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A Case Report of Cautious Use of Levosimendan in Patients of Acute Heart Failure and Multi-organ Damage: Potentially Reasonable and Salvageable

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Abstract

Levosimendan, an amazing organ protector in acute heart failure, is currently not recommended in the events of moderate-to-severe renal impairment and shock. We report two critical cases that suffered from such poor clinical conditions associated with acute heart failure. Given that there was no better solution for enhancing heart function, we used levosimendan with great caution. We also introduced new-generation hemodynamic monitor, and the result suggested the benefit of levosimendan. We concluded that even in the event of multi-organ damage, early and cautious use of levosimendan may not only be safe, but also beneficial in salvaging end-organ functions. Using hemodynamic monitor carefully will warrant the best benefit and evade potential side effects. (J Intern Med Taiwan 2016; 27: 202-206)

Key Words: Renal impairment, Shock, Myocardial dysfunction

Background

Levosimendan, a calcium sensitizer, increases myocardial contractility and dilates both the peripheral and coronary vessels without substantially increasing oxygen consumption. Despite several promising reports, the role of levosimendan in critical illness has not been thoroughly evaluated. Although no benefit on mortality was reported in the SURVIVE randomized trial (The Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support)[1], these two outstanding mechanisms of levosimendan play an important role in multi-organ failure. However, the use of levosimendan is not recommended in the events of moderate-to-severe renal impairment (creatinine clearance < 30ml/min), severe hepatic impairment, severe hypotension and tachycardia.

In this case report, we described two patients who reaped great benefit from levosimendan therapy, even though their initial condition seemed inappropriate.

Case presentation

Case 1

A 75-year-old man under conservative treat-

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ment for NSTEMI (non-ST segment elevation myocardial infarction) and gastrointestinal bleeding had acute decompensated heart failure and acute kidney injury initially. Even under full support of ventilator, oxygenation was still poor. The echocardiography showed global hypokinesis and the LVEF (left ventricular ejection fraction) was 42%. His serum troponin-I level elevated to 68.17ng/ml, BNP (B-type natriuretic peptide) was 2300pg/ml, and creatinine rose to 2.3 mg/dl. We performed the AESCULON, a noninvasive cardiac output electrical cardiometry, which predict patient's hemodynamic by the changes of bioelectrical impedance, and its data revealed hemodynamic compromise of cardiac origin. The CI (cardiac index) was 2.99, SV (stroke volume) was 40.8 ml, and blood pressure was 90/64 mmHg.

Due to extreme high risk of emergent cardiac catheterization or other invasive procedure, levosimendan was prescribed immediately. In face of hypotension, the infusion dosage decreased from 0.1 mcg/kg/min to 0.05 mcg/kg/min. We even held the infusion when blood pressure dropped to 80/62 mmHg. What's comforting is that the hemodynamic data showed preserved heart function (CI 3.01, and SV 42.0ml when holding infusion), so we still kept low dose infusion (0.05 mcg/kg/min). His urine amount increased dramatically, and the pulmonary edema resolved. No significant chest pain or severe arrhythmia occurred. Coronary angiography one week later revealed the left anterior descending artery and the right coronary artery critical lesions, and intervention was done uneventfully. We had a follow-up echocardiography three months later, and the LVEF had improved to 52%.

Case 2

A 60-year-old man suffered from severe sepsis after chemotherapy for lung cancer. There was shock with multiple organ damage, including respiratory failure, hepatic failure (total bilirubin 10.8 mg/dl), kidney damage (creatinine rose to 5.10 mg/dl), and pancytopenia. Acute myocarditis was also diagnosed by positive cardiac markers, ST segment elevation on electrocardiogram, but patent coronary angiography. The echocardiography showed severe hypokinesis (LVEF: 30%). AESCULON data suggested sepsis with low cardiac output. (Systemic vascular resistance 993 dyne•s/cm^5, cardiac index was 3.53 and stroke volume was 43.2 ml.) Under moderate dosage of vasopressor treatment (Norepinephrine 0.23mcg/kg/min), the blood pressure could be scarcely maintained at acceptable range, but tachycardia with atrial fibrillation developed.

We tried adding levosimendan at moderate infusion rate (0.1 mcg/kg/min), and it surprisingly didn't affect blood pressure. Tachycardia subsided with SV improved soon (62.7ml on the next day and 66.5ml on the third day). Vasopressors were tapered off after 2 days, and the CI improved without drop of SVR (CI was 4.04, and SVR was 762 dyne•s/cm^5 on the third day). Follow-up echocardiography on the third day showed improving systolic function (LVEF: 40%), and it reverted to normal (55%) two weeks later. Although immunosuppression caused some difficulties in infection control, his renal function completely returned to normal (creatinine 0.92 mg/dl) three weeks later.

Discussion

The successful recovery of our cases may be attributed to the rapid revival of end-organ functions, for we know multi-organ failure is a vicious cycle, and severe heart failure often comes along with renal failure. In the past, levosimendan therapy was considered controversial in critically ill patients because of renal dysfunction, and severe renal impairment (creatinine clearance <30 ml/min) is thought to be contraindicated. On the contrary, cautious use of levosimendan may be reasonable since the longer half-life of its metabolites, OR-1855 and OR-1896, can prolong its effects in patients of renal failure without sequelae.[2] Besides, levosimendan

could be regarded as a savior of renal function. The preglomerular vasodilation effect of levosimendan may increase renal function.[3] A randomized control study by Hou et al on 66 patients demonstrated great improvement of renal function after continuous infusion for 24 hours.[4] In our case reports, both patients had very poor renal condition during shock. The estimated creatinine clearance rate was 20.4 ml/min in case 1, and 16.9 ml/min in case 2 by Cockcroft-Gault formula, which was much worse than the average of Hou's study population (39.4 ml/min).[4] Since acute kidney injury is only a temporary sequela, the benefits of early levosimendan use may overweigh its potential adverse effects on renal function. Recently, a study had been started on the effect of Levosimendan in Acute Kidney Injury (LAKIS, NCT01720030).

The other contraindication of levosimendan use is shock, because it causes vasodilatation. However, both experimental and clinical studies have shown that levosimendan can improve cardiac function during septic shock.[5] Its anti-inflammatory effects can reduce the release of proinflammatory cytokines.[6] Levosimendan has also been studied in patients with severe septic myocardial dysfunction, showing better outcomes compared to Dobutamine.[7] A meta-analysis of seven small randomized trials revealed that levosimendan may reduce mortality in patients with severe sepsis and septic shock, compared to conventional inotropic therapy.[8] However, this meta-analysis couldn't tell us specifically whether it is more beneficial for patients with severe heart failure and renal failure. On the other hand, in our second case, levosimendan demonstrated a powerful and safe effect on a patient with septic shock, fulminant myocarditis, hepatic failure, and renal failure. In this case, norepinephrine had been infused before the use of levosimendan, which made the use of levosimendan more controversial. (And currently, severe hypotension is a contraindication of the use of levosimendan) Levosimendan is a calcium sensitizer that can accelerate the velocity of calcium signal propagation, and finally preserving myocardial contractility.[9] Therefore, in our case, even though sepsis had resulted in multi-organ failure, the cautious use of levosimendan may sometimes be life-saving. Most promisingly, the LeoPARDS Clinical trial (Levosimendan for the Prevention of Acute oRgan Dysfunction) is still ongoing and may provide more information in the future.

Currently, the contraindication of levosimendan was established since 2006, but experience of using levosimendan had make something difference in this decade. The advanced hemodynamic monitor is the powerful weapon to guard the clinical influence of its side effect, such as hypotension. In a very brief time, we can decide if levosimendan could be kept used or not.

Conclusion

Our case report showed that cautious use of levosimendan may have great benefit in critically ill patients. Whether or not levosimendan is contraindicated during acute kidney injury should warrant more investigations. Even in the event of multi-organ damage, levosimendan may play the role of organ protector, if used sparingly and be monitored carefully.

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謹慎使用心得適在心衰竭與多重器官衰竭病人：合理且能以救命

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摘　要

心得適(Simdax)，學名Levosimendan，是一個透過增加鈣離子敏感度來增強心肌收縮的新奇藥物。他的好處包括不增加心肌的耗氧，還能促使冠狀動脈與周邊動脈的血管擴張，進而在多重器官衰竭中扮演器官保護的重責大任。然而，在中度至重度腎衰竭、嚴重肝損傷、嚴重低血壓與心博過速的況狀時，這個藥物並不建議使用，然而，這些不被建議使用的狀況，卻也是我們亟需挽救的目標。(註1) 因此，我們做了兩位因急性心臟衰竭而病危的個案報告、並加以文獻回顧與自己的見解，來闡明Levosimendan的使用或許可以超越目前的禁忌症，說明它不僅安全，且能在器官的末路上力挽狂瀾。個案一是75歲的老爺爺，因急性心肌梗塞與胃腸道出血來的又快又急，一開始只用藥物治療。過了半天就併發心臟衰竭、急性肺水腫、呼吸衰竭、心因性休克與急性腎衰竭。此時因為極度不穩的血氧與血壓，緊急心導管絕對是極高風險，於是當機立斷使用「心得適」較低劑量輸注(0.05微克/公斤/分鐘)。即便面臨血再度下降的血壓，但過程中也沒有顯著的胸痛及心律不整。個案二是一位肺癌剛作完化學治療的60歲男子，因敗血性休克產生多重臟器衰竭(急性心肌病變合併心臟衰竭、呼吸衰竭、肝衰竭、急性腎衰竭)。在緊急心導管排除急性心肌梗塞之後，即使當時已使用中劑量的升壓劑，仍斷然開始「心得適」的較低劑量輸注(0.1微克/公斤/分鐘)。雖然有心搏過速與心房顫動，但血壓沒有繼續下降。多重器官衰竭是一種惡性循環，必須要出重手迅速打破它。Levosimendan若想扮演好這位拳擊手的角色，就必須證明它在器官衰竭當下，仍然是可以使用的。研究證明，在腎功能衰竭時，Levosimendan的治療半衰期得以拉長且無後遺症。(註2) 也有隨機對照的研究指出，Levosimendan 可以擴張入球小動脈，(註3) 並在輸注24小時後改善腎功能。(註4) 我們的個案也印證Levosimendan對腎臟是大有好處的。至於在敗血性休克時，研究指出，Levosimendan可以改善心臟功能，(註5) 且此藥物也有抗發炎的效果。(註6) 若是敗血症引起的心肌功能障礙，Levosimendan比Dobutamine有更好的臨床效果。(註7) 薈萃分析也統計在出敗血性休克時，Levosimendan的療效比傳統強心藥物來的好。(註8) 更有趣的是，在使用傳統升壓藥物的情形下，心肌細胞會因為鈣離子敏感度減低而減少收縮力，而Levosimendan正是它的解決方案。(註9) 因此，我們認為即使在升壓藥的使用之下，此時再加上Levosimendan是可以被接受的。在血行動力學的監控下，謹慎使用Levosimendan對危急的病人可能有很大的幫助，但是否有目前禁忌症的調整，則需要更多的研究來證明。