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Review

Combining fluids and vasopressors: A magic potion? ☆

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ABSTRACT

Early detection and prompt reversal of sepsis-induced tissue hypoperfusion are key elements while treating patients with septic shock. Fluid administration is widely accepted as the first-line therapy followed by vasopressor use in persistently hypotensive patients or in those with insufficient arterial pressure to ensure adequate tissue perfusion. Recent evidence suggests a beneficial effect of combining fluids with vasopressors in the early phase of sepsis. Compared with fluids alone, combining fluids and vasopressors increases mean systemic pressure and venous return and corrects hypotension better. This approach also limits fluid overload, which is an independent factor of poor outcomes in sepsis. It produces less hemodilution than fluids alone. As a consequence of these effects, combined treatment may improve outcomes in septic shock patients.

Introduction

Management of septic shock is a complicated clinical challenge requiring early recognition and timely treatment of infection, hemodynamic abnormalities, and other organ dysfunctions. The principles of septic shock treatment have remained largely unchanged for decades, but the mortality rate has declined as suggested by epidemiological studies.[1–2] Early recognition of sepsis and timely treatment have contributed to improved outcomes. Besides early treatment of infection, hemodynamic optimization is a cornerstone of septic shock management.[3–4] Correction of hemodynamic abnormalities is based on the administration of fluids and vasopressors, as recommended by the Surviving Sepsis Campaign,[5] since hypovolemia and vasoplegia are the predominant abnormalities.

This review describes the different physiological and pharmacological reasons and benefits of combining fluids with vasopressors, even at the early phase.

Combination of Fluids and Vasopressors Increases the Mean Systemic Pressure More Than Fluids Alone

General concept of mean systemic pressure

According to Guyton's model of circulation,[6] the systemic venous return is proportional to the pressure gradient for venous return divided by the resistance to venous return (Rvr). The pressure gradient for venous return is the difference between the mean systemic pressure (Pms) and the right atrial pressure (Pra). The Pms is a virtual pressure considered to lie at the level of the venules. It refers to the pressure in the vascular system at zero flow and is positively related to the stressed blood volume and negatively related to the vascular compliance. The stressed blood volume, which represents 30–40% of the total blood volume, is hemodynamically active and thus participates in venous return through its impact on Pms. The unstressed blood volume represents 60–70% of the total blood volume, is hemodynamically inactive, and serves as a blood reservoir that can be mobilized by venoconstriction and can be converted to stressed blood volume under some critical conditions.[7] At the bedside, the Pms can be estimated by the method proposed by Maas et al.[8] that exploits the hemodynamic effects of heart–lung interactions.[9] Indeed, by recording pairs of cardiac output and central venous pressure (CVP) values at a steady state of apnea (15-s end-expiratory and end-inspiratory holds), a venous return curve can be constructed according to Guyton's model. As Pms is the vascular pressure at zero flow, the intercept with the *x*-axis of the regression line is assumed to equate the venous return curve and allows Pms estimation. The heart–lung interaction method has been proposed to estimate Pms for research purposes only. While Pms cannot be estimated in clinical practice, it would be relevant to help clarify the physiological effects of fluids or vasopressors on venous return.[10]

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Effects of fluids on mean systemic pressure

Using the heart–lung interaction method, Guérin et al.[10] showed that fluid administration increases the Pms in critically ill patients but only increases the venous return pressure gradient in those who were fluid responsive. In patients who were not fluid responsive, Pms increased after fluid infusion but there was no increase in the pressure gradient for venous return and therefore no increase in venous return or cardiac output. As fluid infusion is assumed not to alter vascular compliance, the results reported by Guérin et al.[10] suggest that fluid infusion can increase Pms by increasing the stressed blood volume. The elevated pressure gradient for venous return with fluid was associated with no change in Rvr. This finding was consistent with an increase in venous return with fluid, which was confirmed by the increase in cardiac output measured by transpulmonary thermodilution.[10]

Effects of norepinephrine on mean systemic pressure

Interestingly, norepinephrine alone can also enhance cardiac output by increasing cardiac preload, as shown by clinical studies from our group.[11–12] In a series of 101 patients with septic shock with profound hypotension, Hamzaoui et al.[11] showed that initiating norepinephrine or increasing its dose also increased cardiac preload assessed by global end-diastolic volume (GEDV) and decreased pulse pressure variation (PPV), a marker of preload responsiveness. Monnet et al.[12] also found an increase in cardiac preload assessed by GEDV, CVP, and left ventricular end-diastolic area. They also showed that cardiac output increased and that preload responsiveness assessed by a passive leg raising (PLR) test decreased with norepinephrine. It can be hypothesized that norepinephrine enhances cardiac preload by increasing the venous return pressure gradient by stimulating α_1-adrenergic receptors in the veins, which could stress the walls of the venous reservoir and increase Pms.[12] However, norepinephrine could also increase the Rvr through venoconstriction, which might counteract the effect of increased Pms on venous return. In a porcine model of endotoxic shock, Datta and Magder[13] elegantly demonstrated that norepinephrine increased Pms without affecting Rvr, leading to an increase in venous return. More recently, Persichini et al.[14] investigated the effects of norepinephrine on the Pms and Rvr in human septic shock using the Mechanical Ventilation Holds Method. They showed that decreasing the norepinephrine dose in septic shock patients was responsible for a decrease in venous return due to the decrease in Pms, which was more pronounced than the concomitant Rvr decrease. To summarize, in addition to its arterial constrictive effect aimed at correcting hypotension, norepinephrine also has significant effects on venous return by promoting redistribution from unstressed to stressed blood volume, mimicking an autotransfusion effect [Figure 1].

Effects of a combination of norepinephrine and fluids on mean systemic pressure

A question that has arisen more recently is: Can norepinephrine potentiate the efficacy of fluid infusion on altering the Pms? Adda et al.[15] answered it using the method proposed by Maas et al.[8] to estimate the Pms in 30 patients with septic

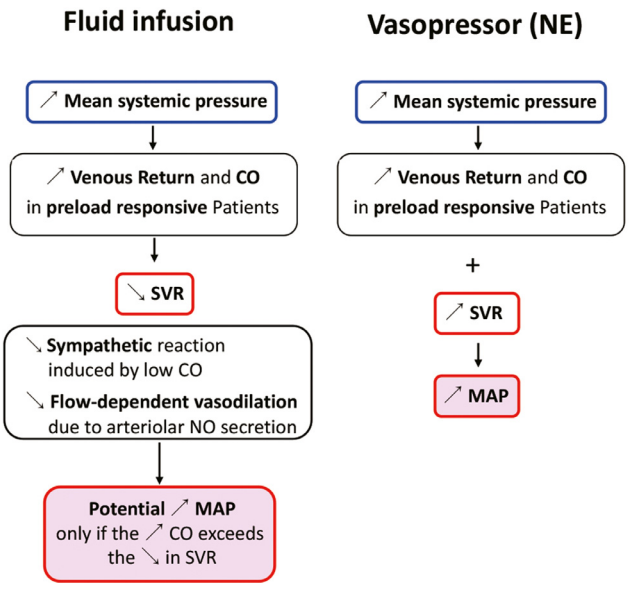

Figure 1. Hemodynamic consequences of each treatment alone: Fluids and vasopressors. CO: Cardiac output; MAP: Mean arterial pressure; NE: Norepinephrine; NO: Nitric oxide; SVR: Systemic vascular resistance. Up arrow means increase; Down arrow means decrease.

shock. Instead of infusing fluids, PLR was performed as it is considered to mimic a fluid challenge.[16] Each patient received two doses of norepinephrine and PLR was performed at each dose. The change in the Pms (ΔPms) induced by PLR at the highest dose of norepinephrine was larger than the addition of ΔPms induced by changing the dose of norepinephrine and ΔPms induced by PLR at the lowest dose. This result suggests that norepinephrine can improve and potentiate the hemodynamic efficacy of fluid administration.

Combination of Fluids and Vasopressors Corrects Hypotension Better Than Fluid Alone

There is a physiological relationship between organ blood flow and mean arterial pressure (MAP), which is generally regarded as the perfusion pressure of most vital organs. Changes in MAP will not affect organ blood flow within a physiological "autoregulation" range of MAP. Nevertheless, below a certain critical MAP value, organ blood flow will decrease.[17] Autoregulation mechanisms are supposed to be impaired in septic shock, making the vital organs more vulnerable in the case of hypotension.[18] Retrospective data showed that the degree and duration of hypotension in the initial phase of septic shock are key determinants of patient outcomes.[19–20]

Improved cardiac output with fluid potentially induces a decrease in systemic vascular resistance due to reductions in sympathetic tone and probable flow-dependent vasodilation.[21] This latter mechanism of arterial adaptation seems to be modulated by increased nitric oxide production and endothelial shear stress stimulus during fluid loading.[22–23] Moreover, recruitment of previously closed vessels increases the effective diameter of the arterial system, which reduces arterial resistance.[24] In a series of 81 critically ill patients with septic shock, Monge García et al.[25] reported a vasodilatory effect of fluid administration in cases with a fluid-induced increase in blood flow. Patients were divided into two groups: (1) preload responders,

who increased their cardiac output >10% after fluid infusion and (2) preload non-responders. Fluid administration only significantly reduced arterial load (effective arterial elastance and systemic vascular resistance) in preload responders. This may account for the absence of improvement in arterial pressure despite the increased cardiac output in preload responders. It suggests that administering fluids alone is not sufficient to correct hypotension and that it makes sense to also administer a vasopressor such as norepinephrine, which increases systemic vascular resistance [Figure 1]. Therefore, it is futile to administer fluids without a vasopressor when hypotension is severe, especially in shock states with a marked vasodilatory component, such as septic shock. The early association of norepinephrine with fluids even before the full completion of fluid resuscitation was recently recommended by 34 experts from the European Society of Intensive Care Medicine because it can correct hypotension faster and prevent prolonged severe hypotension.[26] Accordingly, a recent retrospective study suggested that the time to achieve a MAP of 65 mmHg was shorter when norepinephrine was initiated within the first 6 h of resuscitation compared with more delayed initiation.[27] Another recent single-center randomized controlled trial of septic shock patients showed that the time to achieve MAP 65 mmHg was significantly shorter when norepinephrine was initiated simultaneously with fluid infusion compared with when norepinephrine was initiated only if 30 mL/kg crystalloids failed to achieve the target MAP.[28] Furthermore, in cases of severe hypotension, early norepinephrine initiation may recruit microvessels and improve microcirculation through an increase in organ perfusion pressure. Accordingly, Georger et al.[29] found significantly higher tissue muscle oxygen saturation along with the norepinephrine-induced increase in MAP from 54 mmHg to 77 mmHg in patients with septic shock.

An easy method to decide when to start norepinephrine is to pay attention to the diastolic arterial pressure, which is a marker of vascular tone.[30] Low diastolic arterial pressure (e.g., <40 mmHg) is generally associated with a low vascular tone in the absence of bradycardia and should prompt norepinephrine administration.[31]

Combination of Fluids and Vasopressors Limits Fluid Overload

There is a large body of evidence suggesting that an excessively positive fluid balance is associated with worse outcomes in patients with acute respiratory distress syndrome,[31–32] acute renal failure,[33–34] and septic shock.[35–36] In this regard, Boyd et al.[36] performed a retrospective analysis of data collected during the Vasopressin in Septic Shock Trial. At patient enrolment, which occurred on average 12 h after the presentation, the average fluid balance was +4.2 L. By day 4, the cumulative average fluid balance was +11 L. A more positive fluid balance at 12 h and 4 days was independently associated with an increased risk of mortality. In addition to the growing interest in the dynamic parameters used to predict fluid responsiveness and restrict fluids, early norepinephrine use during septic shock has been proposed for this purpose. The early introduction of norepinephrine enhances cardiac output through an increase in cardiac preload[11–12] and cardiac contractility,[36] which will contribute to the limitation of infused fluids and thus to a lowered risk of fluid overload as reported in clinical studies.[37–38] In their retrospective cohort study using data from 213 adult septic shock patients, Bai et al.[39] reported that the early norepinephrine group (administration in <2 h) received less intravenous fluid within 24 h (6.2 L ± 0.6 L *vs.* 6.9 L ± 0.7 L; $P < 0.001$) compared with the late norepinephrine group. In a recent prospective, randomized, open-label clinical trial, the regimen of restricted fluids and early vasopressor administration was compared with usual care for the initial resuscitation (first 6 h of sepsis) in 99 septic patients with hypotension (systolic blood pressure <100 mmHg after minimum 1000 mL of intravenous fluid) in the emergency department. The restricted volume/early vasopressor strategy resulted in a 30% relative reduction in the total volume of fluid administered up to 24 h and was not associated with any signal of harm.[38] More recently, 337 patients with sepsis requiring vasopressors support for at least 6 h were selected from a prospectively collected database. Patients were classified into very early (VE-VPs) or delayed (D-VPs) vasopressor start, for whom vasopressor support was initiated either before or within the next hour of the first fluid resuscitation load or >1 h after the fluid resuscitation load, respectively. Patients were matched 1:1 with a propensity score based on various factors (age, comorbidities, lactate, heart rate, and systolic and diastolic arterial pressures at vasopressor start). In the VE-VPs group, less use of resuscitation fluids, less fluid accumulation, and possibly a shorter duration of hypotension were observed compared with the D-VPs group. Interestingly, there were no increases in kidney injury or ischemia-related adverse effects in the VE-VPs group.[40] Collectively, these data suggest that a very early combination of fluids and vasopressors has an evident effect on the lower net fluid accumulation mediated by the limited fluid administration. Indeed, faster restoration of blood flow in combination with lower fluid accumulation could promote tissue perfusion and avoid the harm caused by fluid overload.

Combination of Fluids and Vasopressors Produces less Hemodilution Than Fluid Alone

Volume expansion is the first-line treatment for many cases of circulatory failure. The main reason to administer fluid is to increase preload and cardiac output with subsequent effects on increasing oxygen delivery and reducing tissue hypoxia. However, infusions in fluid non-responders may lead to a decrease in oxygen delivery due to a lower hemoglobin level related to hemodilution.[41–42]

Combination of Fluids and Vasopressors May Improve Outcome

Clinical observations have shown that a delay in correcting hypotension is associated with an increased risk of death in septic patients.[19,43,44] A recent phase II randomized controlled trial suggested that early norepinephrine use might help achieve more sustained MAP levels and adequate tissue perfusion parameters.[3] However, this trial was limited by the specificity of the protocol requiring administration of a fixed dose of norepinephrine in the early group, which is not the usual practice. A previous observational study suggested that delayed introduction of vasopressor support after initial fluid loading might be

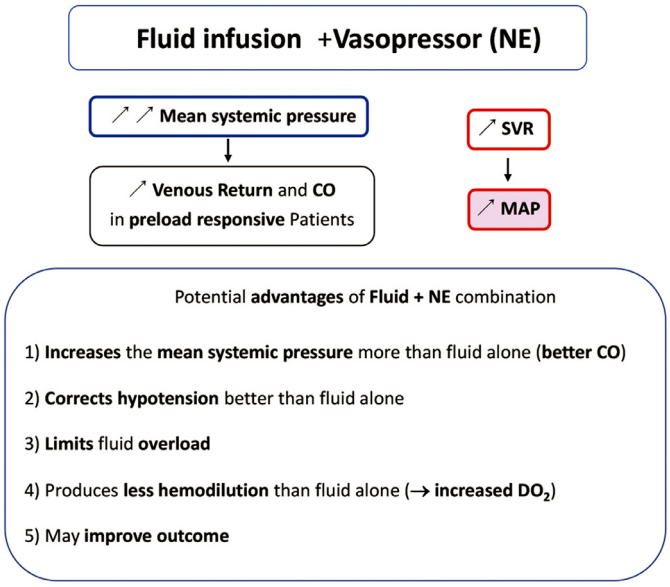

Figure 2. Hemodynamic consequences of combining fluids and vasopressors. CO: Cardiac output; DO_2: Oxygen delivery; MAP: Mean arterial pressure; NE: Norepinephrine; SVR: Systemic vascular resistance. Up arrow means increase; Down arrow means decrease.

related to worse clinical outcomes. In addition to a longer time of pre-vasopressor hypotension, the delayed vasopressor group was subjected to more severe hypotension even after the introduction of the vasopressor support itself, which hinders the actual effect of the timing of vasopressor use.[38] Recently, the issue of the optimal timing for vasopressor initiation in septic shock was addressed in a retrospective analysis of a prospective database using a propensity score of a selected series of 337 patients with sepsis requiring vasopressors.[40] Patients were classified into very early (VE-VPs) or delayed (D-VPs) vasopressor start categories according to whether norepinephrine was initiated or not within/before the next hour of the first resuscitative fluid load. VE-VPs were related to significantly lower net fluid balances 8 h and 24 h after VPs. VE-VPs were also associated with a significant reduction in the risk of death compared with D-VPs (hazard ratio: 0.31, 95% confidence interval: 0.17–0.57, $P < 0.001$) at day 28. This association remained after including patients receiving vasopressors for <6 h. It is noteworthy that all the patients had a diastolic arterial pressure >45 mmHg. Indeed, very early initiation of vasopressors even before completing a predefined volume of fluid resuscitation seems to be a safe intervention with potential beneficial effects on clinical outcomes.

Conclusions

Early treatment with a combination of vasopressors and fluids seems to be a logical therapeutic option for managing septic shock for five reasons: (1) it increases the mean systemic pressure more than fluid alone with a better effect on cardiac output, (2) it corrects hypotension better than fluid alone, (3) it limits fluid overload and therefore produces less tissue edema than fluid alone, (4) it produces less hemodilution than fluid alone and allows increased oxygen delivery, and (5) it may improve outcomes [Figure 2].

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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