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Systematic Review

Stem cell therapy approaches for non-malignant diseases & non-haematological diseases in India: A systematic review

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***Background & objectives*: Our study aims to provide the diversity of stem cell use for non-malignant, non-haematological diseases in India through the lens of clinical trials.**

***Methods*: A PRISMA approach was used to evaluate the safety and efficacy of stem cell use for the period 2001-2021 in India. The outcomes were measured using each disease category, types of stem cells, the origin of stem cells, safety, and efficacy.**

***Results*: Of the 9206 studies screened, 61 studies that were relevant to stem cell use for non-malignant diseases were included for analysis. Autologous stem cells (75%) were used predominantly compared to allogenic stem cells (18.33%), followed by mixed type (6.67%). Use of bone marrow-derived stem cells (51%) was dominant, followed by melanocytes (19%), adipose (7%), haematopoietic (12%), and (11%) other types of stem cells. The study revealed 37 randomized clinical trial studies conducted in the government research hospital compared to the non-government.**

***Interpretation & conclusions*: Maintaining the gold standard for stem cell therapy requires randomized clinical trials with large sample sizes, control groups, failures, adverse effects, *etc*. It is important to have a monitoring and regulation system in stem cell clinical research activities with enough preclinical data and repeated exchanges between the bench and the bedside.**

Key words Allogeneic stem cells - autologous stem cells - clinical outcomes - efficacy - non-malignant disease - safety - stem cell therapy

The World Health Organization (WHO) has expressed serious concerns regarding the increasing incidence of non-communicable diseases (NCDs) worldwide. WHO coordinates with each country to prevent and control NCDs through their leadership. However, WHO set the 2030 Agenda for Sustainable Development Goals (SDG target 3.4) to prevent and control NCDs[1] An estimated 41 million people die due to non-communicable diseases each year[1]. Cardiovascular diseases, cancers, respiratory diseases, and diabetes; these four groups are majorly responsible for premature death[1]. India is now a major hub for NCDs[2]. To reduce the burden of NCDs, the Indian government has implemented the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS)[3].

However, these efforts are limited to prevention and control, not the cure.

Stem cell therapy is an important branch of multidisciplinary regenerative medicine that primarily focuses on repairing, regenerating, or rejuvenating the body function[4,5]. Stem cell therapy is a new hope for individuals suffering from NCDs. This includes malignant and non-malignant diseases, and the treatment plan aims for cure. Because stem cells are defined by their uniqueness of self-renewal and differentiation, their therapeutic potential has been proven in basic research, and their utility in clinical settings is being explored. For example, the treatments of spinal cord injury, heart failure, retinal and macular degeneration, and type 1 diabetes have shown promising results as injecting stem cells at the target may help in reverting to normal functioning[4-6], but large clinical trials on these are still lacking so far. However, the emergence of 'unproven stem cell therapy' through unauthorized clinics that claim the importance of stem cell therapy as 'magic cells or snake oil' has raised concern regarding the safety and efficacy of stem cell therapy[7,8]. Moreover, various adverse effects of stem cell injection have been noted historically[9]. For example, during the treatment of macular degeneration, patients lose their vision[10]. Thus, we need more studies on the mechanisms of action, toxicological studies, and standardization and characterization of transplanted cells[11,12].

For the promotion and regulation of stem cell therapy, the Indian Council for Medical Research (ICMR) and the Department of Biotechnology (DBT) initially released the National Guidelines for Stem Cell Research and Therapy in 2007[13]. It was subsequently modified in 2013 and 2017. The guidelines were renamed as National Guidelines for Stem Cell Research (NGSCR) in 2013 by removing the word therapy and was retained as is in 2017. The NGSCR 2017 is comprehensive and continued to emphasize on consideration of stem cell-based therapy as a drug indicated in NGSCR 2013[14,15]. Therefore, needs to go through rigorous clinical trial procedures. This guideline also provides a list of approved indications where there is no perceived need for clinical trials, and it mainly includes nearly all haematological diseases, whether malignant or not. Additionally, more comprehensive guidelines for haematological diseases are mentioned in the National Guidelines for Hematopoietic Cell Transplantation (NGHCT) 2021, released by ICMR[16]. Considering stem cells as a drug in NGSCR 2017 was not effective, hence the New Drugs and Clinical Trials Rules (NDCTR), 2019 implemented. Since then legal provisions have been made available for stem cells as a drug. It is hence now necessary to check the status of stem cell therapy based on the outcome of clinical trials[17].

The treatment of haematological diseases using allogeneic or autologous bone marrow/blood stem cell transplantation is already established as part of medical treatment through historical development[18-21]. However, stem cell treatments for non-malignant and non-haematological diseases have not yet been established, and current progress is unknown in the Indian context. Hence, the authors in this study have done a comprehensive systematic analysis to study the outcomes of the clinical trials using stem cell therapy for non-malignant diseases and non-haematological diseases in India.

Materials & Methods

A systematic review was undertaken as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist[22]. This review focused on previously published studies from India. Figure 1 describes the PRISMA diagram for search strategy and study selection.

Search strategy: We performed systematic searches with language restriction (only English) using PubMed, Web of Science, and Scopus databases. The period chosen was between 2001 and 2021, and the search was performed on January 31, 2022. The main keywords were 'stem cell therapy', 'clinical trials' and 'India'. These keywords and their allied keywords were used for data extraction from the above databases. For example, on the Web of Science, we used search strings as (Stem OR cell OR cells) AND (Therapy OR treatment OR cure OR intervention OR therapeutic) AND (Clinical) (Topic) and INDIA (Countries/Regions) and Article (Document Types) and English (Languages). This search string was modified for Scopus and PubMed databases.

Eligibility criteria: Research articles included were related to prospective, randomized, non-randomized controlled trials and other uncontrolled clinical trials, including single-arm trials that examined the safety and efficacy of stem cell therapy in Indian adults or mixed adult and paediatric participants. Full-text

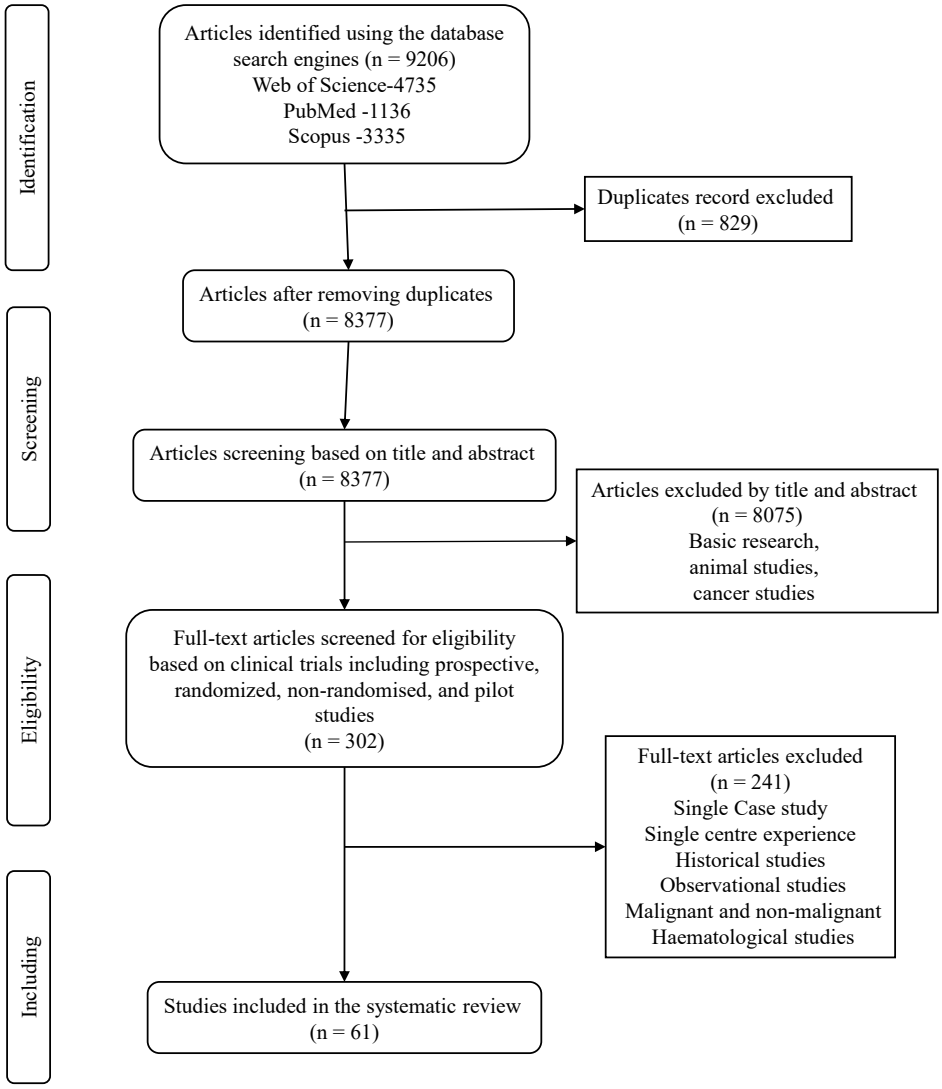

Fig. 1. PRISMA diagram for search strategy and study selection.

articles that were available in the chosen databases were included.

Exclusion criteria: We excluded all animal studies in the first step, and malignant diseases were excluded in the next step. Non-malignant haematological diseases were also excluded because NGSCR 2017 exempted these. Single case reports, observational studies, and single-centre experience studies were excluded.

Screening and article selection: The first and second authors independently screened the selected studies and extracted the data using a standardized form. Doubts and discrepancies were fixed by discussing with the third author.

Search results: With screening and applying exclusion criteria, 8075 articles were excluded, and the remaining 302 articles were considered for full-text selection. Of the total (n=9206) articles screened, 61 articles were included for further analysis (Fig. 1).

Articles particularly related to clinical trials, including prospective, randomized, non-randomized, and pilot studies were included. Of these, single case studies, single centre experiences, historical studies, observational studies, cancer or malignancies, and haematological diseases were all excluded. Among the 61 studies, finally five were included for further analysis recorded before, and 56 were recorded after the release of the National Guidelines for Stem Cell Research and Therapy 2007.

For the purpose of discussion, the studies were sorted on the basis of organ-specificity and disease characteristics (Table I)[23-83]. This included: dental (1 article having 15 participants), diabetes (7 articles having 153), eye (4 articles having 24 participants), heart (9 articles having 484 participants), kidney (4 articles having 539 participants), liver (2 articles 80 participants), neurological (15 articles having 794 participants), musculoskeletal (4 articles having 156 participants) and skin (15 articles 482 participants). Table I describes the main characteristics and outcomes of stem cell therapy (SCT) use for non-malignant non-haematological diseases in India based on this systematic review analysis.

Outcome measure: The safety of the studies was measured based on the treatment protocol reported for stem cell therapy mentioned in these selected studies. This included obtaining stem cells from donors or patients, purification of stem cells (cultured or non-cultured), and injecting to the patients at the targeted site. The efficacy measured in the form of the outcome of the studies included clinical, biochemical, and behavioural parameters or the overall outcome of the study. Adverse events were recorded as: (*i*) no adverse events, (*ii*) mild or treatable adverse events, and (*iii*) serious adverse events, including death or malignancy.

Results

Overall, autologous stem cells (75%) were used dominantly for stem cell therapy as compared with allogenic stem cells (18.33%) followed by mixed type (6.67%). The bone marrow-derived stem cells (51%) were used prominently, followed by melanocytes (19%), adipose (7%), haematopoietic (12%), limbal (6%), dermal (2%), fetal liver (2%) and umbilical cord (1%) derived stem cells (Fig. 2).

Vitiligo (22%) emerged as the disease with a predominant use of stem cell therapeutics, followed by type 1 diabetes mellitus (8%), stroke (8%), spinal cord injury (8%), cerebral palsy (5%), muscular dystrophy (5%), type 2 diabetes mellitus (3%), limbal stem cell deficiency (3%), acute myocardial infarction (3%), cellular cardiomyoplasty (3%), kidney disease (3%), renal allograft (3%), cirrhosis (3%), Parkinson's disease (3%), critical limb ischemia (3%), cystic maxillofacial bony defects (2%), autism (2%), ocular burns (2%), intellectual disability (2%), traumatic brain injury (2%), posttraumatic facial nerve paralysis (2%), femoral head osteonecrosis (2%), osteoarthritis (2%), facial volume loss (2%) and non-healing ulcers (2%). Figure 3 describes the use of stem cells for each disease category.

Lack of enough randomized clinical trials: There were lack of randomized clinical trials in the selected studies. Many studies were conducted without randomisation, had low sample sizes, and control groups were mostly absent (Table)[23-83].

Status of selected clinical studies: Out of 61 selected studies, 37 studies reported clinical trials that were conducted in government research hospitals, and 24 clinical trials were conducted in non-government ones, based on the authors and their affiliated institutes mentioned in the research papers. However, only 16 studies mentioned the clinical trial registration number from the Clinical Trials Registry of India (CTRI number) or from *clinicaltrials.gov*. (National Clinical Trial (NCT) number). Of 61 selected studies, 56 mentioned approval or clearance from the Institutional Review Board, the Institutional Ethics Committee, or the Institutional Ethics Committee for Stem Cell Research (ICSCR).

Uses of stem cells for non-malignant diseases in terms of safety and efficacy: Stem cell therapy can be safe as a treatment protocol mentioned in the studies selected for this systematic review. The treatment protocol includes stem cell extraction from the patient or donor to reinjection of the stem cell aspirate at the specific site in the patient. During this procedure, selected studies did not mention any life-threatening adverse effects of this treatment protocol. However, few exceptions, such as infection or pain at the injection site or aspiration site, were reported[32,43,49,79]. The efficacy level of stem cell therapy varied according to disease type.

Skin diseases: Stem cell therapy for skin diseases like vitiligo, non-healing ulcers, and localized facial volume loss, *etc*., showed good safety and efficacy[69-75]. Though improvement in dermal atrophy and lipoatrophy was observed for localised facial volume loss, adverse effects like erythema, oedema, and pain at the injection site were also observed[81]. Non-healing ulcers treated using stem cells reported significant pain-free walking and reduced ulcer size[71]. In vitiligo, repigmentation was good, and percentages of repigmentation depended on the applied technique and cell concentration. Mild adverse events were also noted in a few studies, such as

Table. Stem cell characteristics and approaches for non-malignant diseases and non-haematological diseases in India

Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
U *et al*[23], 2019	Cystic maxillofacial bony defects	Dental	15	.	6	Evaluate the role of BMA in regenerating new bone	Autologous	Bone marrow-derived Stem Cells	1) Bone defect volume reduction was statistically significant; 2) No tooth mobility; 3) Faster wound healing	.
Bhansali *et al*[24], 2009	T2DM	Diabetes	10	.	6	Efficacy of Autologous Bone Marrow–Derived Stem Cell	Autologous	Bone Marrow-derived Stem Cells	1) Insulin requirements reduced; 2) c-peptide stimulated	1) Self-limiting nausea; 2) Vomiting; 3) Hematoma
Vanikar *et al*[25], 2010	T1DM	Diabetes	11	13 to 43	12	Efficacy and safety of combined	Mixed	Adipose tissue-derived insulin-secreting mesenchymal stem cells (IS-AD-MSC) and cultured bone marrow (CBM)	1) c-peptide assay- increased gradually; 2) Insulin requirement decreased; 3) HBA2c level - decreased; 4) GAD antibodies - decrease in some and others not	.
Dave *et al*[26], 2015	T1DM	Diabetes	10	8 to 45	31.71	Safety and efficacy	Mixed	Adipose tissue-derived MSC-differentiated insulin-secreting cells (ISC) with hematopoietic stem cells (HSC).	1) c-peptide level increased; 2) HbA1c improved; 3) Insulin requirement reduced; 4) GAD ab - positive	No untoward effect
Thakkar *et al*[27], 2015	T1DM	Diabetes	20	8 to 45	12	Compare & assess - safety & efficacy	Mixed	Adipose-derived MSC and Bone marrow-derived HSC	1) Insulin requirement reduced; 2) HBA1c reduced; 3) GAD antibody decreased; 4) Autologous SCT improved better than allogenic SCT for C-peptide	No untoward effect, morbidity (pulmonary embolism, sepsis) or mortality
Thakkar *et al*[28], 2016	T1DM	Diabetes	20	8 to 45	27+	Efficacy and safety of coinfusion	Mixed	Adipose tissue-derived insulin-secreting mesenchymal stem cells and bone marrow-derived hematopoietic stem cells	1) Mean GAD antibody - decreased; 2) Mean insulin requirement decreased; 3) absence of DKA episodes in all; 4) c-peptide level - increased	.
Sood *et al*[29], 2017	T2DM	Diabetes	42	30 to 70	6	To find out optimal routes for deliveryof stem cells	Autologous	Bone Marrow-derived Mononuclear Cells	1) C-peptide assay - difference remained statistically non-significant across all groups; 2) Insulin sensitivity indices of HOMA IR and HOMA B did not show any significant differences; 3) Decrease in Insulin dosages except for peripheral intravenous route; 4) HbA1c - non-significant change	.
Bhansali *et al*[30], 2017	T2DM	Diabetes	40	30 to 60	12	Efficacy and safety of ABM-MSCs and ABM-MNCs transplantation	Autologous	Bone marrow-derived mesenchymal stem cells and mononuclear cells	1) Insulin requirement reduction; 2) HbA1c reduction; 3) Improvement in c-peptide response; 4) Insulin sensitivity also improved	.
Sangwan *et al*[31], 2012	Unilateral limbal stem cell deficiency	Eye	.	.	.	Novel simplified technique of limbal transplantation	Autologous	Limbal epithelial cells	Epithelialised, avascular and stable corneal surface	.
Sharma *et al*[32], 2013	Total limbal stem cell deficiency	Eye	4	8 - 12	26	Clinical outcome with the phenotype of rejuvenated corneal epithelium	Autologous	Limbal epithelial cell (cultured)	1) Epithelial transparency increased; 2) Reduction or absence of corneal vascularization and conjunctivalization; 3) No sign of signs of recurrent LSCD; 4) ocular the surface remained stable and visual acuity improved	.

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Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
Titiyal *et al*[33], 2015	Ocular burns	Eye	20	.	6	Outcomes of live-related limbal allograft (Lr-CLAL) versus cadaveric keratolimbal allograft (KLAL) in limbal stem cell deficiency (LSCD)	Allogenic	Limbal stem cell (live and cadaveric)	Lr-CLAL shows better results than KLAL regarding vision gain and ocular surface restoration.	.
Kaliki *et al*[34], 2017	Ocular surface squamous neoplasia	eye	8	.	12	Compare the surgical outcomes with and without p-SLET	Autologous	Limbal epithelial cells	None of them developed LSCD or tumor recurrence	.
Kaparthi *et al*[35], 2008	dilated cardiomyo-pathy	Heart	5	20 - 65	.	Safety and efficacy	Autologous	Bone marrow-derived mononuclear cells	1) Procedure was safe; 2) improved myocardial contractility and LV function	.
Guhathakurta *et al*[36], 2009	Cellular Cardio-myoplasty	Heart	40	.	6	Safety of protocol	Mixed	Bone marrow mononuclear cells and peripheral blood-derived endothelial precursor cells	Marginal improvement in myocardial function	.
Prasad *et al*[37], 2012	Stroke	Heart	11	30 to 70	12	Feasibility, safety and clinical outcome	Autologous	Bone marrow-derived mononuclear cells	1) Study was feasible; 2) Safe - no evidence of tumour formation; 3) All scores - statistically significant	.
Bhasin *et al*[38], 2013	Stroke	Heart	40	18-65	6	Safety, feasibility and efficacy	Autologous	Bone marrow-derived mesenchymal stem cells and mononuclear cells	Only the modified Barthel Index was statistically significant	.
Prasad *et al*[39], 2014	Ischemic Stroke	Heart	58	18 to 75	6	Efficacy and safety of autologous BMSCs	Autologous	Bone marrow-derived mononuclear cells	No beneficial effect of treatment on stroke outcome	.
Chullikana *et al*[40], 2015	Acute myocardial infarction	Heart	20	.	24	Safety and efficacy of intravenous administration	Allogenic	Bone marrow-derived mesenchymal stem cell	Not significant outcomes compared with placebo	1) 39 treatment-emergent adverse events; 2) SASEs - ventricular tachycardia, pericardial effusion and AMI
Nair *et al*[41],2015	Acute myocardial infarction	Heart	250	20-65	6	Efficacy of stem cells in the improvement of left ventricular function	Autologous	Bone marrow-derived mononuclear cells	1improvement was not significant; 2) Cell dose more than 5x10^8 shows positive impact	1) Chest pain, dyspnoea and other symptoms; 2) One died due to acute stent thrombosis with acute LV failure

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Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
Patel *et al*[42], 2015	Ischemic heart failure or non-ischemic heart failure	Heart	60	.	12	Safety and feasibility	Autologous	Bone marrow-derived mononuclear cells	Not powered to demonstrate statistical significance	1) Elevated troponin levels; 2) Catheterization site hematomas; 3) Bleeding at the marrow aspiration site; 4) Pain at the aspiration site; 5) Congestive heart failure exacerbation requiring hospital admission; 6) Ventricular arrhythmia; 7) Hematomas at the catheterization site and elevated serum creatinine
Bhatia *et al*[43], 2018	Subacute Ischemic Stroke	Heart	.	.	6	Evaluate the Safety and the efficacy of intra-arterial infusion	Autologous	Bone marrow-derived mononuclear cells	1) Good clinical outcomes; 2) modified Rankin Scale score also improved	.
Trivedi *et al*[44], 2002	Paediatric renal transplant	Kidney	44	.	18	To achieve zero-rejection status in pediatric renal allograft recipients,	Allogenic	Peripheral blood stem cell	1) 100% graft survival with sustained low serum creatinine value; 2) Absence of graft vs. host disease	1) Appearance of CMV
Trivedi *et al*[45], 2003	Renal Allograft	Kidney	43	.	12	Tolerance in Living Related Renal Allografts	Allogenic	Bone marrow-derived stem cells	2) Better graft function but not statistically significant	1) Single acute rejection; 2) Appearance of CMV disease; 3) Serum creatine not significant level; 4) No GVHD; 5) rise of donor-specifi cytotoxic allo-antibodies
Trivedi *et al*[46], 2007	Chronic kidney disease	Kidney	357	.	36	Induce tolerance against MHC barriers	Allogenic	bone marrow (BM)-derived and peripheral blood stem cell (PBSC)	1) Significantly better allograft function with low serum creatinine value	1) Acute rejection episode; 2) Acute vascular plus tubulointerstitial rejection; 3) Systemic infections; 4) Patients died
Vanikar *et al*[47], 2014	End-stage renal disease	Kidney	95	.	7 yr	Safety, efficacy and benefits	Mixed	Adipose-derived mesenchymal stem cells (AD-MSC) + hematopoietic stem cells (HSC)	1) No side effects; 2) Survival rate is high; 3) safe and effective strategy for minimization of immunosuppression	.
Khan *et al*[48], 2010	Cirrhosis	Liver	25	.	.	Safety and efficacy of human fetal liver-derived stem cell	Allogenic	Human fetal liver-derived stem cell	1) Decrease MELD score; 2) Improve clinical and biochemical parameters; 3) No episodes related to hepatic encephalopathy recurred	No other clinical complications were observed after follow up
Sharma *et al*[49], 2015	Liver cirrhosis	Liver	55	18-70	3	Effect of peripheral CD+ cells	Autologous	Peripheral blood CD34+ cell	1) Procedure was safe; 2) Statistically significant - improve live function; 3) helps to delay liver transplantation	.
Kumar *et al*[50], 2009	Spinal cord injury	Neuro	297	.	.	Safety and primary efficacy	Autologous	Bone marrow derived mononuclear cell	1) one-third patients show perceptible improvements; 2) No correlation between level of injury and improvements; 3) Number of CD34+ cells injected has direct correlation to outcomes	In some - fever, Headache, Tingling sensation, Neuropathic sensory symptoms

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Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
Pal *et al*[51], 2009	Spinal cord injury	Neuro	30	.	3 yr	Growth kinetics of BM MSC, safety and functional improvement	Autologous	Bone marrow-derived mesenchymal stem cell	1) Protocol is safe; 2) uncontrolled nature of the trial does not permit demonstration of the effectiveness	.
Venkataramana *et al*[52], 2010	Parkinson's Disease	Neuro	7	.	36	Safety and feasibility of BM-MSCs	Autologous	Bone marrow-derived mesenchymal stem cell	1) Improvements in the UPDRS scale; 2) H&Y and S&E score also improved; 3) PD medication reduced	.
Srivastava *et al*[53], 2011	Cerebral palsy	Neuro	30	5–25	12	To evaluate the feasibility, safety, therapeutic potential	Autologous	Bone marrow-derived mononuclear cells	1) Twopatient - fever; 2) Protocol - Safe; 3) mBI score - significantly improved; 4) MRC, Ashworth scale - significantly improved	.
Bhanot *et al*[54], 2011	Spinal cord injury	Neuro	13	18–51	12	Safety and efficacy of	Autologous	Bone marrow-derived mesenchymal stem cells	Only few patients shows improvement	1) 50% patients reported - a transient increase in spasticity; 2) In some - Fever, vomiting, general body ache, tingling/ burning girdle sensation
Sharma *et al*[55], 2012	Muscular dystrophy, spinal cord injury, cerebral palsy, and miscellaneous	Neuro	71	.	15	Outcomes of autologous stem cell therapy	Autologous	Bone marrow derived mononuclear cell	Shows improvements and also improves quality of life	No adverse event
Venkataramana *et al*[56], 2012	Parkinson's disease	Neuro	12	37–69	12	Safety, feasibility, and efficacy of allogenic	Allogenic	Bone marrow-derived mesenchymal stem cells	Subjective improvement observed reported clarity in speech, reduction in tremors, rigidity, and freezing attacks	.
Aggarwal *et al*[57], 2012	Posttraumatic facial nerve paralysis	Neuro	8	18-60	6	Safety profile and role	Autologous	Bone marrow-derived mononuclear cells	1) Significant improvement in ENoG amplitude; 2) statistically significant both for eye closure and for deviation of angle of mouth	.
Sharma *et al*[58], 2013	Autism	Neuro	32	3–33	26	Safety, efficacy, and clinical effects	Autologous	Bone marrow-derived mononuclear cells	1) Statistically significant in CGI-I score and total ISAA score; 2) Not significant in FIM score and Wee-FIM scores; 3) CGI-II scale - global improvement	1) Seizures after therapy controlled using antiepileptic drugs; 2) In some - headache, nausea, vomiting backache, pain at the site of injection, aspiration; 3) Increase in hyperactivity at minimal and persistent level but not interfere with the global clinical improvement
Sharma *et al*[59], 2013	Muscular dystrophy	Neuro	150	2.11–48	Mean 12 months	Safety and efficacy	Autologous	Bone marrow-derived mononuclear cells	Neurological improvements in trunk muscle strength, limb strength	No adverse events

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Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
Sharma *et al*[60], 2015	Cerebral palsy	Neuro	40	17 months to 22 yr	6	To evaluate the efficacy	Autologous	Bone Marrow-derived Mononuclear Cells	95% of patients showed improvements	1) The beneficial effect of MNC (stem cell instillation) on hip survival. Spinal headache, nausea, vomiting, pain at the site of injection, suffered diarrhoea
Rajput *et al*[61], 2015	Muscular Dystrophy, Duchenne	Neuro	11	.	36	Role in the cellular therapy	Allogenic	Human umbilical Cord Mesenchymal Stem Cells	1) Provide muscle stability; 2) Provide muscle strength in the distal and proximal lower limb; 3) Stability in muscle function of other body parts	.
Sharma *et al*[62], 2015	Traumatic Brain Injury	Neuro	14	12-65	6	To promote angiogenesis, axonal remodelling, neurogenesis and synaptogenesis	Autologous	Bone Marrow-derived Mononuclear Cells	1) Improvements - speech, trunk, upper limb activity, muscle tone, voluntary control, ambulation, gait pattern, posture, balance, psychological status, cognition, memory, Adls; 2) improved functional outcome and enhanced quality of life	Side effect noted - seizure
Chhabra *et al*[63], 2016	spinal cord injury, acute	Neuro	21	.	12	The safety and feasibility	Autologous	Bone Marrow-derived Stem Cells	1) No significant adverse effects; 2) No significant improvements; 3) procedure is safe and feasible; 4) No efficacy demonstrated	.
Sharma *et al*[64], 2018	intellectual disability	Neuro	58	4-45	.	Safety, efficacy and clinical effects of autologous bone marrow mononuclear cell	Autologous	Bone Marrow-derived Mononuclear Cells	1) Symptomatic improvements in the intervention the group showed after transplantation compared with rehabilitation	1) No adverse events were recorded; 2) In some - Fever, headache, vomiting
Sen *et al*[65], 2012	Femoral Head Osteonecrosis	Skeleto-muscular	40	.	.	Evaluates the early results of BMNC instillation into the femur head	Autologous	Bone Marrow-derived Mononuclear Cells	1) Statistically, significant differences in HHS and its domains (pain, function, deformity, and motion); 2) the beneficial effect of MNC on hip survival.	.
Gupta *et al*[66], 2013	critical limb ischemia	Skeleto-muscular	20	.	24	Safety and efficacy	Allogenic	Bone marrow derived mesenchymal stem cell	1) Improvements - rest pain scores in both the arms	SAE - death but not related to stem cells
Gupta *et al*[67], 2016	osteoarthritis	Skeleto-muscular	60	.	12	Safety and efficacy	Allogenic	Bone marrow mesenchymal stromal cells	1) Trend towards improvement in subjective parameters; 2) Not statistically significant with placebo	Knee pain and swelling
Gupta *et al*[68], 2017	Critical limb ischemia (CLI) due to Buerger's disease	Skeleto-muscular	36	38-42	24	Efficacy and safety of i.m. injection of allogenic BMMSC	Allogenic	Bone marrow-derived mesenchymal stem cells	Benefit in both the primary endpoints (rest pain relief and ulcer healing) and most secondary endpoints (improvement in total walking distance, ankle brachial pressure index, and quality of life).	1) Two deaths were reported; 2) administered allogeneic cells did not adversely alter the immunological and lymphocytic profile
Mulekar[69], 2003	Vitiligo	Skin	122	12-70	12	To evaluate the usefulness of epidermal cell transplantation	Autologous	Melanocyte-keratinocyte	1) Excellent repigmentation; 2) Recurrence also observed	.
Tegta *et al*[70], 2006	Vitiligo	Skin	20	.	3	Efficacy of Autologous melanocyte	Autologous	Melanocyte	210-250 cells/mm^2 required for satisfactory repigmentation	.

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Author name	Disease	Category	Total sample	Age (yr)	Follow up (months)	Purpose of study	Cell origin	Types of cells	Outcome	Side effects
Dash *et al*[71], 2009	Nonhealing Ulcers	Skin	24	.	3	Assess the efficacy and feasibility	Autologous	Bone marrow-derived mesenchymal stem cells and mononuclear cells	Significant improvement in pain-free walking distance and reduction in ulcer size	.
Mohanty *et al*[72], 2011	Vitiligo	Skin	14	.	.	To evaluate the efficacy of a novel surgical method	Autologous	Melanocyte	Greatly achieved repigmentation	.
Sahni *et al*[73], 2011	Vitiligo	Skin	25	.	.	Compare results of autologous melanocyte trnasplanation with saline and serum	Autologous	Melanocyte	1) Own serum shows better results than saline; 2) Statistically significant DLQI score	1) Mild adverse events; 2) Halo phenomenon and infection at site of injection; 3) Hyperpigmentation; 4) scarring at the donor site
Budania *et al*[74], 2012	Vitiligo	Skin	41	.	4	Comparison of techniques	Autologous	Melanocyte	1) Excellent re-pigmentation observed; 2) NCES better than SBEG	.
Singh *et al*[75], 2013	Vitiligo	Skin	30	.	4	Compare NCES and NCORSHFS	Autologous	Melanocyte	1) Excellent repigmentation; 2) reduction in DLQI score; 3) Both Safe and effective; 4) NCES is superior to NCORSHFS	None any adverse events reported
Vinay *et al*[76], 2015	Vitiligo	Skin	30	.	6	Clinical characteristics and treatment variables	Autologous	Melanocytes and hair follicle stem cells	1) Achieving optimum repigmentation; 2) a strong correlation between repigmentation at 24 week and number of melanocytes and HFSC transplanted; 3) absence of dermal inflammation	.
Donaparthi *et al*[77], 2016	Vitiligo	Skin	11	.	6	Comparative efficacy	Autologous	Melanocyte epidermal	1) >90% repigmentation; 2) safe and effective method; 3) Smaller patches repigmented better than larger ones	.
Kumar *et al*[78], 2018	Vitiligo	Skin	25	.	6	Clinical efficacy, viability and cell compositions of suspension	Autologous	Melanocyte-keratinocyte	1) More than 50% repigmentation; 2) More than 80% cell viability	Recipient site infection
Thakur *et al*[79], 2018	Vitiligo	Skin	40	.	6	Efficacy of transplantation of NCES and NDCS vs NCES	Autologous	Melanocyte-keratinocyte	1) Combination of NCES and NDCS resulted in excellent response than NCES alone	1) Mild hyper-pigmentation or hypopigmentation; 2) Post surgery perilesional halo developed
Sahoo *et al*[80], 2019	localized facial volume loss	Skin	10	15-24	6	Safety and efficacy	Autologous	Dermal mesenchymal stem cells	1) Improvement in dermal atrophy and lipoatrophy	1) Erythema, edema and mild to moderate pain at the site of injection
Gupta *et al*[81], 2019	Vitiligo	Skin	32	13-31	6	Compare the two techniques	Autologous	Melanocyte-keratinocyte	1) 49% repigmentation achieved; 2) No statistically significant between two techniques	Reported 1) Hyperpigmentation; 2) Scarring; 3) achromatic fissures; 4) reactivation of disease
Mrigpuri *et al*[82], 2019	Vitiligo	Skin	30	.	4	Efficacy of NCES	Autologous	Melanocyte-keratinocyte	1) Good repigmentation	.
Gunaabalaji *et al*[83], 2020	Vitiligo	Skin	20	.	.	Comparison of efficacy	Autologous	Melanocyte hair follicle cell suspension and noncultured epidermal cell and	1) ECS was better than HFCS in repigmentation of leukotrichia and vitiligo, although the difference was not statistically significant	.

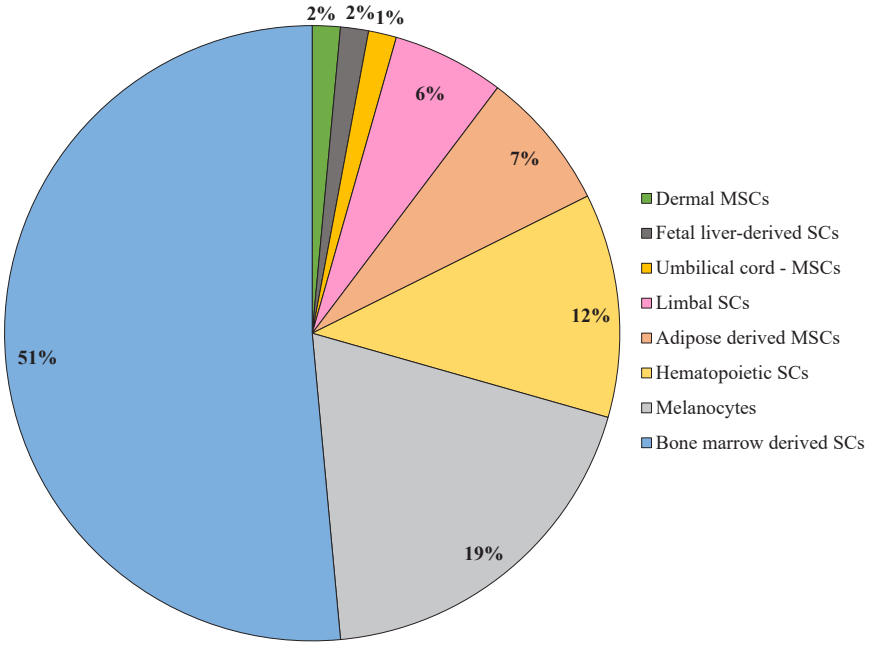

Fig. 2. Types of stem cells. MSCs, mesenchymal stem cells; SCs, stem cells.

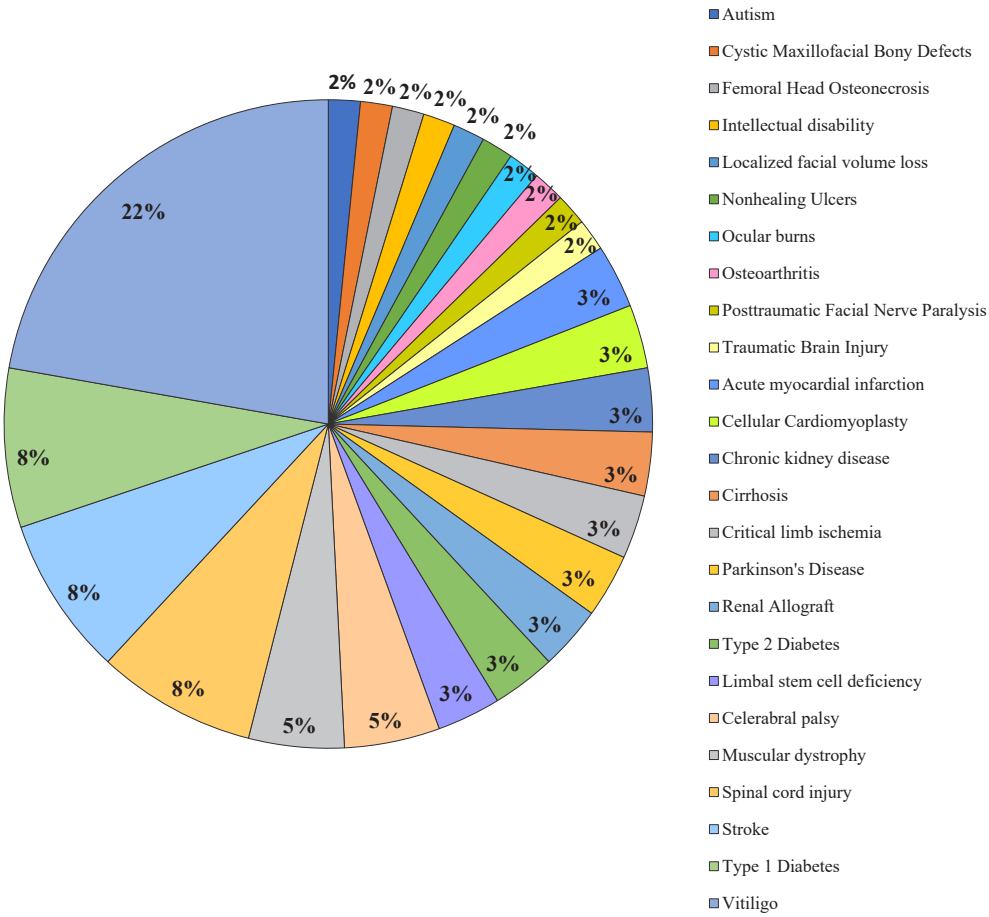

Fig. 3. Types of diseases treated using stem cells during clinical trials.

hyperpigmentation, halo phenomenon, infection at the site of injection, scarring at the donor site, achromatic fissures, and reactivation of vitiligo[73,80-82].

Diabetes: Among diabetic trials, type 1 as well as type 2 diabetes mellitus, the use of stem cells showed increased c-peptide level, reduced HbA1c (haemoglobin A1c or glycated haemoglobin) level, and reduced insulin requirement, but GAD (glutamic acid decarboxylase) antibodies showed mixed results[24-30]. Bone marrow-derived stem cell transplantation type 2 diabetes mellitus patients did not show major complications. However, minor complications like nausea, vomiting, and hematoma were reported[24]. The type 1 diabetes showed significant outcomes in terms of reduction in insulin dose and HbA1c levels, and increased c-peptide levels[24-27].

Dental diseases: In the dental field, the solitary trial outcome showed that the cystic maxillofacial defects were treated using autologous bone marrow-derived stem cells. After six months of followup, bone defect volume was reduced, tooth mobility was not observed, and faster wound healing was achieved[23].

Eye diseases: Studies on eye diseases showed that limbal stem cell deficiency could be treated with limbal stem cells, but after a followup period, it showed increased epithelialized, avascular, stable corneal surface and visual acuity[31-34]. Live limbal stem cells showed better results in allogeneic transplantation than cadaveric limbal stem cells[33].

Cardiovascular diseases: Stem cell therapy was used for stroke, myocardial infarction, cardiomyoplasty, cardiomyopathy, and heart failure[35-43]. For stroke, stem cell treatment showed improvement based on the Rankin scale and Barthel Index, which was statistically significant[38]. No significant outcomes were compared with the placebo; procedure-level safety was found, but serious adverse events were also noted[37]. The adverse events included ventricular tachycardia, pericardial effusion, chest pain dyspnoea, thrombosis, haematoma at the catheterization site, pain at the aspiration site, ventricular arrhythmia, and elevated serum creatinine level[39-41].

Kidney-related diseases: Stem cell therapy has been tried for kidney-related diseases too in India, and it includes chronic kidney disease renal transplants, and end-stage renal disease[44-47]. This therapy helped renal transplantation to minimise the chances of graft rejection through allogenic stem cell therapy, and it was also used for minimizing immunosuppression[47]. The side effects include acute rejection, CMV disease appearance, and donor-specific cytotoxic alloantibodies[45].

Liver disorders: The use of stem cell therapy for the treatment of liver cirrhosis has also been reported. Reports suggest its beneficial effect in improving liver function, improved clinical and biochemical parameters, and provided support to delay liver transplantation[48,49].

Neurological diseases: Stem cell therapy has been used for neurological diseases such as facial nerve paralysis, spinal cord injury, autism, cerebral palsy, traumatic brain injury, intellectual disability, Parkinson's disease, muscular dystrophy, and the outcomes showed mixed results[50-64].

For Autism, stem cell therapy showed a significant difference between CGI (clinical global impression) and ISAA (Indian Scale for Assessment of Autism) scores, but not for FIM (Functional Independence Measure) and Wee-FIM scores[58]. Significant improvement in the mBI (modified Barthel Index) score, MRC (Muscle Power Scale), and Ashworth scale was found for cerebral palsy[49,53]. Symptomatic improvement was found for intellectual disability[64]. Neurological improvements in limb strength and stability in muscle function of the body parts were shown in muscular dystrophy after stem cell treatment[55,58,61].

The use of stem cells for Parkinson's disease showed improvement in the UPDRS (Unified Parkinson's Disease Rating Scale) scale, H&Y (Hoehn and Yahr), and S&E (Schwab and England) scores that helped in the reduction its medication, tremors, rigidity, and freezing attacks, improved clarity in speech and subjective improvement[52,56]. In spinal cord injury, stem cell therapy protocol was safe, but at the efficacy level, only a few patients showed improvement; there was no correlation between injury and improvements[50,51,54,63]. In traumatic brain injury, stem cell therapy helped in the improvement of speech, trunk, upper limb activity, muscle tone, voluntary control, posture balance, and psychological status[62]. No serious adverse were noted for neurological disorders, but seizures, headache, fever, nausea, vomiting, backache, pain at the site of injection, diarrhoea, spasticity, and tingling sensation were reported as minor adverse events[50,54,58,60,64].

Musculoskeletal disorders: In critical limb ischemia, stem cell therapy helped relieve pain and heal ulcers[65-68]. Serious adverse events were reported, resulting in two deaths, during the use of allogeneic stem cell therapy[68]. SCT also shows statistically significant results in HHS (Harris Hip Scale/Score) in hip survival, and subjective improvements were observed in osteonecrosis[65].

Discussion

The findings of this study indicated that India is taking great interest in the benefits of melanocytes (extracted from hair follicle cell suspension) for treating vitiligo. Injection of hair follicle cell suspension containing melanocytes and keratinocytes was found to be useful in managing vitiligo[76,77,79]. Although there was a small population size in some studies, there was a trend towards an improvement in symptoms and disease outcomes in individuals who had received BM-MSC compared with controls[56,57,66]. Two deaths were also reported as serious adverse events when using allogeneic stem cell therapy[68]. On the other hand, statistically significant results were also shown that helped in hip survival, with subjective improvements in osteonecrosis[65].

The findings from this systematic review address important gaps in stem cell therapeutics for non-malignant diseases in India. Study indicates that stem cell therapy could be safe for treating non-malignant, non-haematological diseases, but the smaller number of participants in these clinical trials is a cause of concern. This study highlights important factors that are expected to shape the future of stem cell research and therapy in India. It may include standardization, regulations, basic research and clinical trials support, trained human resources, and infrastructure[84]. Maintaining the gold standard for stem cell therapy requires randomized clinical trials with a large sample size to study success, failures, adverse effects, *etc*[8,85,86].

Future trials would need to incorporate more robust outcome measures that are patient-centered, and RCTs should be done instead of cohort studies and clinical trials with a small number[35,57,59,62]. Studies on assessing potential barriers and enablers to both patient participation and physician involvement in early-phase clinical trials are limited. This is an important knowledge gap that needs to be addressed for safety outcomes in stem cell therapy and research. This study also revealed that government hospitals published more studies than non-government hospitals.

India is aware of the potential of stem cell science, and the key question is, to what extent is India sensitive to the emerging challenges or barriers to stem cell therapeutic commercialization, its clinical implications, and its position in the global scenario? The other question arises: What should be done about desperate patients paying out of pocket for unproven treatments? The factors that affect such clinical practice and research in the public arena need to be identified. There is a need to synthesize more knowledge in stem cell research and therapeutics.

The study limitations include inability to use meta-analysis because of the qualitative outcome of all studies, the smaller number of clinical trials, the low sample size in some disease categories, the significant diversity of diseases, or study heterogeneity.

Overall, we need more clinical studies and the stakeholders' perspectives on stem cell therapy to shift from experimental interventions into routine clinical practice. Despite the potential of stem cell and regenerative medicine research for safety and efficacious outcomes, there is potential for stem cell treatment in non-haematological diseases. However, well-controlled, randomized, large-scale trials are required to establish safety and efficacy. Clinical trials need to be reviewed by IC-SCR, and prospective interventional trials need to be registered with CTRI. Our findings are a call to action to stakeholders (clinicians, industries, policymakers, researchers, etc.) to identify approaches for stem cell therapy that are best suited for treating non-malignant diseases and non-haematological and accordingly can plan to invest resources for further research and development for a particular disease.

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