Levosimendan and Low Cardiac Output Syndrome. Does Mortality Really Decrease?

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In 1977, Goldman stated that elective surgery should not be performed in patients with signs of heart failure.[1] Things have changed considerably in the more than 30 years since the publication of his well-known index. Today, heart failure is no longer necessarily considered a contra-indication to surgical intervention, although it should be carefully evaluated as a risk factor for complications.[2]

In Spain, over 4 million non-cardiac surgical procedures are performed annually. The relative risk of perioperative complications in these procedures ranges from 0.4% to 11%, depending on the type of surgery and the patient's prior clinical status. The latter can be assessed in terms of 5 basic parameters involving the presence of ischemic heart disease, congestive heart failure, cerebrovascular disease, renal dysfunction, and insulin-dependent diabetes.[2]

In comparison to the 4 million patients who receive non-cardiac surgery annually and who have a relatively low risk of cardiovascular morbid-mortality, a total of approximately 15 000 cardiac surgery interventions using extracorporeal circulation (ECC)[3] are performed each year in adults. In this type of surgery, prior cardiovascular status is extremely important for prognosis and the, considerably higher, perioperative mortality is the most important individual factor taken into account when evaluating the quality of surgical programs.

In 2006, mortality in cardiac surgery which used ECC was 6.7% in Spain.[3] There were, nevertheless, considerable differences between different patient groups and, although causes of death were numerous, low cardiac output syndrome (LCOS) was present in many cases.

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Postoperative LCOS in Cardiac Surgery. Is Postoperative Acute Heart Failure Present in Cardiac Surgery?

LCOS can be considered a form of acute heart failure (AHF). In the same way that AHF produces high mortality in non-surgical patients,[4] LCOS is a major cause of perioperative death in patients undergoing cardiac surgery.[5,6] LCOS is, however, a peculiar form of AHF as it differs from the latter in etiology, prognosis, and treatment, all of which are influenced by the combination of surgery and anesthesia.

This is not the appropriate place to go into detail on the influence of this combination. Nevertheless, it is clear that the inflammatory response to surgery, the habitually positive balance suffered by these patients, transfusions and the effect of anesthetic drugs on cardiac frequency, peripheral resistance, and contractility all play a part in the deterioration that these patients suffer in cardiac surgery.[7]

In both AHF and LCOS, there is clearly an underlying myocardial dysfunction, though the term "AHF" is too broad and all-embracing. In the surgical context, "low output syndrome" is preferred, as it more precisely defines the patient's clinical condition. All surgical patients with a cardiac index of <2.2 L/min/m^2 and without hypovolemia have low output syndrome.[5,6]

The concept of hypovolemia in these patients is also potentially a subject for debate, given that normal pulmonary capillary pressure (PCP) in a patient with poor ventricular functioning might indicate relative hypovolemia. There is currently no agreement among authors as to which PCP value would allow relative hypovolemia to be discounted. We use a figure of 15 mm Hg[5]; Levin et al[6] use 16 mm Hg. It could be argued, however, that even in the presence of poor left ventricular functioning a PCP between 15 and 18 mm Hg would allow relative hypovolemia to be discounted. Achieving greater precision would mean using transesophageal echocardiography to quantify ventricular filling. Bearing in mind these provisos, LCOS is easy to diagnose, and although its incidence varies across the different published series, it is approximately 10%, with a mortality rate close to 20%.[5,6]

Although LCOS is not implicated in all deaths after cardiac surgery, it can likely be said to have a part in the majority of deaths. LCOS prolongs the period of invasive monitoring and mechanical ventilation, both of which increase infection rates and are largely responsible for the deterioration in renal functioning. In that sense as well, LCOS' impact on mortality is apparent. In fact, LCOS can be considered a complication of cardiac surgery which directly causes further complications.

Treating LCOS. The Role of Levosimendan

Although the general principles for treating AHF apply in the case of LCOS, there are nevertheless some clear differences. Adequate oxygenation should be ensured by using mechanical ventilation and the usual anesthetic care. In surgical patients with low output, hypertension is not present and vasodilatation should be approached with caution in patients who are already usually vasodilated.

Given that contractility is affected by myocardial ischemia stemming from use of an aortic clip, inflammatory response, and some anesthetic drugs, inotropic agents are used in the operating theater and in the immediate postoperative context much earlier and in higher doses that in non-surgical patients. Balloon counterpulsation or mechanical ventricular assistance are also usually used much earlier and more frequently than in non-surgical patients.

According to the European Society of Cardiology guidelines for the treatment of AHF, levosimendan is the inotropic drug for which most evidence is available.[8]

The same level of evidence is not available regarding the drug's use in surgical patients. Published series have usually included only a small number of patients, have been performed in only 1 center, and have not analyzed survival.[7]

The study by Levin et al[6] is the first to analyze survival in a series of more than 50 patients.

Since it was first used in a clinical context and in spite of an initial lack of data on its use in surgical patients, levosimendan is now well-situated as an option among drugs capable of improving contractility in patients undergoing cardiac surgery.

In spite of the use of highly variable doses, clinical research with the drug in patients undergoing cardiac surgery has shown it increases cardiac output in patients with normal or depressed contractility.[7,9] Given that it is a vasodilatory drug, it also produces a significant reduction in peripheral vascular resistance and a subsequent fall in mean arterial pressure, because the cardiac output does not compensate for the reduction in resistance.

Although the resulting hypotension is moderate, the fact that it was accompanied by an increase in cardiac frequency[5-7,9] meant that prudence was advisable when using the drug in coronary patients. This was due to the fact that the decrease in coronary perfusion pressure could compromise coronary blood flow whilst tachycardia could cause a rise in myocardial oxygen consumption.

After initial precautions, it was confirmed that the drug was safe to use in both operated and non-operated coronary patients. Lilleberg et al[9] also showed, in a small series, that levosimendan was safe in patients who had undergone coronary revascularization. They showed that coronary blood flow increased and that myocardial oxygen consumption was not altered in the patient group treated with levosimendan. This finding helped to rule out the existence of phenomena such as coronary steal.

Tritapepe et al,[10] again in a small series of patients, explored the possibility that levosimendan might produce pharmacological preconditioning. Although this is undoubtedly an interesting avenue for research, further studies are required to confirm the hypothesis. If pharmacological preconditioning of the myocardium is of great interest in coronary patients, the possibility of at least partially recovering stunned myocardium is no less important. Recovery of stunned myocardium using levosimendan has been demonstrated both experimentally and clinically.[11]

The accumulation of publications indicating the efficacy and safety of levosimendan in patients undergoing cardiac surgery means that it is increasingly used in several high risk situations, such as emergency myocardial revascularization, cardiogenic shock, and the disconnection of ECC.[7]

All of these studies included only a small number of patients and none of them were randomized or multicenter studies. The level of evidence they provide is therefore low and they do not provide sufficient basis to make a definitive recommendation for the systematic use of levosimendan.

As regards low output syndrome, the information available is fortunately a little more conclusive, and there are series which confirm improvement.[5,6]

In this context, the study by Levin et al[6] provides further confirmation that levosimendan improves cardiac output in patient with postoperative low output. The study's importance does not stem so much from this contribution, however, as from its contribution to data on morbidity and survival.

Levosimendan and Survival in Cardiac Surgery

Levosimendan was introduced into clinical practice based on favorable results from the LIDO[12] and RUSLAND[13] studies and although the results from the SURVIVE[14] study have not confirmed the tendency, its use in patients with worsening heart failure is based on improvements in survival.

To date, levosimendan's use in cardiac surgery has not been based on a clear demonstration of survival benefit.[7] Levin et al's[6] most original and important contribution

are the new data they provide on survival. There are no studies on differences in survival in surgical patients treated with levosimendan and although a series of 137 patients (69 treated with levosimendan vs 68 treated with dobutamine) may be considered too small to assess hospital mortality it is nevertheless the only series which has analyzed survival to date.[6]

The differences in observed mortality (8.7% in the levosimendan group compared to 25% in the dobutamine group) generate a number of unknowns which require clarification. The first and most important is whether the effect on mortality would be repeated in a multi-center study (the Levin et al[6] study was carried out in only 2 hospitals) and in a larger number of patients. The second question which any future study should aim to answer is whether the difference in mortality is maintained to 6 months.

As well as the gain in survival, Levin et al also show a significant reduction in some of potentially fatal complications in LCOS. Specifically, there was a significant improvement in terms of perioperative infarction, vasoplegia, acute renal failure, ventricular arrhythmias, inflammatory response syndrome, sepsis, and the need for prolonged ventilatory assistance. On the other hand there were no statistically significant differences between the 2 groups in terms of need for dialysis, atrial fibrillation, adult respiratory distress syndrome, pneumonia, or stroke.

There are some contradictory findings here, such as the reduction in the need for prolonged ventilation without a reduction in the incidence of pneumonia or adult respiratory distress syndrome. Undoubtedly, these details could be clarified in a series with a larger number of patients. Among the data provided by Levin et al, some are very suggestive, such as the reduction in inflammatory response syndrome, which was scarce in both groups. The reduction in inflammatory response syndrome finds support in Parissis et al's results,[15] which showed a reduction in mediators of inflammation in patients treated with levosimendan. It is surprising that this finding has still not translated into a useful recommendation in surgical patients, in spite of the fact that inflammatory response is becoming the new "holy grail" in preoperative medicine.

Conclusions

Levosimendan continues to show beneficial effects in patients undergoing cardiac surgery. Nevertheless, its true usefulness remains unclear due to a lack of evidence from large-scale trials. We can guess at its possibilities, but further evidence is required.

The first evidence that levosemindan might lead to improvements in survival is now available, but it is not definitive. A large-scale, multi-center, randomized trial is required to throw more light on the situation. The primary end-points of such a trial should be hospital mortality and mortality up to a minimum of 6 months. Secondary endpoints might include inflammatory response, pharmacological preconditioning, and the effect on stunned myocardium in patients undergoing myocardial revascularization.

In Spain, some groups have published on this topic.[5,11] It will likely be up to us to perform the study. We owe it to our patients. However, we are well aware of how easy it is to perform a study in a small number of patients and centers and how complicated it is to carry out a large-scale, multi-center study. The latter can really only be performed with support from the pharmaceutical industry. In the meantime, our knowledge will only be partial and evidence will be scarce.

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