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The Psychological and Compliance Factors can Modulate the Outcome of STEMI Patients Treated by Stem Cell Therapy - A Pilot Study

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Abstract

Introduction: In the assessment of stem cell therapy post myocardial infarction, the rapport between the medical intervention and the patient's compliance and psychological factors represent a research and treatment management challenge.

Purpose: Identifying the implication of psychological and behavioral factors associated with compliance on therapeutic success in relation to cell therapy in acute myocardial infarction patients.

Methods: The study included 32 patients with acute myocardial infarction with ST elevation, 5 of them being treated with stem cells, subject to a qualitative observational analysis. All the patients were monitored regularly both in terms of clinical indicators, according to the research protocol for post-infarction cell therapy and psychological, health related behavioral using self-rated questionnaire developed for this study, Health Perception Scale, Depression Scale (HADS-D), Health Locus of Control Scale.

Results: The analysis of psycho-behavioral aspects of acute myocardial infarction patients indicates certain statistically significant differences, in the sense of a higher degree of receptivity and responsibility in adopting health promoting behavior expressed by stem cell treated patients. We found a significant correlation between an internal locus of control and the intent to adopt a health promoting behavior (r = 0.473, p < 0.05), while an external locus of control shows a negative, statistically significant correlation, with the same variable (r = - 0.536, p < 0.01).

Conclusions: The psychological and behavioral factors should be part of the algorithm for evaluating eligibility for cell therapy and also should be considered in quantification of the response to the treatment.

Keywords: Acute myocardial infarction, Stem cells, Behavioral factors, Compliance.

Introduction

As an innovative therapy used on top of the treatment recommended by existing guidelines for myocardial infarction, cell transplant is addressing myocardial hypo perfusion and loss of myocytes, aiming the prevention or improvement of remodeling by inducing heart regeneration [1-5]. Also, the optimal functional level achievable through the complex therapy post-infarction is influenced by patients' individual characteristics and their quality of life as emphasized by World Health Organization (WHO) [6]. A series of factors are likely to influence the compliance of ST segment elevation acute myocardial infarction (STEMI) survivors:

- *Information of patients* on their current clinical problem is an integral component of medical care focusing on how patients self-evaluate their level of awareness regarding their acute condition and their *expressed confidence* in the treatment.

- *Health-promoting behaviors* in terms of patient's responsiveness: the intention to adopt healthy behaviors, making lifestyle changes as part of the rehabilitation program, either by personal effort or by requesting professional support as a form of adherence to medical recommendations.

- *Self-perception of health and overall satisfaction,* current and projected, are elements that significantly complete the patient's health profile in terms of general well-being.

- *Family and community support* acts as a motivational resource for the patient, the lack of it being thus considered a risk factor; studies conducted so far indicated that support is a predictive factor for the progress of post-infarction recovery process [7,8].

- *Perceived stress and depressive symptomatology* have been confirmed as risk factors associated with myocardial infarction and coronary heart disease, both at the onset of and in association with the symptoms [9,10]. Among the psychosocial risk factors, chronic or acute stress, depression, lack of social support, socio-economic status was considered relevant risk factors. Patients, who experience difficulties in relation with these factors are less compliant, find it harder to assimilate medical advice and to develop adaptive behaviors specific to their clinical status.

- *Health locus of control* (HLOC) has proved to be a treatment adherence modulator especially in pathology cases where, apart from medication, the changes in lifestyle are essential to maintaining health status, such as cardiac rehabilitation after

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myocardial infarction. HLOC is described as the individuals' perceived control over their own health-related behavior [11]. The "locus" is further conceptualized as "internal", referring to individuals who perceive their own control as decisive for their health state, strongly believing that the events in their life derive primarily from their own actions, as opposed to "external", which indicates an individual's perception of external control (represented by an authority, fate, destiny...) as mainly determinative of events. Patients with *internal locus* of control are more responsive to lifestyle changes, their internal HLOC being positively associated with a higher adherence to treatment [12].

Objective

This pilot study focused on understanding the impact of certain psychobehavioral aspects on therapy compliance in patients who were included in the post-myocardial infarction therapy program. The general research interest was to identify the predictive role of these aspects, whether positive or negative, in the success of the post-infarction therapy as related to the stem-cell treatment.

Material and method

Study design

The study enrolled 32 patients with STEMI, hospitalized and treated at Clinical Emergency Hospital in Bucharest between December 2011 and September 2012. All patients received standard therapy according to up to date guidelines (including both invasive procedures and pharmacological treatment) and *express recommendations for the adoption of healthy behaviors* regarding physical activity, diet, stress management, specific parameters monitoring, check-up visits attendance, according to WHO guidelines, 2007.

Based on acceptance of stem cell therapy, out of the total number of subjects, a subgroup of 5 patients were treated with autologous bone marrow stem cells (the experimental group), as well as according to the protocol of research on post-infarction stem cell therapy as previously described [13,14]. Patients in both groups received standard therapy according current guidelines and were assessed using the same methods. Neither bone marrow aspiration nor sham injection was performed in the control group.

The ethics review board of the Clinical Emergency Hospital of Bucharest approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

The definitions of primary and secondary end points, as well as the inclusion/exclusion criteria, have been previously reported [13,14]. Briefly, patients between 18 and 81 years of age were eligible for inclusion into the study if they had a first acute STEMI treated by successful coronary angioplasty with stenting of culprit lesion. Exclusion criteria were hemodynamic instability, NYHA class IV, severe valvular disease, intraventricular thrombosis, primary haematological or autoimmune diseases, renal, hepatic or respiratory severe impairment, malignant tumors, active infection (viral or bacterial), fever > 38 °C for two consecutive days, pregnancy or lactation, alcohol or drug dependence, psychiatric/neuropsychiatric pathology and unwillingness to participate. Patient's self-reported instruments were administrated during clinical interview for screening psychobehavioral factors in order to reveal individual's unique perspective of myocardial infarct experience.

Instruments

To explore the psychological and health related behaviors of the STEMI patients, the questionnaire devised for this study included patient self-assessment as following:

- Information and knowledge profile - patient's level of knowledge regarding the current clinical condition: myocardial infarction and therapy program, 3 items, scoring 1 to 5 points, higher scores indicating higher level of knowledge; the scores on these three questions were strongly intercorrelated, Cronbach α 0.64, test-retest on 2 weeks.

- Confidence in treatment, 1 item, scored 1 to 5 points, higher scores indicating higher confidence;

- Support of family and community, 2 items, scored 1 to 5 points, higher scores indicating higher perceived support.

- Perceived stress, 1 item, scored 1 to 5 points, higher scores indicating higher perceived stress.

- Adopting health-related behaviors, as compliance and adherence to therapy: smoking cessation, diet, physical activity, medication, monitorization of clinical and bio-physiological parameters, check-up visits attendance, request for additional professional recovery support on nutrition, psychological counseling; 15 items, scoring 1 to 5 point, higher scores indicating higher level of health behavior compliance. The scores on these three questions were strongly intercorrelated, Cronbach α 0.81, test-retest on 2 weeks.

- Health locus of control - Internal and External Health locus of control, 5 items, scored for ILC and ELC 1 to 5 from strong disagreement to strong agreement [12].

- Self-perception of current health state and projective self-assessment were carried out using the Health Perception Scale - 2 items, scoring 1 to 5 points, higher scores indicating higher satisfaction regarding health [15].

- Overall Health and Life Satisfaction were assessed using Cantril's Self Anchoring Ladder [15], a ten-point scale anchored by respondents' own identified values, higher scores indicating higher satisfaction.

- Depression symptoms screening with Hospital Anxiety and Depression Scale HADS-D [16,17], 7 items related to depression, scored from 0 to 3 points, with cut-off point for depression 8 of 21 and three levels of symptoms: normal, borderline, depression.

Statistical processing of data was carried out using the SPSS 15 software for Windows and included a descriptive and inferential analysis. Data were expressed as percentages for categorical variables and as mean ± standard deviation for numeric variables. Continuous variables were tested for normal distribution by Kolmogorov-Smirnov test using Lilliefors correlation. To compare groups we used Student test for quantitative variables with normal distribution, respectively chi-square test for nominal or ordinal variables. All tests were two-sided. Pearson's correlations were used to test associations among continuous key variables. Stepwise regression analysis was performed to determine the relationship between the adoption of healthy behaviors - as dependent variable - and the key variables. Data with $p < 0.05$ were considered statistically significant.

Results

From selected patients, 19 (59.4%) were male, 13 (40.6%) were female, ages ranged from 42 to 86 years old. The mean age per total of subjects was 58.68 ± 11.03 years, the mean age for men being 60.2 ± 12.67 years, and 57.2 ± 8.26 years for women.

The experimental group included male patients (5 males), 40% smokers, with ages between 44 and 69 years, the mean age being 59.8 ± 10.28 years and a BMI ranging from 21.13 kg/m^2 (minimal value) to 33.2 kg/m^2 (maximal value), with a mean BMI of 27.94 kg/m^2, among them, 60% were dyslipidemic, 60% were hypertensive, none of them suffering of diabetes mellitus.

The mean scores and standard deviations of psychobehavioral variables are depicted in table 1 and table 2, respectively.

Predictors of health-related behavior adoption are illustrated in table 3.

Table 1: Psycho behavioral characteristics of patients as a total group and as subgroups.

Psycho behavioral variables	Total group (N = 32)	Experimental group (N = 5)	Control group (N = 27)	P value between groups
Information and knowledge profile	4.12 ± 0.83	4.46 ± 0.44	3.9 ± 0.93	0.05
Confidence in treatment	4.13 ± 0.79	5 ± 0	3.96 ± 0.75	0.005
Family support	3.75 ± 1.08	4.3 ± 0.07	3.65 ± 1.11	0.2
Diet	4.06 ± 1.07	4.8 ± 0.44	3.93 ± 1.1	0.009
Physical activity	3.88 ± 0.91	4.4 ± 0.54	3.78 ± 0.93	0.07
Stress management	3.75 ± 1.16	4.4 ± 0.54	3.63 ± 1.21	0.04
Check-up visits attendance	4.56 ± 0.56	5 ± 0	4.48 ± 0.58	0.001
Self-perception of current health	3.41 ± 0.83	3.40 ± 0.54	3.41 ± 0.88	0.98
Self-perception of projected health	3.97 ± 0.82	5 ± 0	3.78 ± 0.75	0.001
Present overall satisfaction	6.84 ± 1.83	7 ± 1.41	6.81 ± 1.92	0.8
Future overall satisfaction	8.06 ± 2.12	8.80 ± 1.30	7.93 ± 2.23	0.25
Internal HLOC	4.12 ± 0.87	5 ± 0	3.96 ± 0.85	0.01
External HLOC	2.56 ± 1.24	1.80 ± 0.83	2.70 ± 1.26	0.07

HLOC = Health Locus of Control

Table 2: Depressive symptoms of patients as a total group and subgroups.

Depressive sympthoms	Total group (N = 32)	Experimental group (N = 5)	Control group (N = 27)	P value between groups
Normal	12 (37.5%)	2	10 (37.1%)	
Borderline	14 (43.8%)	3	11 (40.7%)	
Depression	6 (18.8%)	-	6 (22.3%)	
Total	32 (100%)	5	27 (100%)	
Mean scores, depressive symptoms				
Mean, S.D.	7.3 ± 3.4	6.4 ± 3.1	8.1 ± 3.5	0.72

Table 3: Predictor variables for intention to adopt health related behavior.

	Variables	β	B	P	R²
Model 1	Information and knowledge profile	0.664	6.748	0.000	0.441
Model 2	Information and knowledge profile	0.664	6.748	0.000	0.641
	Perceived stress	0.476	3.00	0.000	
Model 3	Information and knowledge profile	0.664	6.748	0.000	0.707
	Present stress	0.476	3.000	0.000	
	Overall satisfaction	0.271	1.344	0.018	

Discussions

Is generally acknowledged that a variety of factors are related to therapeutic success in STEMI patients treated by stem cell therapy - such as early infarct-related artery flow grade, body mass index and total ischemic time, but psychological factors interfere as modulators, too. The real therapeutic success which benefits the patient depends on individual factors such as the patient's willingness to adopt the recommended healthy behaviors, comorbidities, the coexistence of specific psychological conditions (depression, anxiety), individual abilities and beliefs, family and social support. In evaluating the impact of a novel therapeutic procedure, the relation between the complexity of the scientific effort and patients' level of responsiveness (adherence to treatment) represents a real challenge for the researcher. In this respect, studies have been conducted to investigate treatment compliance in coronary heart disease and myocardial infarction.

The concept of treatment compliance, which is congruous with the one of adherence, is concisely defined by the WHO as the "the extent to which a person's behavior, in terms of taking medication, following diets or executing lifestyle changes, coincides with medical or health advice" [18]. In this context, the significance of psychosocial evaluation as part of the cardiac rehabilitation after myocardial infarction is also emphasized and conditions such as anxiety and depression are shown to have greater prevalence among patients who suffered a cardiac arrest, being, along with the lack of social support, predictive of their non-compliance to therapy. Last but not least, the need to develop studies on the specific role of psychosocial factors during the process of cardiac rehabilitation has been asserted [19]. Along with the progress of stem cell therapy and the advancements in the clinical and scientific fields, specialists have become increasingly interested in tackling the subject of behavioral compliance in this category of patients. The study entitled "*Mismanaging the gift of life: noncompliance in the context of adult stem cell transplantation*" [20] opens this new direction, focusing on the impact of non-compliance on the increase in morbidity and mortality rates, as well as on additional health care costs. The study outlines current orientations of clinical guidelines towards stem cell therapy programs, underlining the need for evaluation and management of patient compliance, and pointing out the pronounced clinical interest in assessing the incidence, predictors and compliance in these patients, as well as the impact of compliance on therapeutic benefits.

As far as our study is concerned, the *information and knowledge profile* of the patients is characterized by a *positive estimation* as regards the clarity of information on their current clinical state and the recommended health management. The mean scores obtained by the patients indicate their level of knowledge as ranging from "good informed (score 4)" to "very good informed (score 5)" thus, the *overall sample mean score* was of 4.12 ± 0.839, the proportion of patients who achieved good scores being of 28.1%, and of those obtaining very good scores - 46.9%. A certain difference has been noticed between the treatment group and the control group (t = 2.1, p = 0.05) in terms of a greater responsiveness of the treated group to information on post-infarction state. The level of *confidence in treatment,* as expressed by the subjects, was defined by high values, with a mean score of 4.13 ± 0.793 corresponding to levels ranging from "good confidence (score 4)" to "very good confidence (score 5)", with a higher level of confidence expressed by the patients who benefited from the stem cell therapy, the difference in this respect between the two groups being rather significant (t = 3.016, p = 0.005).

The patients' overall level of knowledge, which encompasses their information on the three main aspects: their current clinical state (myocardial infarction), the specific treatment and the recommended behaviors, significantly correlates with overall scores measuring healthy behavior (r = 0.757, p < 0.001), confidence in therapy (r = 0.639, p < 0.001) and subjective health estimation (r = 0.351, p = 0.04).

We thus consider that adequate information of patients, as confirmed by their feedback through positive estimation responses, as well as by their expressed confidence in the *medical management*, builds the basis for an efficient doctor-patient communication with foreseeable impact on treatment compliance. In this respect, the systematized analysis of the cardiac rehabilitation programs efficacy conducted by Dinnes et al. shows that one of the most important predictors of treatment adherence is the patient's perception of the importance of medical advice, along with the access to rehabilitation programs [21].

The evaluation of patients' responsiveness to rehabilitation programs after myocardial infarction - as a fundamental part of health management assessing the chief aspects of the adopted healthy behavior - has revealed significant data, as follows:

- Most of the patients have manifested the intention to change their lifestyle by adopting healthy behaviors as regards their diet, alcohol consumption, smoking, physical exercise, monitorization of clinical and biological parameters. A proportion of 85% out of the total number of smokers (65.62%) have stated their clear intention to quit smoking, and 66.7% of the patients - the intent to give up alcohol.

- The intention to request professional support has been expressed by the vast majority of patients, with a highly increased prevalence in 59.4% of the total of subjects.

Although positive scores measuring desirable behavior changes have been observed in all patients, i.e. a mean score of 4.06 ± 1.07 for the adoption of a healthy diet, a mean score of 3.88 ± 0.91 for physical exercise, a mean score of 3.75 ± 1.16 for stress management, a mean score of 4.56 ± 0.56 for check-up visits attendance, the examination of the data reported from the experimental group indicates certain differences, in that the subjects treated with stem cells showed an increased willingness and a more responsible attitude as regards the adoption of healthy behaviors. The results of the analysis that investigated the significance of the difference between the mean scores for the mentioned indicators reveal mean scores that are significantly higher in the treatment group as compared to the control group, as far as the following parameters are concerned: Monitorization of physiological parameters, e.g. blood pressure (t = 2.85, p = 0.01), specialty check-up visits attendance (t = 4.84, p < 0.001) and stress management (t = 2.27, p = 0.04). Given this statistical difference, we can interpret the results as possibly due to differences in group characteristics - treated group and control group - the group who received stem cell therapy exhibiting an increased receptiveness to a healthy lifestyle and to observance of medical advice.

Self-perception of current health as good (score 4) is indicated by 40.6% of the patients. The mean scores of 3.41 ± 0.83, representing the patients' self-rating of their current health status, and the mean scores of 3.97 ± 0.82, respectively, accounting for their future health-related projections, reveal statistically significant differences (t = 3.59, p < 0.001). Such differences can be attributed to confidence in therapeutic interventions and also to the afore-mentioned intention to change behavior, as illustrated by the examined data.

The psychological status profile of the patients in terms of their overall satisfaction, perceived stress, depressive symptoms and locus of control offers a relevant perspective for the prognosis of individual involvement in the recovery process.

The current level of overall satisfaction of patients is represented by a mean score of 6.84 ± 1.83 (on a 1 to 10 scale), and their projected level of overall satisfaction is illustrated by an increased average score of 8.06 ± 2.12, which indicates a medium level of current satisfaction

and positive overall expectancies. There is a strong correlation between the projected level of overall satisfaction and the self-perceived health state (r = 0.384, p = 0.03), social support (r = 0.557, p = 0.001), patients' general level of knowledge (r = 0.442, p = 0.01).

Depressive symptoms per all subjects have been assessed using a 3-level classification: not present 37.5% (n = 12), depression borderline 43.8% (n = 14) and current depressive symptoms 18.8% (n = 6). No significant differences between the two investigated groups have been noticed in relation to this parameter.

The presence of depressive symptoms was significantly and negatively correlated with the intention to adopt healthy behaviors (r = -0.414, p = 0.01).

Perceived stress has had an average scoring of 3.28 ± 1.44 per total of subjects, adding that 50% of the subjects mention they have been experiencing stressful life events lately.

The assessment of the psychological variable *locus of control* per total number of subjects indicates a high mean score for the *internal locus of control*, that is 4.12 ± 0.87, as compared to *external locus of control*, for which the recorded mean score is of 2.56 ± 1.24, the difference being statistically significant (t = 4.61, p = 0.01). Patients with high internal locus of control scores have been found to be prevalent (74.4%), in comparison with the patients who obtained high external locus of control scores (21.9%). Within the conceptual framework defined by this parameter, the patients with a higher internal locus of control are more responsive to lifestyle changes.

A significant correlation between the internal locus and the intention to adopt healthy behaviors has been noticed (r = 0.473, p = 0.006), and vice versa, the external locus of control has been found to have a negative, statistically significant correlation with the same variable (r = -0.536, p = 0.002). The results are consistent with the studies investigating treatment adherence and open up new prospects for understanding the individual variables which modulate treatment compliance, as well as for predicting non-compliance and developing new clinical approaches on patient education [12].

The identification of the factors that predict health-related behaviors and have a bearing on the success of the therapy, has been carried out by means of a stepwise regression analysis, in which the adoption of healthy behaviors was selected as dependent variable (as an overall score for the 10 behavioral parameters). Within the regression equation, 3 variables were found to be predictors, which we present here by the order they entered the equation: *patients general level of knowledge* - increased level (overall score for the knowledge of current clinical state/myocardial infarction), which accounts for 44.1% of the variance ($R^2 = 0.441$, F = 23.63, p < 0.001), followed by *perceived stress* - increased level, and *overall satisfaction* - increased level, respectively.

Experimental group data analysis

Patients who benefited from stem cell therapy obtained particularly different scores for *the general level of knowledge* and *confidence in treatment*, in terms of a *higher self-rated* level of knowledge regarding their clinical state and a greater confidence in the therapeutic management of their condition, as compared to the overall sample of patients. Amongst recommended lifestyle behaviors as part of the therapy program, there were differences regarding the biological parameters monitoring - for example, blood pressure (t = 2.85, p < 0.01), specialty check-up visits attendance (t = 4.84, p < 0.001) and stress management (t = 2.27, p < 0.04).

The patients in the experimental group have been monitored for psychobehavioral indicators during periodic clinical evaluations - performed every 3 months. Psychobehavioral indicators continued to remain positive, with no significant differences between the two assessment time points (t = 1.22, p = 0.231). We hence estimate, based on our analysis of the data and on clinical observations, that the patients in the experimental group will have a positive adherence to treatment, being receptive and willing to accept behavior changes.

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This approach brought light to a more personal specificity over clinical assessment of stem cell therapy in terms of feasibility of autologous bone marrow-derived stem cell transplantation in STEMI patients with moderate-to severe systolic dysfunction.

Conclusions

This study has revealed certain psychobehavioral aspects in MI patients, highlighting specific subjective elements that are psychologically relevant to the patient's involvement in the therapy program and to maintaining the acquisitions of the interventional program. Moreover, the research targets innovative therapeutic technologies for myocardial infarction, the paper being patient-centered in the theoretical framework of individuals' experiences as modulators of health outcomes.

The investigated patients, and particularly those in the experimental group, have exhibited a general responsiveness and willingness to accept lifestyle changes and to adopt healthy behaviors during assessments. These aspects are consistent with literature data, one of the most important predictors of treatment adherence being considered to be the patient's perception of the importance of medical advice, along with his access to rehabilitation programs, as revealed by the systematized analysis of the cardiac rehabilitation programs efficacy conducted by Dinnes et al. [21].

Despite of small number of enrolled patients (due to particularities of an innovative therapy advancing from bench and bedside), the study opens a new perspective in approaching patient compliance with the rehabilitation program following myocardial infarction. We envisage the necessity of developing research on representative samples and of longitudinal monitoring of the therapy program in terms of psychobehavioral variables.

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