

## Letters to the Editor

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### **Cell therapy plus transmyocardial laser revascularization: a proposed alternative procedure for refractory angina**

Comments to the study "Cell therapy plus transmyocardial laser revascularization: a proposed alternative procedure for refractory angina", from the author PhD Luiz Dallan, presented at the 34th Congress of the Brazilian Society of Cardiovascular Surgery and published in the Brazilian Journal of Cardiovascular Surgery (2008;23[1])

Analyzing international literature on the topic of cell therapy, I noted the rarity of this association of techniques, and I found only two studies from the INCOR group, with the case report of the first patient of this series, from 2005 [1] - the same case presented in a study in which cell therapy was used together with conventional or transmyocardial laser revascularization from 2006 [2] - and one case by H.M. Klein from the University of Dusseldorf, Germany, 2004 [3], where the technique was used in two patients.

In all studies, improvement in left ventricular contractility was reported, proving to be another method of coronary revascularization, using either the antigen from CD 34<sup>+</sup> hematopoietic progenitor cells, as in the INCOR's studies, or the CD 133<sup>+</sup>, as in the Klein's study [3], and concluded by Kobari [4] when he compared CD 133<sup>+</sup> with CD 34<sup>+</sup>.

The technique of transmyocardial laser revascularization (TLMR) is already well established as an option for a cardiac procedure for coronary revascularization, showing an improvement in the angina functional class in most of the patients, according to the Canadian Cardiovascular Society [5].

The technique of using CD133<sup>+</sup> stem cells is also already established as an alternative for patients for whom techniques of conventional coronary revascularization are not susceptible to indication, as proven by H.M. Klein in isolated uses [6].

The combined use of the two techniques performed by Klein in 2004 is now proven by this study. The study yielded excellent results from applying these techniques in nine patients: there was no mortality associated with the disease being studied. However, in the study, the authors do not offer any indirect measurements of improvement of the general situation (either through quality life questionnaires, or through measurement of the left ventricle ejection fraction,) but only to indirect data from angina classification and the ischemic index.

O uso conjunto das duas técnicas realizado por Klein, em 2004, está agora comprovado com este trabalho ao obter um excelente resultado quando de sua aplicação em nove pacientes, sem

mortalidade associada á doença em estudo. No entanto, os autores não fazem referência no trabalho tanto a medidas indiretas mensuráveis de melhora do quadro geral, quer seja através de questionários de qualidade de vida, quer seja através da medida da fração de ejeção de ventrículo esquerdo e apenas a dados indiretos de classificação de angina e índice isquêmico.

However, some authors [7] highlight the fact that the use of these techniques should be performed only in patients in whom the clinical therapy already has been optimized, and some authors suggest that the ejection fraction should be higher than 40% to achieve the best results, due to the weight loss caused directly by the laser injury. This statement is supported by other groups [8] because the results present a lower quality of life and less survival after 18 months for patients with left ventricular dysfunction and heart failure.

Another point that must be clarified is the correct mechanism of action of TLMR, as there is currently no exact understanding of it, even despite study results that have shown a clinical improvement in the patients. However, in the same multicenter study by Samuels [9], it was proven that the performance of TLMR associated with another method (such as the simultaneous use of angiogenic growth factors or stem cells) may increase its effectiveness. In relation to the use of TLMR associated with the use of growth factor, Dr. Dallan's study may be the answer to the Samuels study, as was the case with the Horvath study [10].

I would like to ask the author the following questions, just for clarification:

- 1) Does the author believe that the use of this technique as a method of treatment is viable in the cases of patients with similar characteristics?
- 2) Does your service have an inclusion protocol for patients who receive this new technique?
- 3) If so, what is the minimum ejection fraction necessary for inclusion of patients in this protocol?
- 4) In relation to left ventricular function, although there were no doubts about the improvement of ejection fraction, what was the percent increase?
- 5) Was ventricular assistance (intra-aortic balloon) used in any of the cases presented herein?

I congratulate Prof. Dallan and his group for the excellent scientific contribution accomplished for our society. In the near future, with the continuation of this line of research, I hope to see the results of a more in-depth study with a larger number of patients;

a study that is double-blind, randomized and placebo-controlled, as the author himself suggests.

Thank you very much.

**Rui M. S. Almeida, Cascavel/PR - Brazil**

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#### Reply

We would like to thank Dr. Almeida and reaffirm our group's innovation in the field of cell therapy associated with transmyocardial revascularization with CO<sub>2</sub>-laser [1]. We have been working with transmyocardial laser revascularization since the 1990s [2,3], and with cell therapy since 2002 [4,5]. The successful outcomes that our group found using the CO<sub>2</sub> laser and the proof of safety with the use of cell therapy led to the study of the combination of these two techniques. After Phase I, which demonstrated the safety of the combination of cell therapy with transmyocardial laser revascularization [6,7], we are initiating Phase II, including a prospective randomized study in order to analyze the concrete benefits of the union of these two therapies.

Regarding your questions, we must say that the benefit of this union has not yet been proven. Because of this, in our circle, this procedure is not part of the cardiovascular surgery routine. The patients are indeed carefully selected, and meet specific criteria. To summarize, the inclusion criteria are: refractory angina in spite of maximally tolerated clinical therapy; myocardial ischemia (objectively recorded) by non-invasive methods; left ventricle ejection fraction of  $e^{-} < 50\%$ ; coronariography with multiarterial obstructive pattern that is not susceptible to percutaneous revascularization or classical surgery. After the procedure (and with an average of 6 months follow-up), there was no significant alteration in the left ventricle ejection fraction, which was  $0.54 \pm 0.09$  to  $0.59 \pm 0.07$ ,  $p=0.41$ . However, the study with magnetic resonance showed significant reduction of the ischemic index of the left ventricle, decreasing from  $1.64 \pm 0.10$  (preoperative) to  $0.88 \pm 0.09$  (6 months of postoperative),  $p = 0.01$ . Such a result may have occurred due to the synergic angiogenic potential of these two therapeutic modalities. We await the conclusion of Phase II of the study (prospective and randomized), with which we will be able to either confirm or negate our statement.

**Luis Alberto de Oliveira Dallan – São Paulo/SP - Brazil**

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### Medline

Dear Domingo,

You did right deleting the suffering and the rough time. I hope you get well soon. I know you are going to pull through this and you have all my support. Please let me know if there is anything at all that I can do. Congratulations for the Medline indexation which is going to give an extraordinary contribution to surgical post-graduate courses.

With my compliments,

**Francisco José Barcellos Sampaio – Editor – International Brazilian Journal of Urology. Rio de Janeiro/RJ - Brazil**