PB-HPCs (%)	0.1* (0. 0-2.73) (n=39)	0.01 (0.0-0.8) (n=30)	0.03 (0.0-0.85) (n=25)	0. 40* (0.01-2.3) (n=14)
G-CSF (pg/ml)	264.88* (118,12080) (n=37)	79.1 (65,305) (n=15)	207 (66, 4625) (n=25)	416 (118, 12080) (n=12)
EPO-R (%)	2. 4* (1,6.8) (n=6)	22 (6.1,44.4) (n=13)	-	-

*p value less than 0.05

Table 2: Comparison between BM- HPCs behavior in T/HS (Kumar et al) vs. trauma without hemorrhagic shock (Livingston et al).

HPCs	Kumar et al[1]		Livingston et al[4]	
	Control group	T/HS (n=12)	Control group (n=45)	Trauma without HS (n=12)
CFU-E	71 (n=26)	27*	247	28*
BFU-E	88 (n=20)	11*	120	70*
GM-CFU	34 (n=20)	5*	140	80*

*p value less than 0.05.

Table 3: Comparison between the G-CSF T/HS vs trauma victims with or without hemorrhagic shock.

Variable	Kumar et al[3]		Cook et al[5]			
	T/HS	Control	Trauma without hemorrhagic shock	Control	T/HS	Control
G-CSF (pg/ml)	264. 88* (118,12080) (n=37)	79. 1 (65,305) (n=15)	1640. 4±304. 3* (n=83)	33. 0±6. 8 (n=18)	2528. 7±536. 4* (n=5)	33. 0±6. 8 (n=18)

IPSC-DERIVED HUMAN HEMATOPOIETIC PROGENITOR CELLS

Induced pluripotent stem cells (iPSCs) enable the use of cell-based treatment with no moral qualms. In the same way Embryonic stem cell (ESC) may self-renew and specialise in every kind of cell except placental cells, so can iPSCs. Four transcription factors are expressed in a somatic cell and the resulting iPSCs may be differentiated into any other kind of cell. Sex determining region Y-box2 (SOX2), Octamer-binding transcription factor 4 (OCT4), cellular myelocytomatosis (cMyc) Kruppel-like factor 4 (Klf4) are the four essential transcription factors required to generate embryonic stem cell–like colonies.[27] The efficiency of making iPSCs is low, at 0. 01 or below. The time required to generate mouse and human iPSCs 1-2 weeks and 3–4 weeks, respectively. In 2007, Shinya Yamanaka and colleagues announced the first successful creation of iPSCs.

After transfecting mouse fibroblasts with a retroviral vector containing the transcription factors Oct4, Sox2, c-Myc and Klf4 (Figure 4), the researchers saw the desired effects. The following year, he reported employing a lentiviral system including the transcription factors Oct4, Sox2, Nanog Homeobox (Nanog) and Lin to generate iPSCs from human fibroblasts. Agents like valproic acid, RG108 (non-nucleoside DNA methyltransferase inhibitor), AZA (Azacitidine), Trichostatin A (TSA), N-(1-Benzyl piperidin-4-yl)-6,7-dimethoxy-2-(4-methyl-1,4-diazepan-1-yl)quinazolin-4-amine (BIX-01294) and 3-(6-Methyl-2-pyridinyl)-N-phenyl-4-(4-quinolinyl)-1H-pyrazole-1-carbothioamide (A83-01) may increase the productivity of iPSCs (Figure 2).

Other cell types that have been observed to undergo reprogramming include embryonic and foetal fibroblasts, adipose tissue stem cells, blood cells, keratinocytes and brain stem cells, the bone marrow's resident stem cells. In other words, HSCs develop into myeloid or erythroid lineage cells. Self-renewal, proliferation and differentiation are all abilities of HSCs and HPCs.[27] Medication toxicity, immunosuppressive drug requirements and preconditioning limit their widespread

use in haematological malignancies. Immunologic characteristics of iPSC derivatives were revealed in previous investigations, opening the door to their possible therapeutic use. The T-cell inhibitory ligand, Programmed death (PD-L1) is strongly expressed in iPSC-derived CD34+ hematopoietic progenitor cells, as are cluster differentiation (CD80 and CD86). Allogeneic transplantation of iPSC-derived progenitor cells may benefit from the fact that HPCs obtained from iPSCs may cause T-cell energy in all reactive T cells. One of the most definitive indicators of absolute hematopoiesis, globin gene expression in differentiated erythroid cells, was obtained from HPCs produced from teratomas.[28]

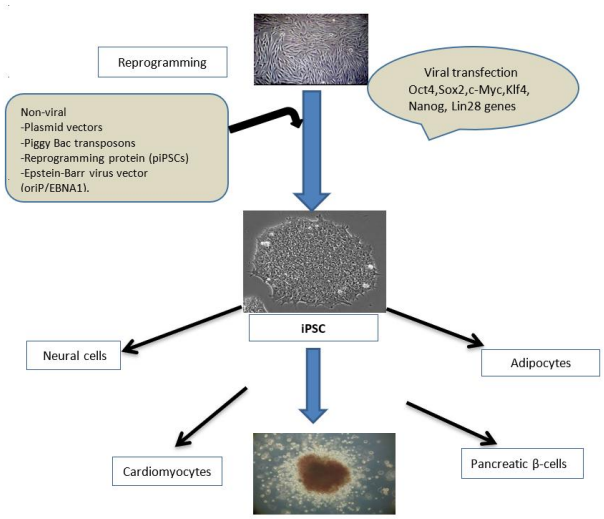

Figure 4: Diagrammatic representation of iPSC derived HPCs.

HUMAN REGULATORY T CELLS CREATED FROM IPSCS

Forkhead boxP3 (FoxP3) controls the genetic programme of Tregs, which are subsets of CD4+ t-helper cells. They are surface-expressed for CD25 (IL-2R-chain). They help in keeping peripheral tolerance at a healthy level.[29] Ag-specific Tregs seem better at suppressing local autoimmune diseases such as Rheumatoid arthritis (RA), autoimmune diabetes and Graft vs host disease (GVHD), despite the fact that polyclonally enlarged populations of Tregs demonstrate suppressive function. Targeting Tregs in specific organs or tissues (such as the joints, pancreas or gut) maintains consistent FoxP3 expression and prevents the production of potentially harmful systemic immunosuppression. The generation of effectors Tregs that have not undergone terminal differentiation is necessary for in vivo re-infusion in order to make the most use of Tregs in treatment. Unfortunately, the number of Tregs that can be generated, expanded and isolated from patients using current methods is insufficient. Generating Tregs from iPSCs (induced pluripotent stem cells) is possible under the correct conditions. To treat a broad variety of autoimmune illnesses, iPSCs provide the possibility of obtaining a renewable supply of healthy Tregs. However, we still don't know everything that if there is to know about how iPSCs become antigen (Ag)-specific Tregs (iPSC-Tregs), including the signalling systems that guide the differentiation of these cells.[29,30]

PSCs and induced pluripotent stem cells (iPSCs) have previously been proven to mature successfully into T cells and differentiate into the T lineage, respectively. It is still debatable, however, whether iPSCs can successfully develop into ag-specific Tregs for use in Treg-based immunotherapy. Tregs and "highly reactive" cytotoxic T lymphocytes (CTLs) will be engineered from pluripotent stem cells and we will investigate the mechanisms that govern this process (PSCs). These highly reactive T cells have a greater capacity to respond to homeostatic cytokines, a more significant proliferative potential and a lower risk of apoptosis compared to terminally differentiated cells. Because they can be generated in vitro from pluripotent stem cells for in vivo re-infusion, highly reactive T cells are ideal populations for adoptive immunotherapy against diseases such as HS, sepsis, cancer, infection and autoimmune.[29-31]

STEM CELLS DERIVED FROM MESENCHYMAL TISSUE

It has been proven that mesenchymal stem cells (MSCs) are effective in reduced the inflammation and promoting tissue regeneration in situations of multiple injuries. Evidence of MSCs' therapeutic potential has been shown in sepsis, acute renal failure and hepatic failure. The potential of mesenchymal stem cells (MSCs) isolated from bone marrow for use in tissue regeneration has been investigated in both laboratory and human studies. MSCs are now the subject of clinical investigations. In all, 283 participants completed 45 trials (www. clinicaltrials. gov). Two of these looked specifically at MSCs and their impact on lung damage. By secreting cytokines and interfering with dendritic cells and T cells, human MSCs are able to maintain an immunosuppressive niche around themselves, protecting them from all recognition. In a rat model of poor wound healing after severe damage, MSCs have demonstrated encouraging effects. An immune-stimulating cell such as MSCs decreases inflammation after being given intravenously by decreasing pulmonary endothelial cell permeability. It is also possible for MSCs to restore bone marrow function. In T/HS, MSCs have potential to serve as therapeutic adjuncts.[1,32]

MONONUCLEAR CELLS EXTRACTED FROM BONE MARROW

The mononuclear cells found in bone marrow (BMMNCs) have the potential to repair damage (Figure 2) in the central nervous system and spinal cord. Intravenous infusion of BMMCs activates signalling pathways to repair the immune response to infection versus host disease in situations of organ injury or dysfunction following hemorrhagic shock. Bone marrow stromal cells (BMSCs) suppress HPCs' mobilization into circulation, promote

HPCs' development in BM, control the immune system and protect bone marrow cellularity. Simple to isolate and immunologically benign, BMMNCs have several potential applications. More importantly, no moral dilemma associated with their use.[33]

INFUSION OF THE PATIENT'S OWN WHITE BLOOD CELLS

The use of AWBCI to enhance the treatment of most traumas, trauma-associated infections, various co-morbidities and immune suppression-derived diseases is helping to raise the bar for trauma care across the world. When combined with T/HS, AWBCI gives trauma patients their "stored" immune systems, which may have been frozen or collected immediately after the trauma event (during surgery, for instance). The advanced trauma life support regimen should be used in conjunction with ABWCI for T/HS patients. The therapy recommendation is based on previous research using both animal models and human tissue and blood samples. To preserve scientific rigor and statistical proof as the foundation for our theories, we must include the idea of customized medicine in an evidence-based framework. This study aims to investigate whether or not AWBCI may be used to enhance the immune systems of T/HS patients.[34,35]

Limitation

However, important areas still require improvement in the translation of cell treatments which include problems with regulations, manufacturing and designing clinical trials, as well as a lack of money or funding source.

CONCLUSION

An increase in the production of cytokines, catecholamines and granulocyte colony-stimulating factors has been linked to HF after T/HS. Furthermore, Epo-R expression reduction was linked to HF. The hematopoietic failure that occurs after T/HS may be reversible with cognitive-behavioral therapy. Among the cell-based treatments are HSCs, iPSC-derived HPCs, iPSC-derived Tregs, BM-MSCs, BMCs and AWBCI (Figure 2). Furthermore, cell-based treatments for HF in trauma patients experiencing hemorrhagic shock need to be tested in clinical studies.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Kumar M, Bhoi S. Impaired hematopoietic progenitor cells in trauma hemorrhagic shock. J Clin Orthop Trauma. J Clin Orthop Trauma. 2016;7 (4):282-5.
2. Cannon JW. Hemorrhagic shock. N Engl J Med. 2018;378 (4):370-9.
3. Kauvar DS, Wade CE. The epidemiology and modern management of traumatic hemorrhage: US and international perspectives. Crit Care. 2005;9(5):54.
4. Griffin GD, Charron D, Al-Daccak R. Autologous white blood cell infusion for trauma, brain trauma, stroke and select immune dysfunction co-morbidities: A promising and timely proposal. Med Hypotheses. 2018;117:7-15.
5. Livingston DH, Anjaria D, Wu J. Bone marrow failure following severe injury in human. Ann Surg. 2003;238:748–53.
6. Badami CD, Livingston DH, Sifri ZC. Hematopoietic progenitor cells mobilize to the site of injury after trauma and hemorrhagic shock in rats. J Trauma. 2007;63:596–602.
7. Millar JK, Kannan KB, Loftus TJ, Alamo IG, Plazas J, Efron PA, et al. Persistent injury-associated anemia: the role of the bone marrow microenvironment. J Surg Res. 2017;15:240-6.
8. Bible LE, Pasupuleti LV, Gore AV, Sifri ZC, Kannan KB. Chronic restraint stress after injury and shock is associated with persistent anemia despite prolonged elevation in erythropoietin levels. J Trauma Acute Care Surg. 2015;79 (1):91-6.
9. Cook KM, Sifri ZC, Baranski GM, Mohr AM, Livingston DH. The Role of Plasma G-CSF and Bone Marrow Dysfunction after Severe Trauma. J Am Coll Surg. 2013;216 (1): 57–64.
10. Kumar M, Bhoi S, Selvi A, Kamal VK, Mohanty S, Rao DN. Evaluation of serum granulocyte colony stimulating factor in patients admitted with trauma hemorrhagic shock. Int J Adv Res Biol Sci. 2015;2(7):107–14.
11. Kumar M, Bhoi S, Kamal VK, Mohanty S, Rao DN, Galwankar S. Evaluation of bone marrow erythropoietin receptor in trauma hemorrhagic shock. Int J Adv Res Biol Sci. 2015;2(8):43-9.
12. Vecchio R, Catalano R, Basile F, Spataro C, Caputo M, Intagliata E. Topical hemostasis in laparoscopic surgery. G Chir. 2016;37(6):266-70.
13. Tien H, Nascimento B Jr, Callum J, Rizoli S. An approach to transfusion and hemorrhage in trauma: current perspectives on restrictive transfusion strategies. Can J Surg. 2007;50(3):202-9.
14. Mount NM, Ward SJ, Kefalas P, Hyllner J. Cell-based therapy technology classifications and translational challenges. Philos Trans R Soc Lond B Biol Sci. 2015;19:370.
15. Pati S, Rasmussen TE. Cellular therapies in trauma and critical care medicine: Looking towards the future. PLoS Med. 2017;14(7):1002343.
16. Kumar M, Rao DN, Mohanty S, Selvi A, Bhoi S. Interleukin (IL)-8 is an early predictor of mortality following trauma hemorrhagic shock. Int J Adv Res Biol Sci. 2015;2(7):12–20.
17. Kelly LS, Darden DB, Fenner BP, Efron PA, Mohr AM. The hematopoietic stem/progenitor cell response to hemorrhage, injury and sepsis: a review of pathophysiology. Shock. 2021;56(1):30-41.

18. Schultze JL, Mass E, Schlitzer A. Emerging Principles in Myelopoiesis at Homeostasis and during Infection and Inflammation. Immunity. 2019;50(2):288-301
19. Kumar M, Rao DN, Bhoi S. Tumour necrosis-α and interleukin-6 suppressed hematopoietic stem cell growth in trauma hemorrhagic shock patients. Shock. 2015;44(2):20.
20. Nolan JP, Pullinger R. Hypovolaemic shock. BMJ. 2014;348:1139.
21. Kumar M, Bhoi S, Selvi A, Kamal VK, Mohanty S, Rao DN. Evaluation of circulating Hematopoietic progenitor cells in patients with Trauma Hemorrhagic shock and its correlation with clinical outcome. Int J Crit Illn Inj Sci. 2016;6:56-60.
22. Huang H, Zhang Q, Liu J, Hao H, Jiang C, Han W. Granulocyte-colony stimulating factor (G-CSF) accelerates wound healing in hemorrhagic shock rats by enhancing angiogenesis and attenuating apoptosis. Med Sci Monit. 2017;23:2644-53.
23. Kumar A, Choudhary S, Kumar S, Adhikari JS, Kapoor S, Chaudhury NK. Role of melatonin mediated G-CSF induction in hematopoietic system of gamma-irradiated mice. Life Sci. 2022;289:120190.
24. Baranski GM, Offin MD, Sifri ZC. β-Blockade protection of bone marrow following trauma: the role of G-CSF. J Surg Res. 2011;170:325–31.
25. Rogiers P, Zhang H, Leeman M, Nagler J, Neels H, Mélot C, et al. Erythropoietin response is blunted in critically ill patients. Intensive Care Med. 1997;23(2):159-62.
26. Kumar M, Bhoi S. Hematopoietic stem cells: Can it be therapeutic option for the hematopoietic failure in patients with trauma hemorrhagic shock. J. Emerg Med Trauma Shock. 2016;9:51-2.
27. Li B, Cohen A, Hudson TE, Motlagh D, Amrani DL, Duffield JS. Mobilized human hematopoietic stem/progenitor cells promote kidney repair after ischemia/reperfusion injury. Circulation. 2010;121:2211–20.
28. Kumar M, Bhoi S. Keshava S. Human-induced pluripotent stem cells derived hematopoietic failure among trauma hemorrhagic shock. Journal of Clinical orthopaedics and Trauma. J Clin Orthop Trauma. 2019;10 (2):269-73. .
29. Haque R, Lei F, Xiong X, Bian Y, Zhao B, Wu Y, et al. Programming of regulatory T cells from pluripotent stem cells and prevention of autoimmunity. J Immunol. 2012;1;189 (3):1228-36.
30. Song J. Stem cell-derived regulatory T cells for therapeutic use in arthritis. Autoimmune Infect Dis. 2016;2(3):875.
31. Haque M, Song J, Fino K, Sandhu P, Song X, Lei F, et al. Stem cell-derived tissue-associated regulatory T cells ameliorate the development of autoimmunity. Sci Rep. 2016;6:20588.
32. Kumar M, Bhoi S. Mesenchymal stem cell: Can it be used for treatment of trauma hemorrhagic shock. Int J Stud Res. 2015;5(1):15-6.
33. Kumar M, Bhoi S. Do bone marrow mononuclear cells can be used as a therapeutic target for trauma hemorrhagic shock. Inter J Medical Sci Res Prac. 2015;2(3):1-10.
34. Griffin GD, Charron D, Al-Daccak R. Autologous white blood cell infusion for trauma, brain trauma, stroke and select immune dysfunction co-morbidities: A promising and timely proposal. Med Hypotheses. 2018;117:7-15.
35. Valade G, Libert N, Martinaud C, Vicaut E, Banzet S, Peltzer J. Therapeutic potential of mesenchymal stromal cell-derived extracellular vesicles in the prevention of organ injuries induced by traumatic hemorrhagic shock. Front Immunol. 2021;12:749659.

Cite this article as: Kumar M, Niharika, Kumar A, Agarwal N, Khanna K, Bhoi S. Cell therapies for hematopoietic failure in trauma hemorrhagic shock. Int J Res Med Sci 2026;14:2677-84.