Early Versus Delayed Administration of Norepinephrine in Patients with Septic Shock and Use of Oral Midodrine in Weaning off Norepinephrine in These Patients

Thesis

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Abstract

edefine sepsis as agreed upon by The Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) as the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) ***(Singer M., et al. 2016)***.

Sepsis: "life-threatening organ dysfunction caused by a dysregulated host response to infection." End organ damage is identified as an acute change in total Sequential [Sepsis-related] Organ Failure Assessment score (SOFA) ≥2 ***(Rhodes A., et al 2016).***

Septic shock: A subset of sepsis "in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. These patients can be clinically identified by a vasopressor requirement to maintain a MAP ≥ 65mmHg and serum lactate >2mmol/L in the absence of hypovolemia ***(Singer M., et al 2016)***.

"Severe sepsis" category was deemed to be superfluous and is no longer recommended for clinical use ***(Rhodes A., et al 2016)***.

Septic shock is the most challenging problem in critical care medicine and has a very high mortality, owing to the complex pathophysiology, the outcomes for septic shock patients remain disappointing ***(Angus DC., et al 2011, Annane D., et al. 2003 & Dombrovskiy VY., et al 2007)***.

Investigating the rational use of vasopressors in septic shock is very important. Thus far, most studies have focused on the rational use of different types of vasopressors ***(Daley MJ., et al., 2013, Russell JA., et al., 2008 & Sandifer JP. And Jones AE., 2013)***, and the third edition of the guidelines for management of septic shock also concentrates on the choice of vasopressors ***(Dellinger RP., et al., 2013)***. However, it is the timing of

vasopressor therapy, rather than the specific agent, that appears to be crucial ***(Parrillo JE., 2008)***.

The current guidelines recommend that vasopressors (norepinephrine as the first choice) be administered for hypotension refractory to initial fluid resuscitation and to maintain a mean arterial pressure (MAP) ≥65 mm Hg ***(LeDoux D., et al., 2000)***. According to the guidelines, physicians currently prefer fluid resuscitation without vasopressors until a lack of hypotension correction is confirmed. However, this may result in prolonged hypotension, and valuable time may have passed. For example, some vital organs could be damaged irreversibly because of low perfusion ***(LeDoux D., et al., 2000)***.

Midodrine is an orally available α1-adrenergic receptor agonist with a labelled indication for the treatment of symptomatic orthostatic hypotension ***(Wright RA., et al., 1998)***. Its therapeutic effect is due to desglymidodrine, an active metabolite formed by enzymatic hydrolysis of midodrine. After oral administration, the prodrug reaches peak serum concentrations within **30 min and desglymidodrine reaches peak serum concentrations in 1–2** h (Wright RA., et al., 1998). Due to midodrine's predictable **pharmacologic response and favourable sympathomimetic effects in patients with orthostatic hypotension, it is utilized as an off-label treatment to provide haemodynamic support to facilitate the weaning of IV vasopressor infusions in ICU patients. The overall goal of midodrine** administration is to minimize the adverse effects of IV vasopressors and **decrease ICU length of stay (Zachariah PK., et al., 1986).**

Keywords

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