

From: joseph wang
To:

Date: Friday, February 06, 2015 05:10PM
Subject: Opinion on the consultation document Regulation of Private Healthcare Facilities

Here is the opinion from

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on the Consultation Document Regulation of Private Healthcare Facilities

Below are the points I wish to consider.

Annex B(1) page 103 3(b)
Removal of tissue and/or fluid of a total volume of 500ml or above [except suprapubic tap]

Annex B(1) page 103 3(e)
Insertion of any prosthesis (including tissue filler)[except prosthesis in ENT cavity, dental prosthesis and implants, extra-ocular prosthesis and implants, intrauterine or vaginal prosthesis, bulking agents of urethra, prostatic urethral stent, urethral sling, testicular prosthesis]

p.104(j)
Transplant of any cell, tissue and organ(including autograft, allograft and processed tissue or blood products⁴) or skin flap(including face lift)[except small skin graft less than 3 cm in any dimension, conjunctival autograft and transplant procedures which primarily involve dental-alveolar region]

p.105 7.(h) Tumescant anaesthesia

We are recommending changes to all 4 of them.

p.105 7(h) is regarding tumescent technique as high risk. It is undisputable in every part of the world that tumescent liposuction is so safe that it is well accepted as an office-based procedure. It is not regulated at all since it has no major injury or death. Liposuction has a higher mortality if it is hospital-based. There is a study of 4380 patients which confirm the safeness of tumescent technique as an office-based procedure. (reference 1,2,3,4)

500ml of volume mentioned in Annex B(1) page 103 3(b) does not have any support. Its calculation does not take the weight into account. One way to do the calculation is to make use of the tumescent formula. In a patient of weight 55kg, the maximum dose of lignocaine is $55 \times 55 = 3025\text{mg}$ (reference 4). If tumescent fluid is 0.8% lignocaine, $3025/400 = 7.6$ bag of 500ml fluid or 3.8 litre of fluid. The volume of lipoaspirate is about 1/3 of tumescent fluid = 1.26 litre. So a patient of 55kg can give 1.26 litre of lipoaspirate in a safe way. The maximum volume calculated by every kg is $1.26\text{L}/55\text{kg} = 23\text{ml/kg}$

Page 103 3(e) mentioned the insertion of any prothesis as high risk. On the contrary, it is generally accepted in the rest of the world that the placement of nasal and chin implant under local anaesthetics has low risk.

In 2010, there was a mortality related to the operation of breast implant placement, the operation was done under local anaesthesia with lignocaine 0.5%. We suggested the use of 0.5% lignocaine in breast augmentation has high risk. On the other hand, the use of Tumescent technique in breast augmentation has low risk.

p.104(j) should be amended that autologous fat grafting is generally regarded as low risk in the globe. Other examples of low risk transplants includes rhinoplasty by placement of auricular cartilage graft under local anaesthetics.

In contrary to p104(j) Autologous or allogenic stem cell transplant in subcutaneous, intramuscular or intravenous route has low risk(reference 4,5,6,7,8,9,10,11,12,13). Administration of stem cells is regarded as low risk if the cells are properly prepared. Indeed, the preparation of the stem cells are already proposed to be regulated by another document (The Report of the Working Group on Regulation of Premises Processing Health Products for Advanced Therapies) On the other hand, there are other ways of administering the stem cells which could be classified as high risk. Examples are intraspinal(14), organ selective delivery by intraarterial and transendocardial route(12). The risk is associated with the invasive nature of the procedure and not with the use of stem cells.

REFERENCES

(1)Dermatology. 2011;222(3):278-81. doi: 10.1159/000327375. Epub 2011 May 24.

Safety of tumescent liposuction under local anesthesia in a series of 4,380 patients.

[Boeni R1.](#)

Abstract

BACKGROUND:

Liposuction is increasingly performed under local anesthesia and in an outpatient setting. The term 'tumescent liposuction' has been used in the literature in patients receiving other forms of anesthesia as well, hence the confusion regarding the safety profile of liposuction performed under local anesthesia alone.

OBJECTIVE:

To analyze the safety of tumescent liposuction performed under local anesthesia in a larger group of patients.

METHODS:

Between 2003 and 2010, 4,380 consecutive patients underwent tumescent liposuction by the same surgeon. The occurrence of complications was recorded in detail.

RESULTS:

There were no serious complications requiring hospitalization. There were no injuries, no nerve damage or permanent lymphedema, no deep venous thrombosis or seroma. Seven patients needed closer follow-up due to large hematoma (n = 3; no drainage needed), allergic drug reaction to doxycycline (n = 2), erysipelas (n = 1) and generalized edema (n = 1).

CONCLUSIONS:

Tumescent liposuction under local anesthesia is a safe method, providing it is performed by an experienced surgeon and the guidelines of care for liposuction are strictly followed.

(2)Dermatol Surg. 2002 Aug;28(8):710-2; discussion 713.

Office surgical incidents: 19 months of Florida data.

[Coldiron B1.](#)

Abstract

BACKGROUND:

In 1999-2000 a series of sensational articles were published in the lay media emphasizing the hazards of office surgery. Since then 31 state medical boards or legislatures have, or are in the process of drafting regulations restricting office procedures.

OBJECTIVE:

To determine the nature, incidence and scope of injuries and deaths resulting from office procedures.

METHODS:

Mandatory reporting by physicians to a neutral central agency of all office surgical incidents that resulted in death, serious injury, or transfer to a hospital in the State of Florida from February 2000 to September 2001. Telephone and Internet follow up to determine reporting physician board status, hospital privilege status, and office accreditation status.

RESULTS:

In 19 months there were 43 procedure related-complications and eight deaths. Liposuction under general anesthesia was the single most common cause of incidents and deaths. There were no injuries or deaths reported with liposuction with tumescent anesthesia. 50% of offices reporting incidents or deaths were accredited by an independent accrediting agency. There were no incidents or deaths reported due to the anesthesia when using conscious sedation anesthesia, or intramuscular sedation or analgesia 98% of physicians reporting incidents or deaths had hospital privileges and were board certified. Anesthesiologists or nurse anesthetists provided all general anesthesia, and deep sedation. There were no physicians performing procedures outside their scope of specialty training.

CONCLUSION:

Liposuction under general anesthesia deserves closer scrutiny. Office accreditation is not associated with fewer patient injuries and deaths. Restrictions on tumescent liposuction, conscious sedation and intramuscular sedation and analgesia would not yield any saved lives or fewer injuries since these modes of anesthesia resulted in no injuries or deaths. Board certification

and hospital privilege requirements for office practice would have very little effect since the vast majority of reporting physicians already had these credentials. These data do not show an emergent hazard to patients from office surgery. This data strongly contradicts the lay media portrayal of the dangers of office procedures. Mandatory reporting of office incidents should be strongly supported, and this data should be available for analysis after protecting patient confidentiality.

(3)[Dermatol Surg.](#) 2002 Nov;28(11):971-8.

The safety of liposuction: results of a national survey.

[Housman TS](#)¹, [Lawrence N](#), [Mellen BG](#), [George MN](#), [Filippo JS](#), [Cervený KA](#), [DeMarco M](#), [Feldman SR](#), [Fleischer AB](#).

Abstract

BACKGROUND:

Liposuction procedures are increasing in frequency and may be performed in hospitals, ambulatory surgery centers, or physician offices. Deaths associated with liposuction and previous surveys of liposuction safety have raised concern about the safety of office-based surgery.

OBJECTIVE:

To determine the safety of office-based, tumescent liposuction among dermatologic surgeons.

METHODS:

A survey mailed out to dermatologic surgeons in August 2001 requested retrospective information regarding the number of patients undergoing liposuction, the setting in which the procedures were performed, and the complications that occurred during the 7-year period from 1994 to 2000. A detailed complication record was requested for each serious adverse event or death reported. Surveys were mailed to 517 worldwide members of the American Society for Dermatologic Surgery (ASDS) listed as performing liposuction; 505 had adequate contact information. The main outcome measure

was the rate of serious adverse events (SAEs) or deaths per 1000 liposuction procedures for each service setting and for each level of conscious sedation.

RESULTS:

The overall response rate was 89% (450/505), and of these, 78% (349/450) perform liposuction. A total of 267 dermatologic surgeons completed the survey; 261 provided data on 66,570 liposuction procedures. No deaths were reported. The overall serious adverse event rate was 0.68 per 1000 cases. The SAE rates were higher for hospitals and ambulatory surgery centers than for nonaccredited office settings. SAE rates were also higher for tumescent liposuction combined with intravenous or intramuscular sedation than combined with oral or no sedation.

CONCLUSION:

Office-based tumescent liposuction performed by dermatologic surgeons is safe, with a lower complication rate than hospital-based procedures. Future legislation should recognize the proven safety of this procedure as performed by dermatologic surgeons in their offices.

(4)Dermatol Surg. 1996 Nov;22(11):921-7.

Tumescent anesthesia with a lidocaine dose of 55 mg/kg is safe for liposuction.

[Ostad A1](#), [Kageyama N](#), [Moy RL](#).

Abstract

BACKGROUND:

The safe upper limit of lidocaine dosage in tumescent anesthesia for liposuction has been reported to be 35 mg/kg.

OBJECTIVE:

This study was undertaken to: 1) evaluate the safety of tumescent anesthesia in liposuction when lidocaine doses greater than 35 mg/kg are required, 2)

determine the time interval when the peak plasma lidocaine level occurs following administration of tumescent anesthesia, and 3) assess if the safety of large volume tumescent anesthesia is due to significant lidocaine removed by liposuction.

METHODS:

Sixty patients who underwent liposuction with a mean lidocaine dose of 57 mg/kg were prospectively evaluated for development of any signs or symptoms of lidocaine toxicity by multiple interviews over a 24-hour period. In addition, another 10 patients who received a mean lidocaine dose of 55 mg/kg had serial plasma lidocaine level measurements over a 24-hour period following liposuction. The lidocaine level of the aspirate was also measured to assess any significant lidocaine removed by liposuction.

RESULTS:

No evidence of lidocaine toxicity was found based on subjective evaluation of 60 patients as well as determined by plasma sampling of 10 patients. The peak plasma lidocaine concentration occurred at approximately 4 or 8 hours after infusion of tumescent anesthesia. The 24-hour plasma lidocaine level suggests that residual lidocaine is present in the subcutaneous tissue allowing for postoperative analgesia beyond this time. A negligible amount of lidocaine was removed by liposuction as determined by the lidocaine level of the aspirate.

CONCLUSION:

This study suggests that tumescent anesthesia with a total lidocaine dose of up to 55 mg/kg is safe for use in liposuction.

(5)Cell Transplant. 2014;23(10):1293-303. doi: 10.3727/096368913X667727. Epub 2013 May 22.

Effects and safety of allogenic mesenchymal stem cell intravenous infusion in active ankylosing spondylitis patients who failed NSAIDs: a 20-week clinical trial.

[Wang P](#)¹, [Li Y](#), [Huang L](#), [Yang J](#), [Yang R](#), [Deng W](#), [Liang B](#), [Dai L](#), [Meng Q](#), [Gao L](#), [Chen X](#), [Shen J](#), [Tang Y](#), [Zhang X](#), [Hou J](#), [Ye J](#), [Chen K](#), [Cai Z](#), [Wu Y](#),

[Shen H.](#)

Abstract

Our objective was to evaluate the feasibility, safety, and efficacy of intravenous (IV) infusion of allogenic mesenchymal stem cells (MSCs) in ankylosing spondylitis (AS) patients who are refractory to or cannot tolerate the side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). AS patients enrolled in this study received four IV infusions of MSCs on days 0, 7, 14, and 21. The percentage of ASAS20 responders (the primary endpoint) at the fourth week and the mean ASAS20 response duration (the secondary endpoint) were used to assess treatment response to MSC infusion and duration of the therapeutic effects. Ankylosing Spondylitis Disease Activity Score Containing C-reactive Protein (ASDAS-CRP) and other preestablished evaluation indices were also adopted to evaluate the clinical effects. Magnetic resonance imaging (MRI) was performed to detect changes of bone marrow edema in the spine. The safety of this treatment was also evaluated. Thirty-one patients were included, and the percentage of ASAS20 responders reached 77.4% at the fourth week, and the mean ASAS20 response duration was 7.1 weeks. The mean ASDAS-CRP score decreased from 3.6 ± 0.6 to 2.4 ± 0.5 at the fourth week and then increased to 3.2 ± 0.8 at the 20th week. The average total inflammation extent (TIE) detected by MRI decreased from 533,482.5 at baseline to 480,692.3 at the fourth week ($p > 0.05$) and 400,547.2 at the 20th week ($p < 0.05$). No adverse effects were noted. IV infusion of MSCs is a feasible, safe, and promising treatment for patients with AS.

(6)Phase 1 trial of autologous bone marrow mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis

[Mohamadnejad, M.^a, Alimoghaddam, K.^b, Mohyeddin-Bonab, M.^b, Bagheri, M.^a, Bashtar, M.^b, Ghanaati, H.^a, Baharvand, H.^c, Ghavamzadeh, A.^b, Malekzadeh, R.](#)

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Abstract

Background: The standard treatment for decompensated liver cirrhosis is liver transplantation. However, it has several limitations. Recent animal studies suggest that bone marrow stem cell transplantation can lead to regression of liver fibrosis. The objective of this study was to determine the safety and feasibility of autologous bone marrow-mesenchymal stem cell transplantation in patients with decompensated liver cirrhosis. Methods: In this phase 1 trial, four patients with decompensated liver cirrhosis were included. Their bone marrow was aspirated, mesenchymal stem cells were cultured, and a mean 31.73×10^6 mesenchymal stem cells were infused through a peripheral vein. Primary outcomes were evaluating the safety and feasibility of the work. Secondary outcomes were evaluating changes in the model for end-stage liver disease score, and the quality of life of the patients. Results: There were no side-effects in the patients during follow-up. The model for end-stage liver disease scores of patients 1, and 4 improved by four and three points, respectively by the end of follow-up. Furthermore, the quality of life of all four patients improved by the end of follow-up. Using SF-36 questionnaire, the mean physical component scale increased from 31.44 to 65.19, and the mean mental component scale increased from 36.32 to 65.55. Conclusion: Mesenchymal stem cell transplantation seems to be feasible and safe in the treatment of decompensated liver cirrhosis.

[\(7\)Ann Rheum Dis.](#) 2010 Aug;69(8):1423-9. doi: 10.1136/ard.2009.123463.

Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study.

[Liang J](#)¹, [Zhang H](#), [Hua B](#), [Wang H](#), [Lu L](#), [Shi S](#), [Hou Y](#), [Zeng X](#), [Gilkeson GS](#), [Sun L](#).

Ann Rheum Dis. 2011 Jan;70(1):237.

Abstract

OBJECTIVE:

To determine the safety and efficacy of allogeneic mesenchymal stem cell transplantation (MSCT) in refractory systemic lupus erythematosus (SLE).

METHODS:

A total of 15 patients with persistently active SLE underwent MSCT. Outcome was evaluated by changes in the SLE disease activity index (SLEDAI), serological features (anti-nuclear antibodies and anti-double-stranded DNA (anti-dsDNA)), renal function and percentage of peripheral blood regulatory T cells.

RESULTS:

From 11 March 2007 to 4 November 2008, 15 patients with persistently active SLE were enrolled and underwent MSCT. The mean follow-up period was 17.2 \pm 9.5 months. A total of 13 patients have been followed for more than 12 months. All patients clinically improved following treatment with mesenchymal stem cells with a marked decrease in the SLEDAI score and 24 h proteinuria. At 12-month follow-up, SLEDAI scores decreased from 12.2 \pm 3.3 to 3.2 \pm 2.8 and proteinuria decreased from 2505.0 \pm 1323.9 to 858.0 \pm 800.7 mg/24 h (all $p < 0.05$, by paired t test, $n = 12$). At 1-year follow-up in 13 patients, 2 had a relapse of proteinuria, while the other 11 continue to have decreased disease activity on minimal treatment. Anti-dsDNA levels decreased. Improvement in glomerular filtration rate was noted in two patients in which formal testing was performed. Non-renal-related manifestations also improved significantly. No serious adverse events were reported.

CONCLUSION:

Allogeneic MSCT in patients with refractory lupus resulted in amelioration of disease activity, improvement in serological markers and stabilisation of renal function. MSCT appears beneficial in treatment of patients with SLE refractory to conventional treatment options.

Ann Clin Transl Neurol. 2014 Nov;1(11):900-8. doi: 10.1002/acn3.134. Epub 2014 Oct 22.

(8)Analysis of graft survival in a trial of stem cell transplant in ALS.

[Tadesse T](#)¹, [Gearing M](#)², [Senitzer D](#)³, [Saxe D](#)⁴, [Brat DJ](#)⁴, [Bray R](#)⁴, [Gebel H](#)⁴, [Hill C](#)⁵, [Boulis N](#)⁶, [Riley J](#)⁶, [Feldman E](#)⁷, [Johe K](#)⁸, [Hazel T](#)⁸, [Polak M](#)¹, [Bordeau J](#)¹, [Federici T](#)⁴, [Glass JD](#)².

Abstract

OBJECTIVE:

The first US Food and Drug Administration-approved clinical trial to treat amyotrophic lateral sclerosis (ALS) with neural stem cell-based therapy is in progress. The goal of the current study was to identify and assess the survival of human spinal cord-derived neural stem cells (HSSCs) transplanted into the spinal cord in patients with ALS.

METHODS:

Spinal cords transplanted with HSSCs were examined from six autopsy cases. Homogenized tissues were interrogated for the presence of donor versus recipient DNA using real-time PCR methods (qPCR). Fluorescence in situ hybridization (FISH) was performed using DNA probes for XY chromosomes to identify male donor HSSCs in one female case, and immunohistochemistry (IHC) was used to characterize the identified donor cells.

RESULTS:

Genomic DNA from donor HSSCs was identified in all cases, comprising 0.67-5.4% of total tissue DNA in patients surviving 196 to 921 days after transplantation. In the one female patient a "nest" of cells identified on H&E staining were XY-positive by FISH, confirming donor origin. A subset of XY-positive cells labeled for the neuronal marker NeuN and stem cell marker SOX2.

INTERPRETATION:

This is the first study to identify human neural stem cells transplanted into a human spinal cord. Transplanted HSSCs survived up to 2.5 years posttransplant. Some cells differentiated into neurons, while others maintained their stem cell phenotype. This work is a proof of concept of the survival and differentiation of human stems cell transplanted into the spinal cord of ALS patients.

(9)Arch Neurol. 2010 Oct;67(10):1187-94. doi: 10.1001/archneurol.2010.248.

Safety and immunological effects of mesenchymal stem cell transplantation in patients with multiple sclerosis and amyotrophic lateral sclerosis.

[Karussis D](#)¹, [Karageorgiou C](#), [Vaknin-Dembinsky A](#), [Gowda-Kurkalli B](#), [Gomori JM](#), [Kassis I](#), [Bulte JW](#), [Petrou P](#), [Ben-Hur T](#), [Abramsky O](#), [Slavin S](#).

Abstract

OBJECTIVE:

To evaluate the feasibility, safety, and immunological effects of intrathecal and intravenous administration of autologous mesenchymal stem cells (MSCs) (also called mesenchymal stromal cells) in patients with multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS).

DESIGN:

A phase 1/2 open-safety clinical trial. Patients Fifteen patients with MS (mean [SD] Expanded Disability Status Scale [EDSS] score, 6.7 [1.0]) and 19 with ALS (mean [SD] Amyotrophic Lateral Sclerosis Functional Rating Scale [ALSFERS] score, 20.8 [8.0]) were enrolled. Intervention After culture, a mean (SD) of $63.2 \times 10(6)$ ($2.5 \times 10(6)$) MSCs was injected intrathecally (n = 34) and intravenously (n = 14). In 9 cases, MSCs were magnetically labeled with the superparamagnetic iron oxide ferumoxides (Feridex).

MAIN OUTCOME MEASURES:

The main outcome measure was the recording of side effects. Follow-up (≤ 25 months) included adverse events evaluation, neurological disability assessment by means of the EDSS, magnetic resonance imaging to exclude unexpected pathologies and track the labeled stem cells, and immunological tests to assess the short-term immunomodulatory effects of MSC transplantation.

RESULTS:

Twenty-one patients had injection-related adverse effects consisting of transient fever, and 15 reported headache. No major adverse effects were reported during follow-up. The mean ALSFERS score remained stable during the first 6 months of observation, whereas the mean (SD) EDSS score improved from 6.7

(1.0) to 5.9 (1.6). Magnetic resonance imaging visualized the MSCs in the occipital horns of the ventricles, indicating the possible migration of ferumoxides-labeled cells in the meninges, subarachnoid space, and spinal cord. Immunological analysis revealed an increase in the proportion of CD4(+) CD25(+) regulatory T cells, a decrease in the proliferative responses of lymphocytes, and the expression of CD40(+), CD83(+), CD86(+), and HLA-DR on myeloid dendritic cells at 24 hours after MSC transplantation.

CONCLUSION:

Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects. Trial Registration clinicaltrials.gov Identifier: [NCT00781872](https://clinicaltrials.gov/ct2/show/study/NCT00781872).

(10)[Biol Blood Marrow Transplant](#). 2014 Dec 30. pii: S1083-8791(14)01469-4. doi: 10.1016/j.bbmt.2014.12.025. []

Single and Multiple Dose MultiStem (Multipotent Adult Progenitor Cell) Therapy Prophylaxis of Acute Graft-versus-Host Disease in Myeloablative Allogeneic Hematopoietic Cell Transplantation: A Phase 1 Trial.

[Maziarz RT](#)¹, [Devos T](#)², [Bachier CR](#)³, [Goldstein SC](#)⁴, [Leis JF](#)⁵, [Devine SM](#)⁶, [Meyers G](#)⁷, [Gajewski JL](#)⁷, [Maertens J](#)², [Deans RJ](#)⁸, [Van't Hof W](#)⁸, [Lazarus HM](#)⁹.

Abstract

We conducted a multicenter, phase 1 dose escalation study evaluating the safety of the allogeneic multipotent adult progenitor cell (MAPC, MultiStem, Athersys, Inc., Cleveland, OH) stromal product administered as an adjunct therapy to 36 patients after myeloablative allogeneic hematopoietic cell transplantation (HCT). Patients received increasing doses of MAPC (1, 5, or 10 million cells per kilogram recipient weight) as a single i.v. dose on day +2 after HCT (n = 18), or once weekly for up to 5 doses (1 or 5 million cells per kilogram; n = 18). Infusional and regimen-related toxicities were assessed for 30 days after the last MAPC dose. Of 36 allogeneic HCT donors (17 related

and 19 unrelated), 35 were 6/6 HLA matched. MAPC infusions were well tolerated without associated infusional toxicity, graft failure, or increased incidence of infection. Median times to neutrophil (n = 36) and platelet (n = 31) engraftment were 15 (range, 11 to 25) and 16 (range, 11 to 41) days, respectively. The overall cumulative incidences of grades II to IV and III and IV acute graft-versus-host disease (GVHD) at day 100 were 37% and 14%, respectively (n = 36). In the group that received the highest single MAPC dose (10 million cells/kg), day 100 incidence of grade II to IV GVHD was 11.1% (1 of 9) with no observed cases of grade III and IV GVHD. We found no evidence for MHC class II allogeneic antibody induction, although some patients showed an increase in serum anticlass I titers compared with baseline. MAPC contribution to blood chimerism was negligible. These phase I data support the safety of stromal stem cell therapy and suggest that MAPC should be tested prospectively as a novel therapeutic option for GVHD prophylaxis after HCT.

[\(11\)J Transl Med.](#) 2013 Jun 10;11:143. doi: 10.1186/1479-5876-11-143.

A double blind randomized placebo controlled phase I/II study assessing the safety and efficacy of allogeneic bone marrow derived mesenchymal stem cell in critical limb ischemia.

[Gupta PK](#)¹, [Chullikana A](#), [Parakh R](#), [Desai S](#), [Das A](#), [Gottipamula S](#), [Krishnamurthy S](#), [Anthony N](#), [Pherwani A](#), [Majumdar AS](#).

Abstract

BACKGROUND:

Peripheral vascular disease of the lower extremities comprises a clinical spectrum that extends from no symptoms to presentation with critical limb ischemia (CLI). Bone marrow derived Mesenchymal Stem Cells (BM- MSCs) may ameliorate the consequences of CLI due to their combinatorial potential for inducing angiogenesis and immunomodulatory environment in situ. The primary objective was to determine the safety of BM- MSCs in patients with CLI.

METHODS:

Prospective, double blind randomized placebo controlled multi-center study was

conducted in patients with established CLI as per Rutherford classification in category II-4, III-5, or III-6 with infra-inguinal arterial occlusive disease and were not suitable for or had failed revascularization treatment. The primary end point was incidence of treatment - related adverse events (AE). Exploratory efficacy end points were improvement in rest pain, increase in Ankle Brachial Pressure Index (ABPI), ankle pressure, healing of ulcers, and amputation rates. Twenty patients (BM-MSC: Placebo = 1:1) were administered with allogeneic BM-MSCs at a dose of 2 million cells/kg or placebo (PlasmaLyte A) at the gastrocnemius muscle of the ischemic limb.

RESULTS:

Improvement was observed in the rest pain scores in both the arms. Significant increase in ABPI and ankle pressure was seen in BM-MSC arm compared to the placebo group. Incidence of AEs in the BM-MSC arm was 13 vs. 45 in the placebo arm where as serious adverse events (SAE) were similar in both the arms (5 in BM-MSC and 4 in the placebo group). SAEs resulted in death, infected gangrene, amputations in these patients. It was observed that the SAEs were related to disease progression and not related to stem cells.

CONCLUSION:

BM-MSCs are safe when injected IM at a dose of 2 million cells/kg body weight. Few efficacy parameters such as ABPI and ankle pressure showed positive trend warranting further studies.

TRIAL REGISTRATION:

NIH website (<http://www.clinicaltrials.gov/ct2/show/NCT00883870>).

Comment in

[Mesenchymal stromal cells for the treatment of critical limb ischemia: context and perspective.](#) [Stem Cell Res Ther. 2013]

(12)JAMA. 2012 Dec 12;308(22):2369-79.

Comparison of allogeneic vs autologous bone marrow–derived mesenchymal stem cells delivered by transendocardial injection in patients with ischemic cardiomyopathy: the POSEIDON randomized trial.

[Hare JM](#)¹, [Fishman JE](#), [Gerstenblith G](#), [DiFede Velazquez DL](#), [Zambrano JP](#), [Suncion VY](#), [Tracy M](#), [Ghersin E](#), [Johnston PV](#), [Brinker JA](#), [Breton E](#), [Davis-Sproul J](#), [Schulman IH](#), [Byrnes J](#), [Mendizabal AM](#), [Lowery MH](#), [Rouy D](#), [Altman P](#), [Wong Po Foo C](#), [Ruiz P](#), [Amador A](#), [Da Silva J](#), [McNiece IK](#), [Heldman AW](#), [George R](#), [Lardo A](#).

Erratum in

JAMA. 2013 Aug 21;310(7):750. George, Richard [added]; Lardo, Albert [added].

Abstract

CONTEXT:

Mesenchymal stem cells (MSCs) are under evaluation as a therapy for ischemic cardiomyopathy (ICM). Both autologous and allogeneic MSC therapies are possible; however, their safety and efficacy have not been compared.

OBJECTIVE:

To test whether allogeneic MSCs are as safe and effective as autologous MSCs in patients with left ventricular (LV) dysfunction due to ICM.

DESIGN, SETTING, AND PATIENTS:

A phase 1/2 randomized comparison (POSEIDON study) in a US tertiary-care referral hospital of allogeneic and autologous MSCs in 30 patients with LV dysfunction due to ICM between April 2, 2010, and September 14, 2011, with 13-month follow-up.

INTERVENTION:

Twenty million, 100 million, or 200 million cells (5 patients in each cell type per dose level) were delivered by transendocardial stem cell injection into 10 LV sites.

MAIN OUTCOME MEASURES:

Thirty-day postcatheterization incidence of predefined treatment-emergent serious adverse events (SAEs). Efficacy assessments included 6-minute walk test, exercise peak VO₂, Minnesota Living with Heart Failure Questionnaire (MLHFQ), New York Heart Association class, LV volumes, ejection fraction (EF), early enhancement defect (EED; infarct size), and sphericity index.

RESULTS:

Within 30 days, 1 patient in each group (treatment-emergent SAE rate, 6.7%) was hospitalized for heart failure, less than the prespecified stopping event rate of 25%. The 1-year incidence of SAEs was 33.3% (n = 5) in the allogeneic group and 53.3% (n = 8) in the autologous group (P = .46). At 1 year, there were no ventricular arrhythmia SAEs observed among allogeneic recipients compared with 4 patients (26.7%) in the autologous group (P = .10). Relative to baseline, autologous but not allogeneic MSC therapy was associated with an improvement in the 6-minute walk test and the MLHFQ score, but neither improved exercise VO₂ max. Allogeneic and autologous MSCs reduced mean EED by -33.21% (95% CI, -43.61% to -22.81%; P < .001) and sphericity index but did not increase EF. Allogeneic MSCs reduced LV end-diastolic volumes. Low-dose concentration MSCs (20 million cells) produced greatest reductions in LV volumes and increased EF. Allogeneic MSCs did not stimulate significant donor-specific alloimmune reactions.

CONCLUSIONS:

In this early-stage study of patients with ICM, transendocardial injection of allogeneic and autologous MSCs without a placebo control were both associated with low rates of treatment-emergent SAEs, including immunologic reactions. In aggregate, MSC injection favorably affected patient functional capacity, quality of life, and ventricular remodeling.

Send to:

(13)Cochrane Database Syst Rev. 2014 Apr 29;4:CD007888. doi:
10.1002/14651858.CD007888.pub2.

Stem cell therapy for chronic ischaemic heart disease and congestive heart failure.

[Fisher SA](#)1, [Brunskill SJ](#), [Doree C](#), [Mathur A](#), [Taggart DP](#), [Martin-Rendon E](#).

Author information

Abstract

BACKGROUND:

A promising approach to the treatment of chronic ischaemic heart disease (IHD) and heart failure is the use of stem cells. The last decade has seen a plethora of randomised controlled trials (RCTs) developed worldwide which have generated conflicting results.

OBJECTIVES:

The critical evaluation of clinical evidence on the safety and efficacy of autologous adult bone marrow-derived stem cells (BMSC) as a treatment for chronic ischaemic heart disease (IHD) and heart failure.

SEARCH METHODS:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2013, Issue 3), MEDLINE (from 1950), EMBASE (from 1974), CINAHL (from 1982) and the Transfusion Evidence Library (from 1980), together with ongoing trial databases, for relevant trials up to 31st March 2013.

SELECTION CRITERIA:

Eligible studies included RCTs comparing autologous adult stem/progenitor cells with no autologous stem/progenitor cells in participants with chronic IHD and heart failure. Co-interventions such as primary angioplasty, surgery or administration of stem cell mobilising agents, were included where administered to treatment and control arms equally.

DATA COLLECTION AND ANALYSIS:

Two review authors independently screened all references for eligibility, assessed trial quality and extracted data. We undertook a quantitative evaluation of data using fixed-effect meta-analyses. We evaluated heterogeneity using the I^2 statistic; we explored considerable heterogeneity ($I^2 > 75\%$) using a random-effects model and subgroup analyses.

MAIN RESULTS:

We include 23 RCTs involving 1255 participants in this review. Risk of bias was generally low, with the majority of studies reporting appropriate methods of randomisation and blinding. Autologous bone marrow stem cell treatment reduced the incidence of mortality (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.14 to 0.53, $P = 0.0001$, 8 studies, 494 participants, low quality evidence) and rehospitalisation due to heart failure (RR 0.26, 95% CI 0.07 to 0.94, $P = 0.04$, 2 studies, 198 participants, low quality evidence) in the long term (≥ 12

months). The treatment had no clear effect on mortality (RR 0.68, 95% CI 0.32 to 1.41, P = 0.30, 21 studies, 1138 participants, low quality evidence) or rehospitalisation due to heart failure (RR 0.36, 95% CI 0.12 to 1.06, P = 0.06, 4 studies, 236 participants, low quality evidence) in the short term (< 12 months), which is compatible with benefit, no difference or harm. The treatment was also associated with a reduction in left ventricular end systolic volume (LVESV) (mean difference (MD) -14.64 ml, 95% CI -20.88 ml to -8.39 ml, P < 0.00001, 3 studies, 153 participants, moderate quality evidence) and stroke volume index (MD 6.52, 95% CI 1.51 to 11.54, P = 0.01, 2 studies, 62 participants, moderate quality evidence), and an improvement in left ventricular ejection fraction (LVEF) (MD 2.62%, 95% CI 0.50% to 4.73%, P = 0.02, 6 studies, 254 participants, moderate quality evidence), all at long-term follow-up. Overall, we observed a reduction in functional class (New York Heart Association (NYHA) class) in favour of BMSC treatment during short-term follow-up (MD -0.63, 95% CI -1.08 to -0.19, P = 0.005, 11 studies, 486 participants, moderate quality evidence) and long-term follow-up (MD -0.91, 95% CI -1.38 to -0.44, P = 0.0002, 4 studies, 196 participants, moderate quality evidence), as well as a difference in Canadian Cardiovascular Society score in favour of BMSC (MD -0.81, 95% CI -1.55 to -0.07, P = 0.03, 8 studies, 379 participants, moderate quality evidence). Of 19 trials in which adverse events were reported, adverse events relating to the BMSC treatment or procedure occurred in only four individuals. No long-term adverse events were reported. Subgroup analyses conducted for outcomes such as LVEF and NYHA class revealed that (i) route of administration, (ii) baseline LVEF, (iii) cell type, and (iv) clinical condition are important factors that may influence treatment effect.

AUTHORS' CONCLUSIONS:

This systematic review and meta-analysis found moderate quality evidence that BMSC treatment improves LVEF. Unlike in trials where BMSC were administered following acute myocardial infarction (AMI), we found some evidence for a potential beneficial clinical effect in terms of mortality and performance status in the long term (after at least one year) in people who suffer from chronic IHD and heart failure, although the quality of evidence was low.

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Intraspinal neural stem cell transplantation in amyotrophic lateral sclerosis: phase 1 trial outcomes.

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Author information

Abstract

OBJECTIVE:

The US Food and Drug Administration-approved trial, "A Phase 1, Open-Label, First-in-Human, Feasibility and Safety Study of Human Spinal Cord-Derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis, Protocol Number: NS2008-1," is complete. Our overall objective was to assess the safety and feasibility of stem cell transplantation into lumbar and/or cervical spinal cord regions in amyotrophic lateral sclerosis (ALS) subjects.

METHODS:

Preliminary results have been reported on the initial trial cohort of 12 ALS subjects. Here, we describe the safety and functional outcome monitoring results for the final trial cohort, consisting of 6 ALS subjects receiving 5 unilateral cervical intraspinal neural stem cell injections. Three of these subjects previously received 10 total bilateral lumbar injections as part of the earlier trial cohort. All injections utilized a novel spinal-mounted stabilization and injection device to deliver 100,000 neural stem cells per injection, for a dosing range up to 1.5 million cells. Subject assessments included detailed pre- and postsurgical neurological outcome measures.

RESULTS:

The cervical injection procedure was well tolerated and disease progression did not accelerate in any subject, verifying the safety and feasibility of cervical and dual-targeting approaches. Analyses on outcome data revealed preliminary insight into potential windows of stem cell biological activity and identified clinical assessment measures that closely correlate with ALS Functional Rating Scale-Revised scores, a standard assessment for ALS clinical trials.

INTERPRETATION:

This is the first report of cervical and dual-targeted intraspinal transplantation of neural stem cells in ALS subjects. This approach is feasible and well-tolerated, supporting future trial phases examining therapeutic dosing and efficacy.