Summer 2020

Norepinephrine Use In Septic Patients Undergoing General Anesthesia

Lauren Reed
University of New England

Norepinephrine Use in Septic Patients Undergoing General Anesthesia

Lauren Reed

University of New England

Abstract

Anesthesia providers are frequently confronted by the problem of caring for patients presenting with sepsis in the operating room. Sepsis is associated with high healthcare costs and a significant mortality rate despite advancements in the understanding of its complicated pathophysiology. The 2016 Surviving Sepsis Campaign recommends norepinephrine as the first-choice vasopressor in septic patients. Its mild beta-adrenergic effects, in addition to its alpha-adrenergic effects, make it an attractive agent for the vasoplegia and myocardial dysfunction associated with sepsis. Earlier achievement of adequate perfusion pressures, earlier lactate clearance, and higher in-hospital survival have all been associated with norepinephrine use in the septic patient. However, it remains underutilized in the perioperative setting. Peripheral intravenous administration of norepinephrine has been associated with very low complication rates and norepinephrine, as an alternative to other vasopressors in patients undergoing general anesthesia, is showing promising results. In patients with sepsis requiring surgical source control, anesthesia providers should see themselves as key players in the critical care continuum and should be encouraged to consider the use of norepinephrine.

Keywords: norepinephrine, sepsis, anesthesia, vasopressor, hypotension, septic shock, surgical sepsis, general anesthesia

Norepinephrine Use in Septic Patients Undergoing General Anesthesia

Sepsis, currently defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Singer et al., 2016), is a significant challenge for healthcare systems, and a leading cause of mortality. In the United States, there are over 970,000 sepsis cases admitted annually at the cost of $24.3 billion (Paoli et al., 2018). Surgical patients account for nearly one-third of all sepsis cases. Despite extensive research, sepsis related mortality remains unacceptably high at 10-20%. When septic shock follows, there is a 30% mortality rate among elective surgical patients, and a 39% mortality rate among emergent surgical patients (Moore & Moore, 2012).

The current treatment for sepsis includes rapid identification of the offending pathogen (i.e. source control), pre-emptive and early implementation of antibiotics, fluid resuscitation, and vasopressor therapy to support perfusion pressure (Khanna & Laudanski, 2014). Source control methods may include surgical intervention: drainage of infected fluids, debridement of infected soft tissues, and removal of infected devices or foreign bodies. Most of these procedures are carried out in the operating room, under general anesthesia (Yuki & Murakami, 2015).

Perioperative resuscitation measures are aimed at rapidly restoring adequate oxygen delivery to peripheral tissues. In high-risk surgical patients with sepsis, early hemodynamic optimization before the development of organ failure has been shown to reduce mortality by 23% (Eissa et al., 2010). The first six hours of resuscitation in septic patients, termed the "golden hours" by Rivers et al. (2001), are crucial and frequently coincide with the time for

emergency surgery. Resuscitation measures begun in the emergency department (ED) or intensive care unit (ICU) can be continued on transfer to the operating room.

Two of the main components of septic shock resuscitation are administration of intravenous (IV) fluids and vasoactive support. Current guidelines recommend an initial crystalloid bolus of 30 mL/kg. That being said, the optimal volume for initial resuscitation is currently unclear. It is, however, critical to restore intravascular volume with some degree of fluid resuscitation in an attempt to optimize fluid status and tissue perfusion. Patients demonstrating signs of hypotension or hypoperfusion despite adequate fluid resuscitation require the administration of vasoactive agents (Sacha et al., 2019).

Patients with sepsis undergoing source control procedures are in an inherently unstable cardiovascular state. The majority of anesthetics not only have direct cardiovascular depressant effects, but also inhibit compensatory hemodynamic responses. Induction of general anesthesia can further aggravate the already unstable hemodynamics of the septic patient.

Vasopressor therapy to support adequate perfusion pressure is an obvious goal to anesthesia providers. The 2016 Surviving Sepsis Campaign (SSC) recommendation for norepinephrine as the first-choice vasopressor for septic shock will be addressed, and its application in septic patients undergoing general anesthesia will be discussed. Additionally, anesthesia providers can play an integral role in facilitating timely surgical source control. The monitoring, resuscitative, and coordinating skills of anesthesia providers are well suited in the case of sepsis requiring surgical source control. Getting a patient to surgery quickly and safely can make a difference to decrease morbidity and increase survival.

Background

In 2001, Rivers et al. published the results of a prospective trial evaluating early goal-directed therapy (EGDT) for patients with severe sepsis or septic shock. This landmark study advocated for crystalloid resuscitation to restore preload, vasopressors to maintain adequate mean arterial pressure, and blood products and inotropes to achieve a goal central venous oxygen saturation. Early goal directed therapy led to a 16% reduction in in-hospital mortality and has since sparked several iterations of the Surviving Sepsis Campaign, as well as many studies to investigate the various components of EGDT.

Current sepsis management is synonymous with the SSC. This multinational initiative was launched in 2004 and has since undergone three revisions. The revisions reflect the evolution of knowledge, new literature, controversy, and the changing environment of sepsis. The most recent guidelines by Rhodes et al. (2016) include 93 statements on early management and resuscitation of patients with sepsis or septic shock. The main elements of treatment include rapid source control, pre-emptive and early implementation of antibiotics, fluid resuscitation, and vasopressor therapy to support perfusion pressure.

Definitions and Criteria

Many anesthesia providers may be familiar with previous definitions and diagnostic criteria for sepsis. Sepsis was previously defined as suspected infection plus two or more systemic inflammatory response syndrome (SIRS) criteria. Sepsis complicated by organ dysfunction was termed severe sepsis, and sepsis-induced hypotension despite adequate fluid resuscitation was termed septic shock (Nunnally et al., 2016). In 2016, Singer et al. published

updated definitions and diagnostic criteria, known as Sepsis-3, to reflect the advancement of knowledge related to pathophysiology, management, and epidemiology.

Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis-3 removed the old SIRS criteria and incorporated the sequential organ failure assessment (SOFA) score, an arguable discriminator of more severe disease, to emphasize the importance of organ dysfunction in sepsis. The SOFA score specifies a population with organ dysfunction as indicated by a score of two or more points (see Figure 1). There is also a simplified assessment of organ failure: the quick SOFA (qSOFA). The qSOFA measures hypotension, mental status changes, and tachypnea in the setting of suspected infection. Patients with known or suspected infection meet this simplified sepsis criteria if they score two or more points. SOFA was intended to be used in ICU settings, whereas the qSOFA is designed for non-ICU settings (Broshteyn et al., 2017).

Figure 1

Sequential Organ Failure Assessment (SOFA) Score

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Note: Adapted from Sepsis-3 by Singer et al., 2016, *JAMA, 315*(8), 801-810

Sepsis-3 intentionally removed several concepts from its guidelines. SIRS has been replaced with SOFA and severe sepsis is no longer included, as all sepsis is felt to be severe. Septic shock continues to be defined as the presence of low systemic arterial pressure or elevated serum lactate concentration in spite of volume resuscitation (Nunnally, 2016).

Pathophysiology of Sepsis

The cause of sepsis is multifactorial and may have many etiologies. It is common in elderly, immune-compromised, and critically ill patients. Although bacterial infections are the most common infectious cause, viruses and fungi can also lead to sepsis (Eissa et al., 2010). Introduction of the microbial source into the body leads to an activation of monocytes, macrophages, and neutrophils that interact with endothelial cells. This results in the production of pro-inflammatory cytokines, pro-coagulation cytokines, and reactive oxygen species. A positive feedback loop is triggered. The microcirculatory dysfunction that occurs leads to a loss of endothelial integrity and tissue hypoxia. Global tissue hypoxia leads to further endothelial activation and generalized inflammation leads to organ failure (Dalimonte et al., 2019).

Hemodynamic derangement in sepsis is mediated by three major cardiovascular events: vasoplegia, microcirculatory failure, and myocardial dysfunction (Fleisher, 2012). Although compensatory responses to endogenous catecholamines, vasopressin, and cortisol can serve to maintain the patient in the early phases of sepsis, these responses can become blunted or deficient over time (Dalimonte et al., 2019). Vasoplegia is a central feature of the response.

This pathologic vasodilation results from a loss of normal sympathetic tone caused by a combination of local vasodilator metabolites. There is a relative hypovolemia in early sepsis,

and to compensate, the precapillary arterioles and postcapillary venules constrict. This serves to draw fluid from the interstitium back into circulation. However, an oxygen debt occurs, and lactic acidosis develops. Eventually, persistent release of cytokines leads to depletion of reserve; there is hyperpolarization of vascular smooth muscle, massive release of nitric oxide synthetase, vasopressin depletion, and widespread increase in intravascular permeability. This leads to extensive capillary leak, maldistribution of flow, arteriovenous shunting, and oxygen utilization defects. Furthermore, there is initial activation of the coagulation system and deposition of intravascular clot leading to ischemia (Fleisher, 2012).

The resultant diminished vascular tone impairs blood flow regulation. Low flow capillary beds receive enhanced blood flow, and their downstream venous capacitance vessels engorge. The effective tank for intravascular blood volume increases, and venous return to the heart decreases. As a consequence of a degraded endothelial glycocalyx, intravascular capacity increases and serum fluids extravasate into surrounding extravascular tissue (Nunnally, 2016).

Circulating myocardial depressant factors, likely thought to be tumor necrosis factor (TNF) - alpha, lead to myocardial dysfunction. The presence of sepsis induced myocardial dysfunction is a major predictor of morbidity and mortality in sepsis. It is present in more than 40% of cases, and its appearance can increase the mortality rate up to 70% (Romero-Bremejo et al., 2011). It is characterized by the dilation of both ventricles leading to a decreased ejection fraction. Cardiac output (CO) is maintained by a dramatic increase in heart rate (HR). In this state, there is a decreased response to fluid resuscitation and catecholamines. In its most severe form, the degree of myocardial depression may imitate cardiogenic shock. Treatment

focuses on infection control and optimization of hemodynamic parameters with the use of vasoactive and inotropic therapy.

Septic shock is the most common cause of hyperdynamic distributive shock. It is characterized by high CO and vasodilation. The etiology of the organ dysfunction is related to a maldistribution of blood flow, rather than inadequate blood flow. Patients can present with warm skin, bounding pulses, a widened pulse pressure, and brisk capillary refill. In patients with normal pre-septic myocardial function, the hyperdynamic response is notable on echocardiography. Enhanced contractility paired with low preload means that the left ventricular cavity can nearly obliterate in systole (Nunnally, 2016).

Immunologic changes in function are most consistent with sepsis. These include apoptosis of immune cells, impaired cellular immunity, and enhanced susceptibility to opportunistic infection. However, multiple organ systems can express dysfunction during the response to sepsis. Most critically, cardiovascular dysfunction manifests as shock; respiratory failure develops as gas-exchange abnormalities and pulmonary capillary leak; and renal tubular dysfunction becomes acute kidney failure. Metabolic abnormalities include hyperglycemia, protein catabolism, suppressed ketogenesis, and enhanced concentrations of stress hormones. Neurologic abnormalities manifest commonly as delirium (Nunnally, 2016).

Pharmacology of Norepinephrine

Adrenergic receptors include alpha-1, beta-1, and beta-2. The alpha-1 receptor is located throughout the peripheral vasculature and centrally in the heart, and stimulation leads to vasoconstriction and an increase in blood pressure (BP) and systemic vascular resistance (SVR). Beta-1 receptors are found in the heart, and when activated cause an increase in HR,

contractility, and CO (Espinoza et al., 2019). Norepinephrine stimulates alpha-1 and beta-1 adrenergic receptors causing increased contractility and HR, as well as vasoconstriction, thereby increasing systemic blood pressure and coronary blood flow. Clinically, alpha effects (vasoconstriction) are greater than beta effects (inotropic and chronotropic).

Norepinephrine is the adrenergic vasopressor of choice in septic shock because of its ability to restore both arterial tone and the effective circulating volume. The increase in effective circulating volume is due to the recruitment of unstressed volume from the venous capacitance vessels. This leads to an increase in stressed volume, mean systemic filling pressures and the driving pressure for venous return. In addition, by its beta-1 and alpha-1 adrenergic properties, it also increases the contractility of the myocardium (Espinoza et al., 2019).

According to the norepinephrine (LEVOPHED) package insert (Hospira Inc., 2007), norepinephrine is indicated for blood pressure control in certain acute hypotensive states, including sepsis. In regard to the site of infusion the manufactures recommend that norepinephrine be administered into a large vein, particularly an antecubital vein, and the infusion site should be checked frequently for free flow. Average dilution is recommended to be 4mcg/mL.

Anesthetic Implications

The majority of anesthesia providers are most conversant with the use of phenylephrine for treatment of hypotension. Phenylephrine is not a catecholamine, but rather a sympathomimetic amine and a pure alpha-adrenergic receptor agonist with no beta-adrenergic receptor activity. It induces arteriolar vasoconstriction to increase SVR and mean arterial

pressure (MAP) which reflexively leads to a dose-dependent decrease in HR and, in turn, CO (Wang et al., 2019). The use of phenylephrine in anesthesia has been comprehensively studied.

Norepinephrine is not commonly used in United States' anesthetic practice due to concerns that drug extravasation could result in significant arterial and venous constriction with associated permanent skin damage. Norepinephrine's vasoconstrictive properties conducted in ex-vivo human radial arteries have found that norepinephrine is seven times more potent than phenylephrine. Moreover, the in-vivo relative vasoconstrictive property of norepinephrine is 76% higher than phenylephrine in human saphenous veins (Pancaro et al., 2019). It is commonly thought that a central venous line is needed to avoid the risk of localized tissue necrosis in the case of drug extravasation.

In 2011, the US Food and Drug Administration (FDA) announced a severe nationwide shortage of norepinephrine which persisted until February 2012. Vain et al. (2016) performed a retrospective cohort study of 26 hospitals and included 27,835 adults with septic shock to determine if there was an effect on patient outcomes during the shortage. During this time, phenylephrine use significantly increased and was associated with an increased rate of in-hospital mortality (35.9% vs 39.6%).

Literature Review

A literature search was performed on the following major databases: PubMed, Cochrane Library, and CINHAL. Experimental studies, randomized control trials (RCT), and systemic reviews of RCTs were preferentially selected. The search also included results with lower levels of evidence such as quasi-experimental and non-experimental studies, clinical practice guidelines, consensus panels, literature reviews, and review articles. Literature from

2009-2019 was preferred and any literature mentioned outside of this time frame was only considered if it was deemed a landmark study.

The initial search for specific literature regarding norepinephrine use in septic patients undergoing general anesthesia had limited results. This prompted additional searches with expanded terms related to "anesthesia + sepsis," "anesthesia + norepinephrine," and "norepinephrine + sepsis" in order to find all applicable and relevant studies.

Anesthesia and Sepsis

Anesthesia providers are critical in treating surgical patients with sepsis and septic shock and likely have an opportunity to reduce mortality through therapeutic intervention. However, research explicitly related to sepsis and anesthesia is lacking. It is generally accepted that induction and maintenance of anesthesia will augment hypotension in sepsis and may require an increase in vasopressor requirements. There is, however, no specific data or evidence to suggest the use of one vasopressor over another in the operative setting. Several anesthesia review articles exist, however, several new RCTs and guidelines have been published since the majority of these review articles.

In a review article by Eissa et al. (2010), the authors acknowledge that anesthesia providers play a central role in the multidisciplinary management of patients with sepsis. It is emphasized that the objective of preoperative resuscitation is to rapidly restore adequate oxygen delivery to peripheral tissues. If the patient is hemodynamically unstable, the authors suggest invasive arterial pressure monitoring, central venous access, and plan for admission to ICU. Skrupky et al. (2011) discuss the fact that anesthesia providers are increasingly confronted with the difficult problem of caring for septic patients in the operating room. The authors focus

mostly on immune modulation and selection of anesthetic therapies based on an immunotherapeutic approach. Both authors discuss the use of norepinephrine as the initial vasopressor of choice. The use of norepinephrine is advocated even before optimal intravenous fluid loading has been achieved.

Yuki and Murakami (2015) reviewed the 2012 Surviving Sepsis Campaign recommendations and advocate for its use in the intraoperative management of septic patients. The authors discuss the relatively recent advancement in the knowledge of sepsis pathophysiology, focusing on immune modulation and developments in new clinical therapeutic approach to sepsis. In a more recent review article by Nunnally (2016), the new Sepsis-3 definitions are discussed. The author states that care of the septic patient is an opportunity for anesthesia providers to reduce mortality in the perioperative setting. This is achieved through early recognition, improved patient monitoring, adequate resuscitation, and timely source control. The author states that when volume resuscitation is insufficient, vasoconstrictors and/or inotropes may be useful. Norepinephrine is recommended to treat vasoplegia, and in the setting of impaired myocardial contractility, the addition of dobutamine is suggested.

Norepinephrine Use in Sepsis

Initial resuscitation for hypotensive shock usually includes administration of intravenous fluids followed by initiation of vasopressors. Although the immediate effects of vasopressors on hemodynamics are obvious, their effect on relevant patient outcomes, such as mortality, as well as the selection of one agent versus another, remain controversial. In a Cochrane review by Gamper et al. (2016), the effects on mortality of one vasopressor regimen versus another in

critically ill patients with hypotensive shock are evaluated. Of 28 studies, 18 of them included patients with septic shock, and 17 of these studies provided norepinephrine as the intervention. The authors ultimately found no substantial differences in total mortality between the vasopressors and stated that evidence is insufficient to prove that any of the vasopressors are superior over another in terms of mortality. With exception, there is sufficient high-quality evidence to state that dopamine increases the risk of arrythmias and may present a mortality disadvantage versus norepinephrine. While this study does include a large number of randomized trials (28 RCTs which compared six different vasopressors), the sample population for specific comparison in studies is lacking, and ultimately the choice of a specific vasopressor is recommended to be individualized and left to the discretion of the treating provider.

Guidelines by the Scandinavian Society of Anesthesiology and Intensive Care Medicine are consistent with the 2016 Cochrane Review by Gamper et al. (2016). A meta-analysis of RCTs and the use of a specific methodology for assessment of quality of evidence were used for the generation of recommendations. Various subpopulations were assessed, including those in septic shock. The use of norepinephrine is strongly recommended, with moderate quality of evidence, over dopamine, based on the increased risk of dysrhythmias and short-term mortality in patients treated with dopamine. For all other comparisons (epinephrine, vasopressin analogues, and phenylephrine), the recommendation is weak, and the quality of evidence is low (Møller et al., 2016).

Oba and Lone (2014) and Zhou et al. (2015) both performed systematic reviews and Bayesian network meta-analyses to compare the effects among different types of vasopressor agents in patients with septic shock. Bayesian meta-analysis varies from other traditional meta-

analyses as the authors are able to combine the results of direct comparisons to indirect comparisons extrapolated by trials that have treatments in common. Study selection included randomized control trials in adults with septic shock. Except for the superiority of norepinephrine over dopamine, the mortality of patients treated with any vasopressor agent or combination was not significantly different. Compared to dopamine, norepinephrine was found to be associated with decreased cardiac events, decreased HR, decreased cardiac index, and increased SVR. Otherwise, there is insufficient evidence to suggest that any other vasopressor agent or combination is superior to another.

More recently, Cheng et al. (2019) performed a Bayesian network meta-analysis to evaluate the effects of different types of vasoactive medications on patients with septic shock. This included the question of vasopressin analogues and calcium sensitizers, in addition to adrenergic agents. The results suggest that the use of norepinephrine plus dobutamine is associated with lower 28-day mortality for septic shock, especially among patients with low CO.

Ducrocq et al. (2012) acknowledged that myocardial depression is a frequent event during septic shock and may even mimic cardiogenic shock. In this experimental animal study, the effects on myocardial function of three commonly administered vasopressors (norepinephrine, epinephrine, and phenylephrine) were compared. Septic shock was induced in rats by causing peritonitis, and was associated with arterial hypotension and both systolic and diastolic dysfunction. Phenylephrine was associated with decreased ventricular performance, whereas epinephrine and norepinephrine improved global hemodynamics and myocardial function in severely hypokinetic and hypotensive septic shock. Epinephrine was,

however, associated with increased myocardial oxygen consumption. Norepinephrine appeared to be more reliable and a safer strategy as a first-line therapy in this setting.

Raising the MAP with vasoactive agents in patients with septic shock ultimately improves global tissue and organ perfusion. These vasoconstriction mediated effects can be detrimental at higher doses, compromising perfusion and causing side effects such as splanchnic hypoperfusion and tissue necrosis. Splanchnic vasoconstriction and hypoperfusion can be detrimental if not identified early, resulting in mucosal and cellular damage that can progress to intestinal ischemia. Existing literature shows conflicting data on the effect of catecholamines on splanchnic perfusion. Jhanji et al. (2009) found that in patients with septic shock, targeting higher MAP by increasing the dose of norepinephrine resulted in an increase in global oxygen delivery, cutaneous microvascular flow, and tissue oxygenation. However, Krejci et al. (2006) found that norepinephrine appeared to divert blood flow aware from the mesenteric circulation and decrease microcirculatory flow in the jejunal mucosa and pancreas.

The argument of the adverse effect of early initiation of norepinephrine on vital organ perfusion has been counteracted by more recent data supporting its early use in septic shock by preventing hypotension and improving survival (Permpikul et al., 2019; Elbouhy et al., 2019). Ultimately, the true effect of vasoactive agents on perfusion is still in question and may be due to the fact that it is rarely documented in clinical practice. It may be appropriate to limit high dose catecholamines (norepinephrine > 1mcg/kg/min). Higher catecholamine doses were independently associated with mortality rates as high as 90% in patients receiving norepinephrine doses greater than 1 mcg/kg/min (Sacha et al., 2019).

The systematic review by Gamper at al. (2016) included current literature up until 2015. These findings were consistent with the recommendations made in the 2016 SSC guidelines. Since then, there has been evidence to suggest that early initiation of norepinephrine may provide some patient benefit. This is reflected in the 2018 update of the SSC bundle which recommends starting vasopressors if the patient is hypotensive during or after initial fluid bolus administration (Levy et al., 2018). Several new studies have been published in the meantime to address the potential benefit of early norepinephrine use in septic patients.

Hamzaoui et al. (2018) conducted a prospective observational study to investigate whether norepinephrine increases cardiac contractility when administered during the early phase of septic shock. The study included 38 patients in the ICU who had been resuscitated for less than three hours and whose MAP remained less than 65 mm Hg. Echocardiographic variables were obtained before and after either initiation or an increase in the dose of norepinephrine infusion to increase MAP to greater than 65 mm Hg. Although the study did not evaluate the effects over time, the study found that early use of norepinephrine in patients with septic shock to target MAP values $\geq$ 65 mmHg improved left and right ventricle systolic function, increased CO and decreased blood lactate without increasing HR. This was a single center study with a small population sample.

The CENSER trial (Permpikul et al., 2019) is a single center, randomized, double-blind, placebo-controlled trial (n= 310 adults with sepsis and hypotension). Patients were randomized into early norepinephrine (at 0.5mcg/kg/min) or standard treatment according to the SSC. The primary outcome was shock control rate (MAP > 65 mmHg, with urine flow > 0.5 ml/kg/hr for two consecutive hours, or decreased serum lactate > 10% from baseline) by six

hours after diagnosis. The shock control rate by six hours was significantly higher in the early norepinephrine group (76.1% vs 48.4%). However, the 28-day mortality was not different between groups. Secondarily, the early norepinephrine group was associated with decreased pulmonary edema and decreased new onset arrythmia. This is the first randomized study to assess the benefit of early norepinephrine administration for sepsis-related hypotension resuscitation on short-term shock control endpoints. The selected hemodynamic endpoints represent macrocirculation and microcirculation restoration.

The timing of norepinephrine administration in septic shock continues to be controversial. Elbouhy et al. (2019) evaluated the impact of early norepinephrine administration simultaneously with fluid resuscitation in septic patients (n= 101). Patients admitted to the ED with septic shock were randomized to early norepinephrine with IV fluid administration, or initiation of norepinephrine after persistent hypotension despite fluid resuscitation. Results showed early norepinephrine caused earlier restoration of blood pressure, better lactate clearance, and improved in-hospital survival.

Norepinephrine Use in Anesthesia

Due to the lack of data directly related to norepinephrine use in septic patients undergoing general anesthesia, the literature review was expanded to include general norepinephrine use in anesthesia. The expansion allows for discussion of norepinephrine's role in everyday anesthesia. Information regarding its utility will be extrapolated while bearing in mind the limitations of this method.

Hiltebrand et al. (2011) evaluated regional and microcirculatory blood flow with norepinephrine use under general anesthesia in an animal model. Twenty anesthetized pigs

were randomly assigned to a control or treatment (norepinephrine) group. The norepinephrine group received norepinephrine to incrementally increase MAP to 65 and 75 mmHg. Regional blood flow was measured in the splanchnic arteries. Microcirculatory flow was measured in the small bowel and colon. The study showed that hepato-splanchnic and kidney blood flow remained unchanged after MAP was returned to 75 mmHg with the norepinephrine group. The study concluded that treatment of perioperative hypotension with norepinephrine had no adverse effects on microcirculatory blood flow or tissue oxygenation. As a limitation, this study only simulated mild hypotension in otherwise healthy subjects that only required low doses of norepinephrine. This study's scope did not include the effects of norepinephrine in severe hypotension/shock (Hiltebrandt et al., 2011).

Poterman et al. (2015) performed a randomized control study on the dissimilar working mechanisms of norepinephrine and phenylephrine, and their effect on macro and microcirculation under general anesthesia. The study found that phenylephrine and norepinephrine produced similar clinical effects when used to counteract anesthesia-induced hypotension. A rapid increase in MAP with a simultaneous decrease in HR, CI, and cerebral tissue oxygenation can be seen. Norepinephrine was associated with a slight decrease in peripheral tissue oxygenation; however, this was clinically irrelevant as the value remained above the baseline. In this study, normovolemia was achieved before the induction of anesthesia, therefore, the patients' hearts were relatively preload independent; the heart is on the more horizontal part of the Frank-Starling curve.

Hassani et al. (2018) compared ephedrine versus norepinephrine in treating anesthesia induced hypotension in spinal surgery. This randomized, double-blinded study included

patients between the ages of 20 and 75, with a history of hypertension, under general anesthesia for spinal surgery. Exclusion criteria included a physical status of three or greater, history of arrhythmia, heart valve disease, cerebrovascular disease, kidney failure, beta-blocker use, diabetes, and significant intraoperative blood loss. After initiation of general anesthesia, when MAP pressures reached less than 60, the patient entered the protocol and simultaneously received a 5mL/kg bolus of crystalloid and a vasopressor. Patients were randomized to the ephedrine group (received 5 mg of ephedrine) or the norepinephrine group (received 10 mcg of norepinephrine). If the MAP was not reached the same dose could be repeated at a maximum of three times.

Results show that the mean number of hypotension times, the number of vasopressor doses in the first episode of hypotension, the total number of doses consumed during anesthesia, and the heart rate at the end of anesthesia were all lower in the norepinephrine group (Hassani et al., 2018). MAP five minutes after the first episode of hypotension and MAP at the end of anesthesia were higher in the norepinephrine group. This study concludes that norepinephrine is more effective than ephedrine in maintenance of MAP in patients with a history of hypertension undergoing spinal surgery under general anesthesia.

Norepinephrine can counteract the effects of anesthesia induced vasodilation and hypotension, and it allows for decreased intraoperative hydration. Wuethrich et al. (2014) compared the effects of a preemptive norepinephrine infusion. This single center, double-blind, randomized, superiority trial, included 166 patients undergoing radical cystectomy and urinary diversion. The low volume group received an infusion of LR at 1 mL/kg/hr until the end of the cystectomy and then increased to 3 mL/kg/hr until the end of the

surgery combined with preemptive norepinephrine infusion at an initial rate of 2 mcg/kg/hr (0.03mcg/kg/min). The control group received 6 mL/kg/hr of LR throughout surgery. Rates of gastrointestinal and cardiac complications were lower in the low-volume control group than in the control group (6% vs. 37%).

The use of norepinephrine combined with a low-volume fluid regimen was demonstrated to be safe and not clinically harmful to cardiac function. The restrictive deferred hydration group resulted in adequate tissue perfusion. Additionally, fluid restriction and the adjuvant use of norepinephrine did not result in more renal complications. A major concern is the vasoconstrictive effect of norepinephrine. However, the results showed that the preemptive norepinephrine infusion at an initial rate of 2 mcg/kg/hr (or 0.03 mcg/kg/min) had no identifiable negative consequences and may actually provide positive clinical effects. The authors suggest that norepinephrine counteracts the decreased sympathetic tone and vasodilation induced by epidural anesthesia, anesthetics, and analgesics. Therefore, it may have a more physiological profile for compensating for vasoplegia than the liberal use of intravenous fluids (Wuethrich et al., 2014).

During general anesthesia, arterial hypotension is frequent and may be an important contributor to perioperative morbidity. Vallee et al. (2017) performed a prospective observational study which included neurosurgical patients who were sedated under general anesthesia. The participants were sorted into two groups; one group included patients with low cardiovascular (CV) risk, and the other group included patients who presented with at least two CV risk factors. The study assessed the effect of a 5mcg bolus of norepinephrine when compared with 50mcg of phenylephrine to treat hypotension during maintenance anesthesia.

Effects on MAP, CO, and arterial stiffness parameters were measured. There were 269 bolus administrations of vasopressors in 47 patients. A decrease in stroke volume was observed with phenylephrine when compared with norepinephrine.

This study suggests that a 5mcg bolus of norepinephrine administered as a bolus in a peripheral venous line could treat general anesthesia induced hypotension with several benefits. With norepinephrine, an adequate target of a 20% increase in MAP can be achieved with no adverse effects. Norepinephrine also had a better effect on ventricular afterload with a lower decrease in stroke volume and arterial compliance when compared to phenylephrine. These effects were present in both high and low CV risk patients, with a potentially more pronounced beneficial effect in high risk patients (Vallee et al., 2017). Although prospective in nature, the study was unblinded and the use of vasopressors was not protocolized. Additionally, only bolus administration of vasopressors was considered in this study, and patients were not particularly preload dependent at the time of vasopressor administration.

In a prospective observational study, Vos et al. (2014) studied the hemodynamic stability and tissue oxygen saturation in 40 patients undergoing general anesthesia with goal-directed therapy and norepinephrine. The authors were concerned that the combination of potent analgesics and vasopressor therapy would lead to a negative effect on cardiac output and, ultimately, on tissue oxygenation. The decrease in blood pressure after the induction of anesthesia was anticipated with a single bolus of 10mcg norepinephrine at induction, and at the same time a background infusion of norepinephrine was started. The study found that goal-directed fluid and vasopressor therapy was able to preserve the MAP at 80% of baseline values,

with an insignificant decrease in CO and adequately preserved tissue oxygen saturation, as measured by the non-invasive Nexfin and Inspectra monitors respectively.

Norepinephrine Use in Obstetric Anesthesia

At present, phenylephrine is the first-line vasopressor used in obstetric anesthesia to manage maternal hypotension. The use of norepinephrine has recently become an attractive idea due to its mild beta-adrenergic effects in addition to its alpha-adrenergic effects. Wang et al. (2018) performed a literature review of nine RCTs published from 2015-2018 that investigated norepinephrine use as an alternative to phenylephrine. Participants included healthy parturients without comorbidities. An intrathecal injection of bupivacaine or ropivacaine in combination with fentanyl and/or morphine, fluid loading, and left uterine displacement were used in all reports. Various dosing regimens included the following: fixed rate infusion, intermittent bolus, manually controlled variable rate infusion, or a closed-loop feedback computer-controlled infusion. Commonly used variables to evaluate vasopressor safety included maternal side effects such as nausea, vomiting, dizziness, shivering, local tissue ischemia, and neonatal outcomes, including Apgar and umbilical cord blood gas analysis.

The recommendation from this review is that norepinephrine is similarly effective to phenylephrine in managing maternal hypotension. This comes without obvious maternal or neonatal adverse outcomes and positive effects including decreased incidence of bradycardia and increased stroke volume. The use of norepinephrine in obstetric anesthesia is a novel practice and available data related to its efficacy is still limited. This conclusion is obtained using less than ten reports and therefore confidence must remain guarded compared to the hundreds of reports of phenylephrine efficacy and safety. The available literature suggests

norepinephrine is likely a promising alternative for rescuing maternal hypotension on obstetric anesthesia. However, there are a relatively small number of available studies and likely not enough to provide treatment recommendations (Wang et al., 2018).

Ngan Kee (2017) performed a random-allocation, graded dose-response study to determine the relative potencies of phenylephrine and norepinephrine. Parturients (n=180) undergoing spinal anesthesia for elective cesarean delivery received a single bolus of norepinephrine, in one of six different doses ranging from 4 to 12 mcg, or phenylephrine, in one of six doses ranging from 60 to 200 mcg. The magnitude of response was measured as the percentage of full restoration of systolic blood pressure to the baseline value. The estimated mean effective dose (ED50) of norepinephrine was 10mcg and phenylephrine was 137 mcg. The estimated dose equivalent of 100mcg of phenylephrine is 8mcg of norepinephrine. The dose response was based on the treatment of a single episode of spinal induced hypotension. It is unknown if these results are applicable to general anesthesia induced hypotension and the non-parturient.

Anesthetic Implications

Cardenas-Garcia et al. (2015) evaluated the safety of vasoactive medication administered through peripheral intravenous (PIV) access in a single-arm consecutive patient study. A total of 734 patients received vasoactive medication via PIV access; norepinephrine was used in 506 of the patients, and the duration of the infusion was 49 (+/- 22) hours. Extravasation of the PIV access during administration of vasoactive medication occurred in 2% of patients without any tissue injury following treatment with local phentolamine injection and application of local nitroglycerine paste. The authors of the study

suggested several requirements for the use of PIV access for the infusion of vasoactive medications: (a) vein diameter >4mm measured with ultrasonography, (b) position of PIV access documented to be in the vein with ultrasonography before starting infusion, (c) upper extremity only and contralateral to BP cuff, (d) 20 gauge or 18 gauge, (e) no hand, wrist, or antecubital fossa PIV access position, (f) blood return from the PIV access prior to vasoactive medication administration, (g) assessment of PIV access function every 2 hours, and (h) in place for 72 hours maximum.

This study was retrospective, observational and performed in a single-center medical ICU. Lacking a control group, it cannot be definitively stated that vasoactive medications via PIV is safer (or as safe as) than administration via a central catheter. That being said, rate of extravasation was extremely low and treatment options were effective in preventing local ischemic injury. Anesthesia providers should not regard the use of norepinephrine as an automatic indication for central venous access.

Severe damage from extravasation has been found to most often occur in patients with several comorbidities and while treating circulatory shock using high concentration infusions. In a prospective study by Medlej et al. (2018), 50 patients in the ED with various shock etiologies (septic shock; n=46) were observed for adverse events during vasopressor infusion through PIV access. Three patients (6%) had extravasation of norepinephrine with only minor complications with no intervention required. Two of these incidents were in the hand and one was in the antecubital fossa.

Pancaro et al. (2019) performed a multicenter, retrospective cohort study to estimate the rate of occurrence of adverse effects when norepinephrine peripheral extravasation occurs.

The study included 14,385 patients who received norepinephrine PIV infusions in the perioperative setting. Drug extravasations were observed in five patients (0.035%) and there were zero related complications requiring surgical or medical intervention.

Rates of extravasation in the study by Pancaro et al. (2019) were significantly lower than those performed in other care settings. The authors hypothesize that anesthesia providers are able to provide hypervigilant surveillance of the patient position and infusion sites. A limiting factor to the study was that all extravasations occurred on patients presenting for elective surgical cases making it difficult to make a statement on the risk of patients with septic shock.

The SSC does recommend that all patients requiring a vasopressor have an arterial catheter placed as soon as practical and if the resources are available. This is notably a weak recommendation with very low quality of evidence. Rhodes et al. (2017) state that the estimation of blood pressure using a cuff in shock states may be inaccurate, and that the use of an arterial catheter may provide more accurate results and allow for beat-to-beat analysis so that decisions can be based on immediate information. Insertion of radial arterial catheters is generally safe with observational studies showing that the incidence of bleeding or limb ischemia is less than 1%. Ultrasound guidance may lead to even lower complication rates. In the survey submitted by Scheeren et al. (2019), there was a perfect consensus and a strong degree of recommendation for the use of invasive blood pressure management via an arterial catheter.

Discussion

Clinical trials specifically evaluating norepinephrine use on the outcome of septic patients undergoing general anesthesia are lacking. As the anesthesia review articles discussed,

anesthesia providers are integral in the care of the surgical sepsis patient. The SSC recommendations should be acknowledged and adapted to anesthetic practice. The authors draw upon the data gathered by emergency, surgical, and critical care specialist practice in order to extrapolate intervention recommendations likely to be applicable to the anesthesia provider.

The appropriateness of norepinephrine as a first-line vasopressor in septic patients undergoing surgical source control is recognized, but there are many barriers to its use. Foremost, the use of phenylephrine is ubiquitous with anesthesia and, as such, anesthesia providers are well versed in its utility. Hundreds of studies support the efficacy and safety of phenylephrine to restore MAP in patients undergoing general anesthesia. Its alpha-adrenergic effects cause an increase in BP and may be a suitable choice for the septic patient undergoing general anesthesia, particularly those with known tachyarrhythmias. Moreover, there is no current evidence to suggest that phenylephrine is inappropriate to treat hypotension in the septic patient undergoing general anesthesia. More evidence is needed to prove the benefits of norepinephrine compared to phenylephrine to motivate anesthesia providers to make a change. Anecdotally, the limited availability of norepinephrine may also be a barrier to its use, as many anesthesia departments may not stock norepinephrine in an easily and quickly accessible place.

Concerns for extravasation during PIV administration of norepinephrine may be another obstacle. Cardenas-Garcia et al. (2015), Medlej et al. (2018), and Pancaro et al. (2019) all show a very low rate of complications with PIV administration of norepinephrine. Extravasation rates in Pancaro et al. (2019) were significantly lower than those performed in other settings (0.035%

vs. 2% and 6%), leading the researchers to suggest that anesthesia providers can offer hypervigilant surveillance of the patient position and infusion site.

A limiting factor to Pancaro et al. (2019) was that all extravasations occurred in patients presenting for elective surgical cases, making it difficult to draw a conclusion regarding the risk of patients with septic shock. Cardenas-Garcia et al. (2015) was carried out in a medical ICU where the median age of the patients was 72. This older, and sicker, population may be more reflective of the patient population coming to the OR for surgical source control. In this group the rate of complications was still very low (2%). Lastly, Medlej et al. (2018) followed patients from the ED, with a less strict protocol for IV site selection and a relatively low complication rate (6%). PIV sites included the hand, wrist, and antecubital fossa, as well as an IV size of 20-gauge or 18-gauge. These PIV attributes can be commonly seen in a patient coming straight from the ED to the OR for emergency procedures and may be more reflective of a real-world scenario.

Cardenas-Garcia et al. (2015) used norepinephrine at a concentration of 8mcg/mL or 16mcg/mL while Pancaro et al. (2019) used a standard concentration of 20 mcg/mL of norepinephrine. Pancaro et al. (2019) suggest starting an initial infusion dose of 0.01-0.02 mcg/kg/min, then titrating as desired to blood pressure targets. Wuethrich et al. (2014) initiated a preemptive 0.03 mcg/kg/min norepinephrine infusion on induction of anesthesia. If hypotension persisted, an initial bolus of 10mcg norepinephrine was administered and the drip was titrated to a maximum rate of 0.13 mcg/kg/hr. This is consistent with the early norepinephrine group in the CENSER trial that received norepinephrine at a fixed rate of 0.05

mcg/kg/min. Considerations for the infusion of dilute norepinephrine should be the same as phenylephrine, which is widely used in clinical anesthesia practice.

Bolus administration of norepinephrine may also be appropriate to temporize transient hypotension, and anesthesia providers should be comfortable with bolus dosing of norepinephrine. According to Ngan Kee (2017), 100mcg of phenylephrine is equivalent to 8mcg of norepinephrine. This is consistent with the dosing used by Hassani et al. (2018): patients were randomized to receive either 5mg of ephedrine or 10mcg or norepinephrine. Lastly, Vallee et al. (2016) randomized patients to receive 5mcg of norepinephrine or 50 mcg of phenylephrine.

The SSC recommends Norepinephrine as the first line vasopressor therapy in patients with sepsis. This is a strong recommendation despite only moderate evidence to support the statement. Many RCTs and network meta-analyses of RCTs have come to the recommendation that there is no mortality benefit in the use of one vasopressor over another. The exception is the use of norepinephrine versus dopamine. Based on the large sample sizes and the nature of network meta-analyses, there is high quality evidence to confer this recommendation. Only a few large, multi-center, randomized control trials have evaluated the most effective initial vasoactive agent in patients with septic shock. Despite the absence of strong evidence supporting the use of norepinephrine as a first-line therapy for septic shock, convincing data is also lacking to suggest any agent other than norepinephrine should be used first line. Thus, norepinephrine remains the standard of care in patients presenting with septic shock.

Permpikul et al. (2019), Elbouhy et al. (2019), and Hamazoui et al. (2018) all show promising results for the early initiation of norepinephrine in sepsis. Initiation of

norepinephrine was associated with improved ventricular function, CO and MAP, lactate clearance, and in-hospital survival. Additionally, the use of early norepinephrine was associated with decreased rates of pulmonary edema and new onset arrythmia, suggesting that norepinephrine may be effective in keeping peripherally administered IV fluid in the intravascular space. These studies have promising results but are limited by their small sample size and the nature of single center trials. Extrapolation to other care environments, such as the patient undergoing general anesthesia, is difficult.

Trials investigating the use of norepinephrine in patients undergoing general anesthesia have shown that it is effective in counteracting the effects of anesthesia induced vasodilation and hypotension. It has been associated with no adverse effects on microcirculatory flow or tissue oxygenation, and overall decreased amounts of intraoperative fluid administration. Initiation of norepinephrine plus restrictive intraoperative hydration may lead to less vasodilation, less blood loss and lower rates of transfusion. It is also associated with decreased rates of excessive fluid administration-related complications, such as pulmonary edema. In patients with a history of hypertension undergoing general anesthesia, bolus administration of norepinephrine was more effective than ephedrine in maintaining MAP, and in a group of high-risk CV patients, bolus norepinephrine was more effective than phenylephrine in maintaining MAP.

The anesthesia related studies discussed included a heterogenous surgical population plus the use of norepinephrine. The studies were not specific to patients with sepsis and, in fact, most of the studies excluded patients that were not medically optimized. The patients were normovolemic and therefor preload-independent, or on the flat part of the Frank-Starling

curve, at the time of vasopressor administration. These studies did not include the effects of norepinephrine in states of severe hypotension or shock, thus making it difficult to extrapolate the safety of its use in septic patients. The Wuethrich et al. (2014) study did, however, show that fluid restriction and the use of norepinephrine resulted in adequate tissue perfusion and no increased renal complications.

The use of norepinephrine is attracting attention as an alternative to traditionally used vasopressors in the treatment of anesthesia induced hypotension. Unfortunately, available data is lacking. Some promising RCTs have been discussed, and there is favorable data on the efficacy and utility of norepinephrine use. Ultimately, a relatively small number of studies are available and not enough data to provide strong treatment recommendations.

Norepinephrine is gaining attention in obstetric anesthesia to manage spinal induced maternal hypotension. Its use has not been associated with obvious maternal or neonatal adverse outcomes, and positive effects include decreased incidence of bradycardia and increased stroke volume. The available literature suggests norepinephrine is a promising alternative to phenylephrine for treating maternal hypotension. Nevertheless, there is a lack of available studies to provide treatment recommendations.

Conclusion

Patients with sepsis often require surgical source control and the anesthesia provider is well suited to assume care. These patients require may require advanced monitoring and hemodynamic resuscitation. The administration of general anesthesia may further deteriorate the unstable cardiovascular state of the patients, and all efforts should be made to optimize the patient intraoperatively. Norepinephrine is currently considered the first-line agent for patients

with septic shock. Its use is associated with earlier achievement of adequate perfusion pressures, earlier lactate clearance, and higher in-hospital survival.

Norepinephrine as an alternative to other vasopressors is an emerging trend in all specialties of anesthesia. It is showing promising results on hemodynamic variables and decreased crystalloid administration. No strong recommendations can be made based on the current body of evidence but, again, the anesthesia provider should be encouraged to consider the use of norepinephrine when caring for the septic patient undergoing general anesthesia.

Anesthesia providers are often a key player in the critical care continuum of the septic patient, and there should be an association or society level recommendation for the use of norepinephrine in septic patients undergoing general anesthesia. There are no experimental trials evaluating anesthetic practice when caring for septic patients, only review articles and editorial commentaries. Literature regarding norepinephrine use is specifically lacking. The concept of improving mortality in sepsis has been investigated by many medical specialties and should not fall short with anesthesia, where perfusion and hemodynamic support are integral to its practice.

References

Bronshteyn, Y. S., Lemm, J., Malinzak, E., Ghadimi, N., & Udani, A. D. (2017). Sepsis in the operating room: A simulation case for perioperative providers. *MedEdPORTAL: The Journal of Teaching and Learning Resources, 13* doi:10.15766/mep_2374-8265.10563

Cardenas-Garcia, J., Schaub, K.F., Belchikov, Y.G., Narasimhan, M., Koenig, S.J., Mayo, P.H. (2015). Peripheral Administration of Vasoactive Medication. *Journal of Hospital Medicine, (9),*581-585. doi:10.1002/jhm.2394

Cheng, L., Yan, J., Han, S., Chen, Q., Chen, M., Jiang, H., & Lu, J. (2019). Comparative efficacy of vasoactive medications in patients with septic shock: A network meta-analysis of randomized controlled trials. *Critical Care, 23*(1), 168. doi:10.1186/s13054-019-2427-4

Dalimonte, M. A., DeGrado, J. R., & Anger, K. E. (2019). Vasoactive agents for adult septic shock: An update and review. *Journal of Pharmacy Practice,* 897190019844124. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/31057085

Ducrocq, N., Kimmoun, A., Furmaniuk, A., Hekalo, Z., Maskali, F., Poussier, S., . . . Levy, B. (2012). Comparison of equipressor doses of norepinephrine, epinephrine, and phenylephrine on septic myocardial dysfunction. *Anesthesiology, 116*(5), 1083-1091. doi:10.1097/ALN.0b013e31824f9669

Eissa, D., Carton, E. G., & Buggy, D. J. (2010). Anaesthetic management of patients with severe sepsis. *British Journal of Anaesthesia, 105*(6), 734-743. doi:10.1093/bja/aeq305

Elbouhy, M. A., Soliman, M., Gaber, A., Taema, K. M., & Abdel-Aziz, A. (2019). Early use of norepinephrine improves survival in septic shock: Earlier than early. *Archives of Medical Research, 50*(6), 325-332. doi: S0188-4409(19)30515-6

Espinoza, E. D. V., Hernandez, G., & Bakker, J. (2019). Norepinephrine, more than a vasopressor. *Annals of Translational Medicine, 7*(Suppl 1), S25. doi:10.21037/atm.2019.01.76

Fawzy, A., Evans, S., & Walkey, A. (2015). Practice patterns and outcomes associated with choice of initial vasopressor therapy for septic shock. *Critical Care Medicine, 43*(10), 2141-2146. doi:10.1097/CCM.0000000000001149

Fleisher, L. A. (2012). Anesthesia and uncommon diseases: Sixth Edition. Elsevier Inc.

Gamper, G., Havel, C., Arrich, J., Losert, H., Pace, N. L., Müllner, M., & Herkner, H. (2016). Vasopressors for hypotensive shock. *The Cochrane Database of Systematic Reviews, 2*(2). doi:10.1002/14651858.CD003709.pub4

Hamzaoui, O., Jozwiak, M., Geffriaud, T., Sztrymf, B., Prat, D., Jacobs, F., . . . Teboul, J. L. (2018). Norepinephrine exerts an inotropic effect during the early phase of human septic shock. *British Journal of Anaesthesia, 120*(3), 517-524. doi:10.1016/j.bja.2017.11.065

Hassani, V., Movaseghi, G., Safaeeyan, R., Masghati, S., Yekta, B. G., & Rad, R. F. (2018). Comparison of ephedrine vs. norepinephrine in treating anesthesia-induced hypotension in hypertensive patients: Randomized double-blinded study. *Anesthesiology and Pain Medicine, 8*(4). doi:10.5812/aapm.79626

Hiltebrand, L. B., Koepfli, E., Kimberger, O., Sigurdsson, G. H., & Brandt, S. (2011). Hypotension during fluid-restricted abdominal Surgery: Effects of norepinephrine treatment on regional and microcirculatory blood flow in the intestinal tract. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 114*(3), 557-564. doi:10.1097/ALN.0b013e31820bfc81

Hospira Inc. (2007). Levophed [package insert]. Lake Forest, Il: Hospira Inc.

Jhanji, S., Stirling, S., Patel, N., Hinds, C., & Pearse, R. (2009). The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock*. *Critical Care Medicine, 37*(6), 1961-1966. doi:10.1097/CCM.0b013e3181a00a1c

Khanna, A. K., & Laudanski, K. (2014). Septic shock and anesthesia: Much ado about nothing? *Journal of Anaesthesiology Clinical Pharmacology, 30*(4), 481–483. https://doi.org/10.4103/0970-9185.142804

Krejci, V., Hiltebrand, L., & Sigurdsson, G. (2006). Effects of epinephrine, norepinephrine, and phenylephrine on microcirculatory blood flow in the gastrointestinal tract in sepsis*. *Critical Care Medicine, 34*(5), 1456-1463. doi:10.1097/01.CCM.0000215834.48023.57

Levy, M., Evans, L., & Rhodes, A. (2018). The surviving sepsis campaign bundle: 2018 update. *Critical Care Medicine, 46*(6), 997-1000. doi:10.1097/CCM.0000000000003119

Medlej, K., Kazzi, A. A., El Hajj Chehade, A., Saad Eldine, M., Chami, A., Bachir, R., . . . Abou Dagher, G. (2018). Complications from administration of vasopressors through peripheral venous catheters: An observational study. *Journal of Emergency Medicine, 54*(1), 47-53. doi:10.1016/j.jemermed.2017.09.007

Møller, M. H., Claudius, C., Junttila, E., Haney, M., Oscarsson-Tibblin, A., Haavind, A., & Perner, A. (2016). Scandinavian SSAI clinical practice guideline on choice of first-line vasopressor for patients with acute circulatory failure. *Acta Anaesthesiologica Scandinavica, 60*(10), 1347-1366. doi:10.1111/aas.12780

Moore, L. J., & Moore, F. A. (2012). Epidemiology of sepsis in surgical patients. *Surgical Clinics of North America, 92*(6), 1425-1443. doi:10.1016/j.suc.2012.08.009

Ngan Kee, W. D. (2017). A random-allocation graded Dose–Response study of norepinephrine and phenylephrine for treating hypotension during spinal anesthesia for cesarean delivery. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 127*(6), 934-941. doi:10.1097/ALN.0000000000001880

Nunnally, M. E. (2016). Sepsis for the anaesthetist. *BJA: British Journal of Anaesthesia, 117*(3), iii44-iii51. doi:10.1093/bja/aew333

Oba, Yuji, MD, FCCP, & Lone, Nazir A., MD, MPH. (2014). Mortality benefit of vasopressor and inotropic agents in septic shock: A Bayesian network meta-analysis of randomized controlled trials. *Journal of Critical Care, 29*(5), 706-710. doi:10.1016/j.jcrc.2014.04.011

Pancaro, C., Shah, N., Pasma, W., Saager, L., Cassidy, R., van Klei, W., . . . Lirk, P. (2019). Risk of major complications after perioperative norepinephrine infusion through peripheral intravenous lines in a multicenter study. *Anesthesia & Analgesia, Publish Ahead of Print*. doi:10.1213/ANE.0000000000004445

Paoli, C., Reynolds, M., Sinha, M., Gitlin, M., & Crouser, E. (2018). Epidemiology and costs of sepsis in the United States—An analysis based on timing of diagnosis and severity level. *Critical Care Medicine, 46(*12), 1889-1897. doi:10.1097/CCM.0000000000003342

Permpikul, C., Tongyoo, S., Viarasilpa, T., Trainarongsakul, T., Chakorn, T., & Udompanturak, S. (2019). Early use of norepinephrine in septic shock resuscitation (CENSER). A randomized trial. *American Journal of Respiratory and Critical Care Medicine, 199*(9), 1097-1105. doi:10.1164/rccm.201806-1034OC

Poterman, M., Vos, J. J., Vereecke, H. E. M., Struys, Michel M. R. F., Vanoverschelde, H., Scheeren, T. W. L., & Kalmar, A. F. (2015). Differential effects of phenylephrine and norepinephrine on peripheral tissue oxygenation during general anaesthesia: A randomised controlled trial. *European Journal of Anaesthesiology (EJA), 32*(8), 571. doi:10.1097/EJA.0000000000000247

Rhodes, A., Evans, L. E., Alhazzani, W., Levy, M. M., Antonelli, M., Ferrer, R., . . . Dellinger, R. P. (2017). Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Intensive Care Medicine, 43*(3), 304-377. doi:10.1007/s00134-017-4683-6

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., . . . Tomlanovich, M. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock*. New England Journal of Medicine, 345*(19), 1368-1377. doi:10.1056/NEJMoa010307

Romero-Bermejo, F. J., Ruiz-Bailen, M., Gil-Cebrian, J., & Huertos-Ranchal, M. J. (2011). Sepsis-induced cardiomyopathy. *Current Cardiology Reviews, 7*(3), 163. doi:10.2174/157340311798220494

Sacha, G. L., Bauer, S. R., & Lat, I. (2019). Vasoactive agent use in septic shock: Beyond First-Line recommendations. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 39*(3), 369-381. doi:10.1002/phar.2220

Scheeren, T. W. L., Bakker, J., Backer, D. D., Annane, D., Asfar, P., Boerma, E. C., . . . Teboul, J. (2019). Current use of vasopressors in septic shock. *Annals of Intensive Care, (9)*. doi:10.1186/s13613-019-0498-7

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., . . . Angus, D. C. (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA, 315*(8), 801-810. doi:10.1001/jama.2016.0287

Skrupky, L. P., Kerby, P. W., & Hotchkiss, R. S. (2011). Advances in the management of sepsis and the understanding of key immunologic defects. *Anesthesiology, 115*(6), 1349-1362. doi:10.1097/ALN.0b013e31823422e8

Vail, E., Gershengorn, H. B., Hua, M., Walkey, A. J., Rubenfeld, G., & Wunsch, H. (2017). Association between US norepinephrine shortage and mortality among patients with septic shock. *JAMA, 317*(14), 1433-1442. doi:10.1001/jama.2017.2841

Vallée, F., Passouant, O., Gall, A. L., Joachim, J., Mateo, J., Mebazaa, A., & Gayat, E. (2017). Norepinephrine reduces arterial compliance less than phenylephrine when treating general anesthesia-induced arterial hypotension. *Acta Anaesthesiologica Scandinavica, 61*(6), 590-600. doi:10.1111/aas.12905

Vos, J. J., Poterman, M., Hannivoort, L. N., Lavalette, Victor W. Renardel De, Struys, M. M., Scheeren, T. W., & Kalmar, A. F. (2014). Hemodynamics and tissue oxygenation during balanced anesthesia with a high antinociceptive contribution: An observational study. *Perioperative Medicine, 3*(9). doi:10.1186/2047-0525-3-9

Wang, X., Shen, X., Liu, S., Yang, J., & Xu, S. (2018). The efficacy and safety of norepinephrine and its feasibility as a replacement for phenylephrine to manage maternal hypotension during elective cesarean delivery under spinal anesthesia. *BioMed Research International*, 2018 doi:10.1155/2018/1869189

Wuethrich, P. Y., Studer, U. E., Thalmann, G. N., & Burkhard, F. C. (2013). Intraoperative continuous norepinephrine infusion combined with restrictive deferred hydration significantly reduces the need for blood transfusion in patients undergoing open radical cystectomy: Results of a prospective randomized trial. *European Urology, 66*(2), 352-360. doi:10.1016/j.eururo.2013.08.046

Yuki, K., & Murakami, N. (2015). Sepsis pathophysiology and anesthetic consideration. *Cardiovascular & Hematological Disorders Drug Targets, 15*(1), 57. Retrieved from https://www-ncbi-nlm-nih-gov.une.idm.oclc.org/pmc/articles/PMC4704087/

Zhou, F., Mao, Z., Zeng, X., Kang, H., Liu, H., Pan, L., & Hou, P. C. (2015). Vasopressors in septic shock: A systematic review and network meta-analysis. *Therapeutics and Clinical Risk Management, 11*, 1047-1059. doi:10.2147/TCRM.S80060