Levosimendan in Septic Shock

Comment on and Summary of:
Gordon AC, Perkins GD, Singer M, et al. Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis. N Engl J Med 2016; 375: 1638-48.

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Sepsis, which is defined as organ dysfunction due to the irregular host response developing against infection, is among the leading causes of death in the world. Septic shock is a clinical condition that requires vasopressors to ensure blood pressure targets despite adequate fluid resuscitation (1). It is known that catecholamines used as the first option in the treatment of septic shock cause serious adverse effects such as myocardial damage and peripheral ischemia at high doses (2). For this reason, there is a need for treatment options that can be used as an alternative to catecholamines in the treatment of septic shock.

The argument that levosimendan which is used in the treatment of heart failure may be among the treatment options for these patients has been on the agenda recently. Levosimendan, which is defined as a calcium sensitizer agent, has been shown to ensure improvement in the contractile performance without increasing myocardial oxygen consumption (3). Therefore, it may be considered to be an appropriate option in treatments of patients with septic shock. In the literature, there are some studies evaluating the effects of the use of levosimendan in sepsis on hemodynamic parameters, renal and hepatic functions. In the meta-analysis carried out by Zangrillo et al. (4) on the use of levosimendan in sepsis, 7 studies including a total of 246 patients were evaluated. It was stated that mortality rates were lower in patients administered levosimendan compared to patients administered standard inotropic treatment protocols.

Although there are several studies and meta-analyses carried out on the use of levosimendan in septic shock, there are still question marks on many issues such as in which cases levosimendan will be added to treatment, at what dose it will be used and with which medications it will be combined. The results of the multicentric, double-blind, placebo-controlled, randomized clinical trial carried out by Gordon et al. (5) were expected to answer these questions. This study, which was published in NEJM and in which the effects of the use of levosimendan in sepsis to prevent development of acute organ dysfunctions were evaluated, was carried out with the concurrent participation of 34 intensive care units in the United Kingdom. In addition to routine treatment, levosimendan was added to the half of the patient group at a dose range of 0.05 to 0.2 µg/kg/min, while placebo was added to the other group. The study drug was administered as 24-hour infusion. A total of 516 patients consisting of 259 patients in the levosimendan group and 257 patients in the placebo group were included in the study in which adult patients with septic shock receiving vasopressor support for at least four hours were included. At the beginning of the study, the mean norepinephrine dose administered to patients was determined to be 0.28 µg/kg/min. If patients developed hypotension, IV fluid bolus was administered, or the dose of the vasopressors administered was increased. The clinicians were able to use other inotropic agents in case of necessity, primarily as dobutamine. The mean arterial pressure was found to be lower in the levosimendan group in the first 24 hours during infusions continued, and it was observed to be similar between groups after 24 hours. It was observed that the duration and doses of norepinephrine infusion were higher in the levosimendan group while the need for dobutamine was less. The heart rate was reported to be higher in the levosimendan group during the first four days.

The primary outcome, the mean SOFA score was determined to be 6.68±3.96 in the levosimendan group and 6.06±3.89 in the placebo group (mean.dif. 0.61; 95% [CI],0.07-1.29; p=0.053). For the evaluation of the effects of levosimendan on individual organ systems, sub-analyses were performed by evaluating each component of the SOFA score separately. However, as a result of the study, it was observed that levosimendan had no positive effect on the total SOFA score and its individual parameters.

Mortality at 28 days was considered the secondary outcome and no significant difference was found between the groups. The mortality rates were found to be lower in this study compared to other similar studies carried out with levosimendan in the literature. Gordon et al. (5) stated that this situation could be explained by the fact that patients from a wider population were included in the study and low cardiac output was not a prerequisite for study entrance. The rate of the incidence of tachycardia was found to be higher in the levosimendan group, and it was stated that this could be explained by the fact that higher doses of norepinephrine were used in the group who was administered levosimendan, and by catecholamine-induced myocardial dysfunction.

The fact that other inotropes were also used in patients is one of the limitations of this study. For example, dobutamine was more frequently used in the placebo group compared to the levosimendan group. This can be shown as the reason for the fact that the parameters such as cardiac index and stroke volume were not found to be better in those administered levosimendan compared to the placebo group. The fact that regular echocardiographic analyses were not performed to give more detailed information about myocardial functions in patients administered levosimendan can also be among the limitations of the study. For these reasons, this study, contrary to expectations, cannot be considered as a study that can be a guide in the use of inotrope in patients with sepsis, as it is stated by the authors.

In conclusion, levosimendan can be considered as an alternative to catecholamines in the treatment of septic shock that develops especially in patients with heart failure when its effects like ensuring improvement in contractile performance without increasing myocardial oxygen consumption and not disturbing diastolic relaxation are taken

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into account. However, it is observed that there are still not enough studies carried out on this subject and that the results of the studies carried out do not exactly support the use of levosimendan in septic shock. There is no clear recommendation regarding this issue in the recently published sepsis guideline (6). It is thought that comprehensive studies on the use of levosimendan in patients with septic shock should be carried out.

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