

High Technology and Placebo Effect: Myocardial Laser Revascularization in the Palliative Treatment of Refractory Angina Pectoris

Mário Sérgio Soares de Azeredo Coutinho

Universidade Federal de Santa Catarina, Instituto de Cardiologia de Santa Catarina - Florianópolis, SC, Brazil

Since 1933, when Wearn et al¹ described a sinusoidal network in the human heart, some forms of indirect myocardial revascularization have been proposed in an attempt to improve cardioischemic symptoms. In 1935, Beck² developed the cardio-omentopexy, in which the omentum was sutured to the heart with the objective of increasing its perfusion. In 1946, Arthur Vineber³, a Canadian surgeon, proposed the direct implantation of the internal thoracic artery on the myocardium as a form of reestablishing the coronary flow in patients with angina. Due to inconsistent results and the development of direct coronary artery revascularization techniques this procedure was gradually abandoned. In 1965, Sen et al⁴ proposed the creation of transmural channels in the left ventricular wall to enable the direct perfusion of the ischemic myocardium with oxygenated blood from the LV. This concept was based on reptilian hearts, in which the left ventricle is directly perfused by endothelium-lined channels radiating from the ventricular cavity. In the 1980's, the "cardiac sinusoids" concept was resumed and the laser revascularization era began^{5,6}. Using carbon dioxide or Holmium Laser (Light Amplification by Stimulated Emission of Radiation), the myocardium of a supposedly ischemic area was perfused with the objective of increasing perfusion and decreasing symptoms in refractory angina. Channel opening using laser was histologically investigated, and there is no evidence that they remain patent after the procedure. On the contrary, they are almost immediately filled with cells and blood and, thus, blocked. Other mechanisms hypothesized to explain the effect of laser in the improvement of angina are neoangiogenesis, cardiac sympathetic denervation⁷, in addition to the procedural placebo effect. The first two are also hypothetical and there is no definitive proof that they have any effect on the process of improvement of anginal symptoms. The placebo effect is another possibility that will be discussed further on.

Currently, two modalities of laser revascularization are available. The first is surgical (TMLR – transmyocardial laser revascularization), via a small lateral thoracotomy through which laser perforations are performed; the second is performed percutaneously (PMLR – percutaneous myocardial laser revascularization). The laser catheter is advanced up to

the left ventricle and the perforations are performed from the endocardium toward the epicardium. The first method was approved by the FDA in 1998, and the second is still considered experimental. The FDA did not approve the concomitant use of laser with revascularization, although in a recent record 67% of the procedures were associated with myocardial revascularization surgery⁸.

Randomized double-blind placebo-controlled studies

To date, only three randomized double-blind placebo-controlled trials with transmyocardial laser, all percutaneous, have been published.

Stone et al⁹ evaluated patients with refractory angina caused by one or more total occlusions of native coronary arteries. A total of 141 consecutive patients with CCS (Canadian Cardiovascular Society) class III-IV angina and complete coronary artery obstructions – in which percutaneous balloon intervention failed – were randomized at 17 medical centers to PMLR plus maximum medical therapy (MMT) or MMT only. Patient blinding was achieved through sedation and dark goggles. Assessment of endpoints in the follow-up period was made without awareness of the treatment used. Patients with LVEF < 30%, MI in the past three months, inability to perform an exercise test, among other criteria, were excluded. The primary endpoint was improvement in the exercise test duration. PMLR was performed using Holmium laser with fluoroscopic guidance. The exercise test duration was assessed in only half of the patients six months after the procedure and did not show any difference between the groups. Anginal symptoms after six months were also similar between the groups. No differences were observed as regards clinical events, including mortality and MI, although a higher tendency of events in the laser group was observed (cardiac tamponade, pericardial effusion, ventricular tachycardia / fibrillation, cardiac marker elevation).

Salem et al¹⁰ randomized 82 patients with CCS III and IV angina to PMLR or placebo procedure. The two groups were comparable as regards their baseline characteristics, and patients with myocardial infarction, heart failure, unstable

Key words

Angina do peito refratária, revascularização a laser, efeito placebo.

Mailing Address: Mário Sérgio Soares de Azeredo Coutinho •

R. Dr. Percy João de Borba, 129 - 88036-200 – Florianópolis, SC, Brazil

E-mail: mcoutinho@cardiol.br

Manuscript received March 28, 2006; revised manuscript received May 1, 2006; accepted May 18, 2006.

angina requiring hospitalization within 14 days prior to the procedure, and others, were excluded. The primary endpoint was improvement of angina class (CCS). In the six and 12-month post-procedure assessment, a significant improvement of the group treated with PMLR in comparison with the placebo group was observed. However, in the objective measurements of exercise tolerance (treadmill time, respiratory exchange rate, and oxygen consumption), the two groups showed similar results. No changes in ejection fraction were observed after 12 months of follow-up, and the event-free survival showed to be similar in the two groups by the end of one year.

Leon et al¹¹ conducted a randomized double-blind placebo-controlled trial with PMLR in 298 patients refractory to the usual therapy with beta-blocker, calcium antagonist and nitrate. They were randomly assigned to three groups (laser-placebo, low-dose, and high-dose laser). The primary endpoint was exercise test duration. Patients who received laser (low or high dose) had a 30-day mortality higher than the placebo group ($p=0.03$). At six months, no difference was observed between the three groups as regards exercise tolerance. Likewise, no significant improvement was observed in any of the groups as regards CCS angina class. No changes in myocardial perfusion as measured by nuclear SPECT (rest and stress) performed 6 months after the procedure were observed either. The authors conclude that "all other randomized studies on this subject should be analyzed with caution and skepticism, unless appropriate attention is given to the placebo-effect of experimental laser therapies".

Randomized open-label non-placebo-controlled trials compared with medical therapy

Six other randomized open-label medical-treatment controlled trials without placebo control were published.

In 1999, Frazier et al¹² published the results of a randomized study of 192 patients (91 treated with TMLR and 101 with medical therapy), where the primary endpoint was severity of angina according to the CCS classification. Open and blind assessments were performed and no difference was observed between them. Patients undergoing TMLR had better angina scores when compared with the control group (67% vs. 20%). No difference was observed in the 12-month mortality between the groups. Likewise, no difference was observed between the groups of pharmacologic-stress perfusion SPECT studies at any moment of the follow-up, that is, no objective evidence of perfusion improvement was demonstrated with the procedure. Of the 101 patients randomized for medical therapy, 60 (59%) eventually underwent TMLR, which, to a certain extent, distorted the results, since randomization was disregarded. The investigators acknowledge this study limitation and argue that the patients were offered the cross-over to TMLR as an encouragement to remain in the study. This shows that there was a bias on the part of the investigators who took a pro-TMLR attitude. In the face of these flaws, this study was heavily criticized in its respective editorial¹³.

Allen et al¹⁴ published their results concomitantly with Frazier's study. A total of 275 patients with class IV refractory angina with no potential for angioplasty or surgery were

randomized. One hundred and thirty two received TMLR plus medical therapy and 143 received only medical therapy. Parameters related to angina class and tolerance to exercise (the latter measured only in one third of the individuals and not measured in the study baseline), as well as the number of individuals considered as therapeutic failures were better in the TMLR group. No difference in mortality was observed between the groups in the 1-year follow-up. However, once again, perfusion studies did not show any differences between the groups, raising doubts about one of the mechanisms proposed to explain the beneficial effects of laser therapy. Also, no improvement in ventricular function after the procedure was verified.

In the editorial that accompanies the two studies described above, Lange and Hills¹³ mention that TMLR is not risk-free and that in early observational studies mortality was between 10% and 20% and was higher among individuals with depressed ejection fraction. When these patients were excluded, mortality dropped to 5%. Perioperative morbidity is between 32% and 68% in different studies (non-fatal infarction, heart failure, arrhythmias, and surgical and respiratory infections). The editorialists also mention that procedural costs are not negligible and conclude their comments in a skeptical tone as regards the laser revascularization procedure.

Schofield et al¹⁵ studied 188 individuals with refractory angina in the United Kingdom. They were assessed at 3, 6 and 12 months as to their physical ability in the treadmill test and 12-minute walking test. No difference in these parameters was demonstrated between the groups randomly assigned to TMLR and medical therapy. Mortality was similar between the groups, but angina scores were better in the TMLR group. Once again, perfusion studies did not show any difference between the groups after 12 months, and the same occurred with the LV ejection fraction. The editorialists mention the inconsistency between these results and those of another study, saying that in March et al's study¹⁶ countless problems occur regarding the presentation of key data, which seriously affects the interpretation of the findings. They conclude saying that "relegating laser to a mere and costly analgesic procedure ruins most of the expectations of those who believed in a laser 'revascularization'"¹⁷.

Burkhoff et al were the investigators in the ATLANTIC study (Angina Treatments-Lasers and Normal Therapies in Comparison)¹⁸. They recruited 182 patients from 16 centers in the USA with CCS III-IV angina, reversible ischemia, and incomplete response to other therapies. The patients were randomly assigned to TMLR ($n=92$) or medications ($n=90$). After 12 months a significant increase in exercise tolerance, as well as in angina scores, was observed in the TMLR group. Perfusion studies and LV ejection fraction did not show significant modifications at 3, 6, and 12 months post-procedure in both groups.

The PACIFIC study (Potential Angina Class Improvement From Transmyocardial Channels)¹⁹ randomly assigned 221 class III-IV patients with poor response to medication to Holmium laser TMLR plus medication or medication only. The primary endpoint was exercise tolerance at 12 months. The results showed an 89-second increase in exercise tolerance when compared with the 12.5-second increase in the TMLR and

medication groups ($p=0,008$), respectively.

The PACIFIC and ATLANTIC studies were fully sponsored by the manufacturer of the laser equipment used. The investigators acknowledge that one of the problems with both studies was the non-blinding of the investigators and patients, which introduces an important assessment bias, mainly when dealing with subjective endpoints. Additionally, they mention that the mechanism of the occasional improvement of patients remains unknown, and they do not deny that the placebo effect may explain the results to a certain extent.

A Norwegian study conducted by Aaberge et al²⁰ randomly assigned 100 patients to medical therapy or TMLR using symptoms, physical ability and maximum oxygen consumption as measured by the exercise test as the primary endpoint. Although angina scores were better in the TMLR group in relation to the group medically treated, the objective parameters of physical ability such as treadmill time and maximum oxygen consumption were not different between the groups. Morbidity and mortality after one year was similar between the two groups. No change in the ejection fraction was observed one year after the procedure. The authors mention that “cardiac laser treatment” (rejecting the term ‘transmyocardial revascularization’) may work in the reduction of symptoms but “there is no convincing evidence that it improves cardiac function or reduces the number of ischemic events”. They acknowledge that double-blind, placebo-controlled studies with PMLR are essential to assess the role of the “placebo effect” in the results of the procedure.

A meta-analysis by Liao et al²¹ included seven randomized trials completed up to 2003. They were all randomized open-label non-placebo-controlled studies. Control groups were usually comprised of patients using conventional therapy for angina. The meta-analysis concludes that there are no differences in mortality between the groups with laser treatment and those with standard treatment. The group treated with laser showed a reduction of symptoms (≥ 2 CCS classes) up to one year after the procedure. The authors do not mention the role of open-label studies and the absence of placebo controls as potential sources of biases.

Non-controlled observational studies

Observational studies are not methodologically adequate to study the efficacy of interventions in the clinical practice. In a recent review on laser revascularization in the treatment of refractory coronary artery disease²², the several non-randomized non-controlled case series showed an overall improvement of symptoms and, in a few studies, showed an improvement of the physical ability as measured by exercise time. However, there was no objective confirmation of improvement of myocardial perfusion with the imaging methods used. Since the phenomenon of a greater number of “positive studies” in the records and case series is already known, these conclusions should not be used as guidelines for the adoption of interventions, but only as generators of hypotheses to be tested in randomized trials. In this review, the authors conclude that “the results of recent double-blind studies are conflicting, suggesting a significant placebo effect in response to PMLR. Further larger clinical trials are

recommended to elucidate the value of this technique”.

Guidelines

The Brazilian Guideline of Chronic Coronary Artery Disease²³ recommends TMLR as class IIb-B (acceptable reasonable evidence, considered alternative treatment, based on small randomized studies, and non-randomized and observational studies), acknowledging the lack of consensus regarding its indications and its real efficacy. The study with 40 patients of the *Instituto do Coração* mentioned in the guidelines does not appear in the references of the document. The only Brazilian reference is a series of 20 cases published in 1999²⁴. The American guidelines for stable angina²⁵ published in 2002 recommend TMLR as class IIa but acknowledge that there are no long-term studies assessing the results of this technique. They also recommend studies to evaluate the performance of TMLR alone or in addition to surgical revascularization.

Scientific research, biases, and placebo effect

Any scientific research may be invalidated by systematic errors called biases. In the case of laser in refractory angina, the sources of biases start with the assessment of angina. Since angina is a symptom, it is impossible to assess it objectively and precisely. The three randomized blind studies⁹⁻¹¹ published to date did not show any differences in exercise time and in perfusion after laser procedure when compared with controls. Only one of these studies¹⁰ with a small sample showed improvement of symptoms six months after the procedure. These discrepancies have been explained by technical differences in laser application^{26,27}. However, differences observed between non-blind non-placebo-controlled studies and randomized blind placebo-controlled studies may be possibly attributed to differences in the study methodology more than to technical issues related to the procedure.

In clinical studies, physicians and patients always have expectations regarding the results of the procedure being evaluated. Highly motivated patients eager for a new treatment modality able to relieve their symptoms naturally expect a clinical benefit. The word “laser” is associated with – in the patients imagination, as well as in the physicians’ – a highly efficient state-of-the-art technology as a “last resource”²⁸ in the treatment of angina. Therefore, symptoms will very likely be evaluated in a distorted manner, since laser is “expected” to produce a positive effect. A direct relation between the degree of stress and the placebo effect is also known to occur, especially if the endpoint assessed is pain²⁹.

The control of assessment bias is achieved using double masking (investigator and patient) or double blinding. The use of placebo in studies on new interventions is a must to define usefulness or futility. Until the most recent studies with placebo-laser, laser therapy in angina pectoris was compared with the standard medical therapy. In the case of surgical transmyocardial laser intervention, blinding was unfeasible, thus results were weakened by potential biases. In the case of percutaneous laser in angina, the comparison with placebo is feasible, although methodologically more complex⁹⁻¹¹. In the most recent randomized study published comparing laser at

two “doses” and placebo-laser¹¹, the latter group showed a 30% improvement in the symptoms and in exercise time after the procedure, a result that was not different from that of the groups that received laser.

The placebo effect in cardiovascular diseases has already been described in several situations, including angina³⁰. Improvement of symptoms in patients with stable chronic effort angina is estimated to be possibly achieved with placebo in 30%-80% of the cases³⁰. Invasive and surgical procedures have great potential for a placebo effect³¹. The classical example of placebo effect in cardiovascular surgery is credited to the internal mammary artery ligation procedure in the treatment of angina. This procedure was proposed in the 1950's and was routinely used until a randomized study³²

with a control group (thoracic incision was performed without artery ligation) showed that there was no difference between the groups regarding the improvement of symptoms. That is, the simple act of sectioning the skin on the chest was able to provide subjective benefits.

In this review, we sought to synthesize the clinical and scientific experience on the use of laser therapy in the treatment of refractory angina pectoris. Preliminary randomized observational studies showed positive results with this therapy. However, randomized placebo-controlled, which are, therefore, methodologically stronger studies, highly suggest the possibility of occurrence of a placebo effect of laser therapy in refractory angina.

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