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Implantation of Adult Stem Cells in Patients with Heart Disease: Clinical Practice Implications for Nurses

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Abstract

This is a systematic review that aims to identify scientific publications in databases that cover the bone marrow-derived adult stem cells implantation in heart disease patient with changes in ejection fraction. For the study were used the databases LILACS, MEDLINE, Cochrane, Embase, CINAHL, PubMed and Ovid. In the five eligible trials with 279 patients, bone marrow – derived adult stem cells implantation indicates that there is statistical significance, although the number of studies are not conclusive for expressive statements to allow inferences about the effectiveness of the outcome. Based on the results we point out that the nurse should be focused on promoting adherence to treatment through conventional education measures.

Keywords: Nurse; Cardiology; Stem Cells; Systematic review

Background

Heart diseases are considered one of the major risk factors for deaths in the population, both in developed and in those in underdevelopment. Most patients with heart disease, when they survive this health problem, evolve to a heart failure frame (HF), which reduces considerably the quality of life of these patients [1].

Despite recent advances in health, in Brazil, the main cause of heart failure is acute or chronic ischemic heart disease associated with hypertension, therefore, in many cases, patients do not respond to conventional treatments, and justified the growing search for new researches associated with the HF treatment [2]. Cell therapy is an innovative idea, with a huge perspective to contribute to the acute and chronic heart diseases treatment, to improve the heart muscle performance. From several studies of various specialties, cardiology studies have developed from stem cells, which are a promising research area in the cardiac muscle regeneration [3].

To address the care of nurses to patients with cardiovascular disease who are undergoing experimental treatment with adult stem cells, it is necessary to have knowledge of research currently in progress with bone marrow-derived adult stem cells implantation in these patients.

Given that premise, the study question: "What is shown by the scientific publications about bone marrow derived - adult stem cells implantation in heart disease patients with changes in ejection fraction (EF)?

Objectives

The paper aims to identify through evidence found in scientific publications the use of bone marrow derived - adult stem cells in a heart disease patient with changes in EF

Methods

This is a systematic review.

Work Plan

Sample

Were randomized controlled trials that address the patient with cardiomyopathy underwent CT-MO implantation published until March - December 2009.

Identification and selection of articles

Inclusion criteria

- Participant: adult cardiomyopathy patients with ejection fraction below 50%.
- Intervention: Therapy with bone marrow derived – intracoronary or intramyocardial adult stem cells implantation.
- Outcomes: ejection fraction.

Exclusion criteria

- The use of stem cells which were cultured prior to implantation and use of cell stimulating factors.
- Follow-up less than 06 months.
- Use of stem cells combined with coronary artery bypass grafting.
- methodological quality according to the Jadad scale less than 3 points.

Search strategy and identification of studies

Search strategy for studies: We used the Lilacs, SciELO, Pub Med / Medline, Embase, Cochrane Register of Controlled Trials (Evidence Portal), and OVID CINAHL databases from 2000 to 2009.

Terms used: standardized by the Medical Subject Heading (MESH) and Descriptors in Health Sciences (MeSH). The descriptor Stem cells

were combined using the Boolean operator AND with the following terms: heart failure, acute myocardial infarction, controlled clinical trial, and bone marrow. Terms in Portuguese and English language were applied. For each database the following filters were used: title, subject, and type of publication (Figure 1)

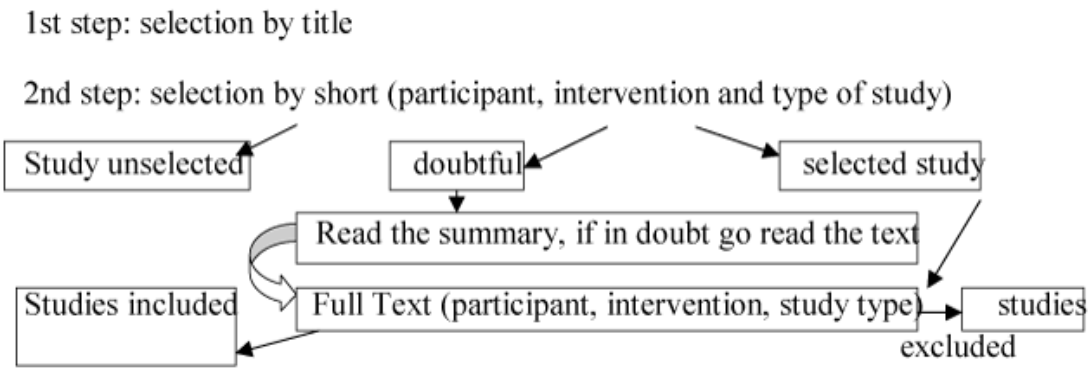

Figure 1: Technical study selection was done by question and type of the study. The selection was divided in two steps

Each study was assessed independently by two reviewers and the inclusion decision was by consensus based on the inclusion criteria and methodological quality of the Jadad scale. To systematize the analysis of the studies quality, a form for data collection with the following vestments was created: general information (title, year of publication, country of origin, language of publication, source of publication), eligibility data (criteria inclusion), methodological data (type of study, sample number, quantity of injected cells, numbers of centers, follow-up assessment, type of test used to assess ejection fraction and value of the Jadad scale) and outcome (value of the fraction ejection before and after stem cells administration in experimental and control groups).

Analysis

Data analysis was obtained by meta-analysis. The meta-analysis aims to combine the results of each study overall effect of the intervention, enabling the analysis of sources of heterogeneity. Data extracted from the studies were analyzed using STATA (version 11.0). Categorical variables were described as counts and the number and proportion as mean and standard deviation when normally distributed, and median and interquartile range in other cases. Effect measures used were the difference and the standardized difference between the experimental group and the control, modification of ejection fraction compared to baseline values. For the analysis of the standardized difference the g Hedges estimator and its standard error were calculated by the formula described by Hedges and Olkin. For each outcome random-effects meta-analysis by the method of DerSimonian and Laird was performed, weighted by the variance inverse, the result of which was exposed visually through graphic forest. The degree of heterogeneity between studies was assessed by Cochran Q test and I-squared.

Results

In total 2081 studies identified, 05 studies were selected by reviewers. The total number of studies were excluded in 2076, 106 of these are recurrent and 1962 are out of the inclusion criteria (such as animal studies, studies in phase I and II non-randomized). Besides these, we had 08 abstracts in other languages (06 Chinese and 02 German), which were not possible to retrieve the full articles when asked to Bireme and COMUT (the library UFRJ), because these journals are not registered.

Presentation of studies

Methodological quality

The JADAD scale was used for analysis of the studies and those who received score 4 points were selected.

Characterization of the population

The main clinical characteristics were similar between experimental and control group underwent percutaneous coronary intervention with improvement of blood flow in the coronary arteries and the participants were randomized three days after the intervention. Both groups had risk factors (RF) for coronary heart disease and average age between the two groups was 58 years.

Description of studies

The studies have diverse origins, despite having in common the same etiology-acute myocardial infarction.

Among the identified imaging studies that stratify the value of ejection fraction, echocardiography (Simpson's method) was used in two studies. The SPECT (Single Photon Emission Tomography / Computed Tomography single photon emission) was another imaging test used in two studies to evaluate the FE, and cardiac Magnetic Resonance (MR) was used in one study. Only the Dill study [4] was up longer than six months, making it as relevant to the management of treatment measures in an attempt to prevent remodeling cardiac. The Lund study [5] was that presented a higher number of participants in a single center. Mononuclear cells were used for implantation in four studies, as mononucleated cells characterized by being the primary portion among bone marrow cells and progenitor cells are the most common type of adult stem cells (Table 1).

Study	Year	Origin	Etiology	Exam	Center	Follow	Sample	Type of cells	Number (n16)
Lunde	2006	Norway	AMI	ECHO	only	6	100	mononucleate	68
Meluzin	2007	Czech Republic	AMI	SPECT	only	6	40	mononucleate	100
Dill	2009	Germany	AMI	MRI	multi	12	54	progenitor	100
Yao	2008	China	AMI	ECHO	only	6	47	mononucleate	120
Piepoli	2009	Italy	AMI	SPECT	only	6	38	mononucleate	418

Table 1: Description of studies

Description of Ejection Fraction Values

Studies with the primary outcome assessment of global left ventricular function from the EF evaluation and in both control and experimental groups were not statistically significant when compared to other outcomes, but their results highlight that there is statistical significance when the experimental group is evaluated separately, although there is no change from the infarcted area. Studies have demonstrated safety of the implantation stem cells procedure, without any adverse events. The studies presented as limiting the small number of patients in the study. Both groups showed an improvement in ejection fraction (Table 2).

Study	EF (pre) control	EF (post) control	EF (pre) exp	EF (post) exp
Lunde	46.9	49	45.7	48.8
Meluzin	40	43	40	47
Dill	47.8	49.4	47.7	51.5
Yao	45.4	47.6	46.3	49.8
Piepoli	36.6	39.7	37.5	45

Table 2: Ejection fraction (EF) in the pre and post implantation of adult stem cells

Meta-analysis

Forest graphics values of ejection fraction (Figures 2 and 3).

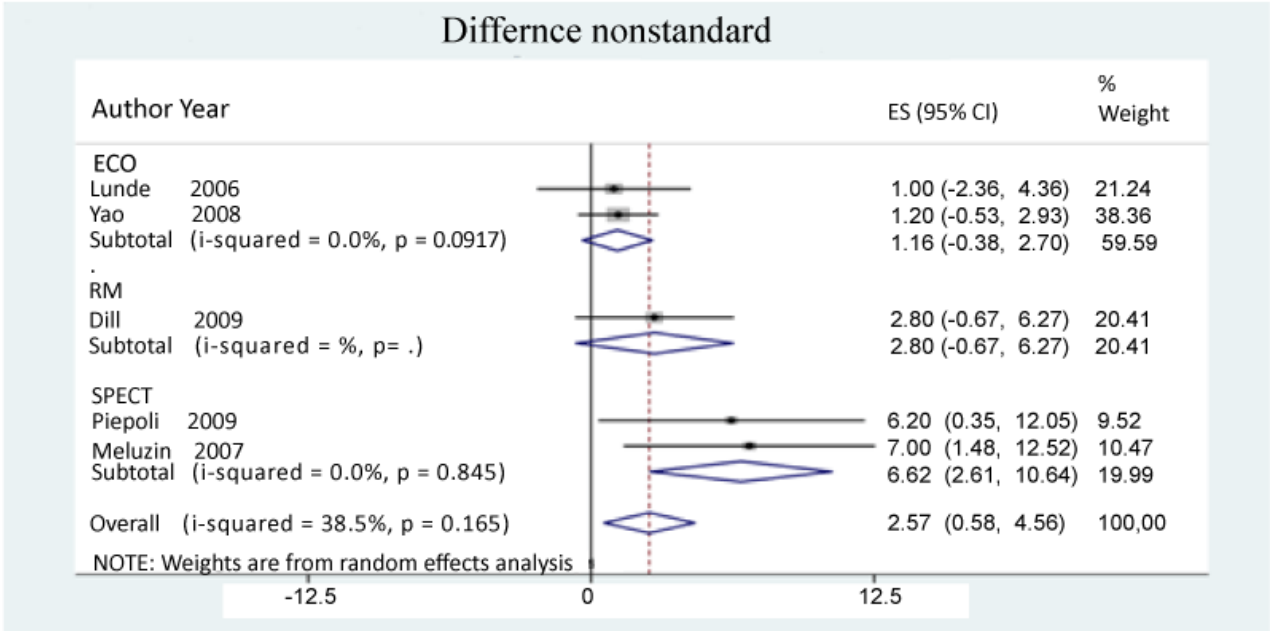

Figure 2: Nonstandardized difference

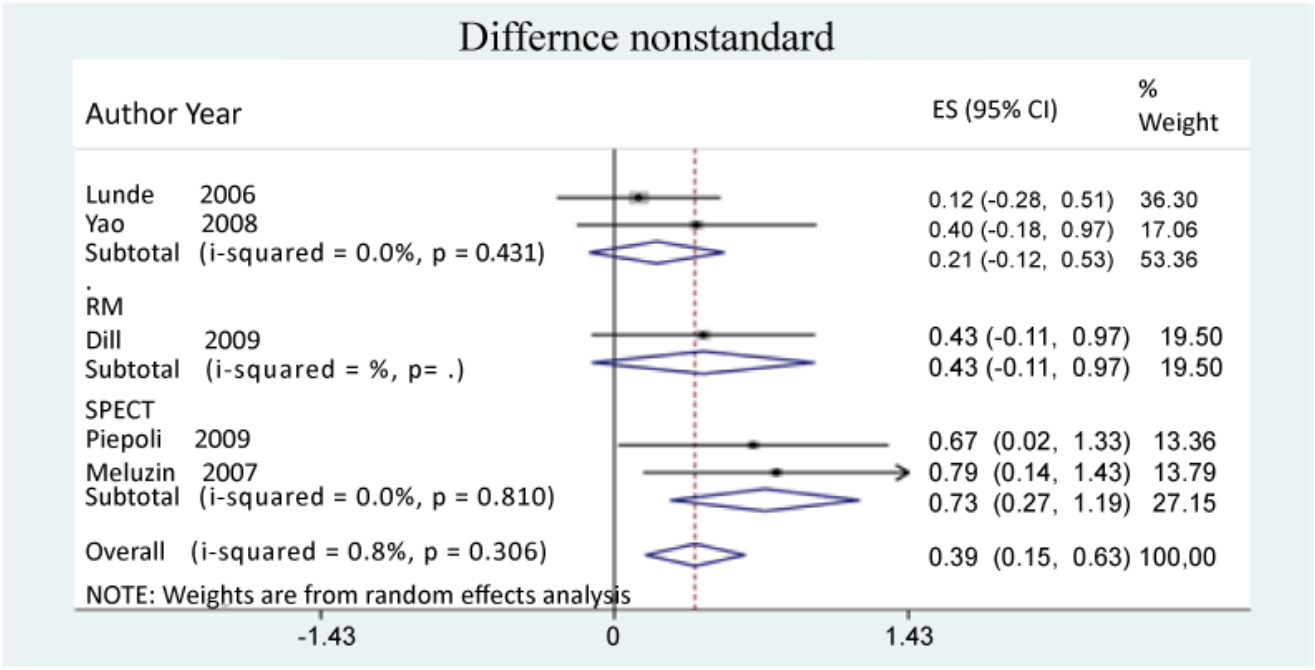

Figure 3: Standardized difference

Discussion

Whereas the horizontal lines of the studies represented in the graph of meta-analysis, with the exception of the line referring to studies Meluzin [6] and Piepoli [7], cross the vertical line, we can say that there is no statistical difference between the groups (experimental and control) When a study despite not cross the vertical line ends with arrow it means that the confidence interval extends beyond the graphs scale.

Therefore, the confidence interval increases as the sample size is small. In this sense, we can infer that the Meluzin study [6], while expressing its results in a significant improvement in ejection fraction in the experimental group can not claim that this improvement is effective for the intervention compared to other studies.

We can also observe that the central point of the horizontal lines of the studies is to the right of the graphic, which can be interpreted as not having the effect of the intervention size. Even in this analysis, we highlight the central point size, which indicates the relative weight of each study in the final result, which is based on the number of participants and the number of events. Whereas the central point of the horizontal lines is similar in terms of weight expressed in reduced form, we can interpret that the selected studies did not show relative weight on the end result.

In combination studies represented by the diamond at the bottom of the charts, the centerpiece has to be similar to these, and its extended form means an increase in the confidence interval, showing that even with the combination, studies of the sample remains small to affirm the effectiveness of the intervention on the outcome. When analyzing the results of related studies from the exams used to assess ejection fraction after implantation of stem cells it was observed the need for standardization of results considering that the studies used different methodology examinations to assess the outcome (Figure 3).

When reading the subgroups from each examination carried out, it was found that among Lunde and Yao studies, there was no significant difference, being confirmed by the metadata. Dill study did not allow a comparative analysis as the only study to use MRI as the examination to evaluate the outcome [4,5,8].

Meluzin and Piepoli studies showed significant relation to the outcome both in subgroup analysis and the meta-analysis [6,7].

Comparing the results of meta-analyzes related to non-standardized and standardized difference, we observe a statistical significance, although the number of studies are not conclusive for expressive statements, not allowing inferences about the effectiveness in outcome related to EF. Thus, when analyzing more critically the graphs we found that Meluzin and Piepoli studies are responsible for the tendency of the diamond displacement to the right, giving margins for the interpretation of the implantation effectiveness [6,7].

Therefore, the results of this systematic review allow us to infer that although cell therapy show improvement in ejection fraction in each selected study, it is maintained at the same level or below 50% even in the Meluzin study with the highest percentage of improvement in the pre and post-implantation, which does not remove the characteristic picture of heart failure after myocardial infarction [6].

We consider in this meta-analysis that despite the small improvement in ejection fraction, suggesting less severe symptoms presented by the HF patient after AMI by the increase in ejection fraction, it does not imply changes in your lifestyle. However, the Hristov meta-analysis results showed a positive effect in FE before implanting adult stem cells in acute MI, but without statistical significance between the groups, noting that the studies presented

number of stem cells and different segments despite present similarities related to the type of studies and clinical characteristics of the study population [9].

Heart failure (HF) is a marked functional limitation syndrome, it imposes worsening the life quality of patients. Although they are the most important causes of hospital readmission in this cardiac group, decompensation resulting from poor adherence to pharmacological and non-pharmacological are the predominant episodes [10]. Within this unfavorable scenario, one of the objectives of the HF management is to achieve and maintain clinical stability of patients at the expense of a very complex treatment regimen.

We believe the most important is to emphasize the consistency of the experimental studies, which demonstrated an improvement in ventricular function after implantation. However, only the most advanced and multicenter studies with many patients can determine the exact place of this type of therapy in clinical treatment and improve the life condition of heart failure patients [11-14].

Conclusion

This study allowed us to verify that it is not possible inference related to the stem cells effectiveness in cardiology, that leads to the need for better outcome assessment from the research development combined with other types of stem cells.

In addition to the studies that met the inclusion criteria for this meta-analysis, several other clinical trials of CT-MO implantation combined with surgery and use of cellular stimulation factors were fundamental to scientific trajectory, allowing evidence of change in EF, justifying the persistence in the pursuit of new studies that express results in order to target this intervention as a treatment in cardiology. Therefore, the studies show as consensus that the quantity and implanted stem cells lineage can affect the outcome of the ending.

The evolution of research involving stem cells in cardiology has played an important way to therapeutic innovation, generating demand for new knowledge for health professionals especially nurses that besides having the commitment to follow the progress technology they play an important role in monitoring changes in lifestyle necessary to everyday life of the patient and their subsequent life quality.

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