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Septic shock better controlled with earlier administration of norepinephrine

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ABSTRACT A clinical decision report appraising Elbouhy MA, Soliman M, Gaber A, Taema KM, Abdel-Aziz A. Early use of norepinephrine improves survival in septic shock: earlier than early. *Archives of Medical Research*. 2019;50(6):325–332. https://doi.org/10.1016/j.arcmed.2019.10.003.

Keywords: *Septic shock, norepinephrine, early, earlier*

Clinical Context

Theo Walters [pseudonym] is an 86-year-old male with past medical history of severe COPD with a history of multiple intubations (most recently 10 days ago), abdominal aortic aneurysm, coronary artery disease with myocardial infarction in 1997 requiring quadruple bypass, and congestive heart failure. He is accompanied by his daughter who states "He has been more delirious and confused" since being discharged from the hospital one week ago. During that hospital stay, he was admitted to the ICU for influenza and intubated for three days. Mr. Walters' daughter states that he has had decreased appetite for three to four days, episodes of urinary incontinence for three to four days, and shortness of breath and a cough for three to four days. Yesterday, Mr. Walters was unable to get up and walk which is new. Prior to his last hospitalization, Mr. Walters was able to cook, care for himself, and drive as he lives alone, but has been staying with his daughter since his most recent hospital discharge.

Upon arrival, Mr. Walters was tachypneic and placed on 6L oxygen via nasal canula with SpO2 92%. He became progressively hypotensive and we had concern for septic shock. Laboratory workup was significant for acute kidney injury (AKI), with creatinine up to 3.12 from baseline of 0.71 one week prior, lactate 2.1 down trending to 0.6, and leukocytosis of 17.2. Chest x-ray shows bibasilar infiltrates versus atelectasis. Mr. Walters received 4.5 L isotonic crystalloids and was started on Vancomycin/Zosyn. Oxygen requirements continued to increase to high flow oxygen at 70% FiO2 and 10 L/ minute. He then became more hypotensive and was placed on norepinephrine, with doses quickly escalating from 2 mcg/minute to 35 mcg/minute at the time of intubation or worsening mentation and hypoxia. Overall, there was a time interval of 120 minutes between initiation of antibiotics and the norepinephrine. The patient's daughter was confused about his condition. We tried to explain the diagnosis of septic shock in words that she would understand. We engaged in shared decision making related central IV line placement for initiation of pressor therapy. She agreed to accept the risk of the central line because we had informed her of the poor prognosis associated with septic shock. She asked multiple questions, but in the end, she trusted us to make the medical recommendations. We initiated an end of life discussion and she asked for a full code.

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Clinical Question

Does earlier norepinephrine administration in septic shock patients improve hemodynamic control and overall patient outcomes?

Research Article

Elbouhy MA, Soliman M, Gaber A, Taema KM, Abdel-Aziz A. Early use of norepinephrine improves survival in septic shock: earlier than early. *Archives of Medical Research*. 2019;50(6):325–332. https://doi.org/10.1016/j.arcmed.2019.10.003

Related Literature

A search for original research was done using the keywords "Early", "Norepinephrine", and "Septic Shock" on Google Scholar and PubMed. For each relevant article that was found, the references were reviewed for more original research that addressed the clinical question. Much of the research regarding this clinical question compares the efficacy of norepinephrine to other pressor medications. However, six of the articles specifically focus on the effect of earlier norepinephrine administration. Two such articles focused predominantly on norepinephrine's effects on cardiac preload and not on patient survival[1-2]. Additionally, Morimatsu et al. conducted a retrospective study in 2004 that focused on ICU patients and found that faster administration of norepinephrine could improve outcomes, which laid the framework for more recent works[3]. A critical appraisal led to a double-blind placebo-controlled study, but its primary focus was achieving better shock control by 6 hours postdiagnosis, rather than overall patient outcomes[4-5]. Finally, two studies, both of which focused on early administration of norepinephrine and its effects on patient survival, were found [6-7]. Both studies focused directly on the question at hand, however, Elbouhy et al.[7] utilized a prospective randomized control study, while the Bai et al.[6] is a retrospective cohort study. Considering the similarities and similar power of the studies, the former study was deemed superior than the later due to the SORT Level 1 Level of Evidence compared to the former study and SORT Level 2 study quality of the latter. Given the limited nature of available data on the subject, the overall body of literature meets criteria for (SORT) level B Strength of Recommendation[8].

Critical Appraisal

This publication describes a prospective, randomized, control study that is SORT level 1[8]. The study recruited patients admitted to the emergency department with septic shock from January 2017 until December 2018. Patients were deemed to have septic shock if they were hypotensive and had a lactate greater than 2mmol/L along with a positive qSOFA score which requires two or more of the following: systolic blood pressure less than 100, respiratory rate greater than 22, and Glasgow Coma Scale (GCS) less than 15. Patients found to be positive for septic shock were randomized in a 1:1 ratio into a study and control group. The control group contained 44 patients who received fluid resuscitation and immediate ICU transfer, where norepinephrine infusions were only administered to patients with a MAP < 65 mmHg. In contrast, the study group contained 57 patients who received initial resuscitation with simultaneous infusion of crystalloid fluids and norepinephrine. This timing averaged out to patients in the control group receiving norepinephrine after 120 minutes following emergency department admission, while patients in the study group received norepinephrine after 25 minutes following emergency department admission. The mean age of participants was 63 years old, ranging from patients 50 to 75 years of age and a 58% male distribution. Patients were hemodynamically monitored, recording systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, temperature, central venous pressure, and Glasgow coma scale, of which only the worst recording in each 24-hour period was reported. There was no conflict of interest and the study was self-funded via the hospital where the study was conducted.

The primary outcome was increased in-hospital survival in patients with septic shock who received norepinephrine earlier. The secondary outcomes were the time to restoration of MAP of 65 mmHg, lactate clearance within 6 hours of admission, the development of acute kidney injury (AKI) according to Kidney Disease Improving Global Outcomes (KDIGO) criteria, and the volume of IV fluids required for resuscitation. The study protocol was approved by Cairo University's institutional review board. The in-hospital survival rate of the study group was 71.9% compared to 45.5% seen in the control group (p = 0.007), and the number needed to treat (NNT) was 3.79.

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Patients were recruited based on vital signs indicative of septic shock. Although cases were randomization were 1:1, there is no mention of the method for randomization, resulting a potential for bias. This study was not subject to participation bias, as patients were taken according to inclusion criteria rather than accepting volunteers. Indication bias was also avoided by adhering to the inclusion criteria, as patients of both groups were equally sick.

Fifteen of the control patients were excluded from the trial compared to three from the study group which resulted in slightly lopsided groups of 57 to 44 patients in size. Exclusion criteria was based on less than a 24 hour stay in the ICU or concomitant left ventricular disfunction. This could reflect some bias, as more patients were healthy enough to leave the ICU in the control group, yet this would strengthen the primary outcome since despite this finding more patients survived in the study group.

There may be a source of performance bias, as healthcare workers were not blinded in the study. Of course, it would have been very difficult to blind healthcare workers, as the administration of pressors requires a central line, whereas strict fluid resuscitation can be performed with a peripheral line only.

The reporting method of only using the worst recording for each 24-hour period introduces a source of error. In some cases, this method would report outliers that may not be indicative of the patient's status over that 24-hour period. Instead, an average of all the vital signs from that day would provide a more accurate picture of each patient's status.

Moreover, while the therapeutic adjustment being tested is feasible in our practice, the patients studied were dissimilar to my patient, who was 11 years older than the oldest patient in the study. Therefore, this study can be applied to many patients whom we treat but may not directly apply to patients older than 75 years of age, though age's actual effect is unclear and was not studied.

Clinical Application

Elbouhy et al.'s study can be applied to our clinical scenario to improve future patient outcomes. The current hospital protocol is to conduct two fluid bolus challenges prior to initiating a norepinephrine drip. However, this study suggests that in-hospital survival rates in patients with septic shock would improve if norepinephrine was initiated in synchrony with IV crystalloid fluids in hypotensive patients. Keeping in mind that norepinephrine drips require central venous access, this protocol could be adjusted to initiate norepinephrine therapy after one fluid challenge instead of two, with understanding of limiting invasive procedures on patients whom it may not be necessary.

Regarding internal validity, the study's conclusion does make sense based on the results of the study. Understanding that when the patient's MAP is less than 65, they are not properly perfusing vital organs, it makes sense to prophylactically maintain the patients MAP whose condition (septic shock) characteristically leads to hypotension due to vasoparesis. Even though our patient does not necessarily fit the age group of the study, the illness follows the same pathophysiology. Although the analysis here is only retrospective, based on this study, our patient would have benefited from earlier norepinephrine therapy. This is supported by his gradually rising creatinine, likely due to prerenal azotemia driven by hypotension. Had we initiated norepinephrine treatment earlier, renal perfusion likely would have been better supported. Potential benefits of this study include limiting hypoperfusion in septic shock patients, which ultimately leads to end organ damage. The potential harms of initiating norepinephrine therapy earlier include conducting more invasive procedures (central line placements) that carry their own risks.

New Knowledge Related to Clinical Decision Science

Although survey of the existing literature offers evidence that norepinephrine therapy, if initiated early, leads to better in-hospital survival rates in patients with septic shock, our patient was not given norepinephrine early in his clinical course, and eventually developed end-organ dysfunction. Although we cannot be certain that earlier intervention with norepinephrine would have helped, retrospective analysis of his clinical outcome draws attention to the need for constant revision of existing protocols as evidence accumulates in favor of new approaches.

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Implications for Clinical Decision Science that arise from this report bring up the issue of protocols versus individually treating patients. In an Emergency Room setting, protocols are helpful. That implies that groups of stakeholders must agree that the clinical evidence supports a change in practice. Based on this report, I will continue to have this discussion with my colleagues and other stakeholders to shorten the time from publication of evidence to adoption of evidence in clinical practice.

References

1. Hamzaoui O, Georger JF, Monnet X, Ksouri H, Maizel J, Richard C, Teboul JL. Early administration of norepinephrine increases cardiac preload and cardiac output in septic patients with life-threatening hypotension. *Crit Care.* 2010;14(4). https://doi.org/10.1186/cc9207
2. Monnet X, Jabot J, Maizel J, Richard C, Teboul JL. Norepinephrine increases cardiac preload and reduces preload dependency assessed by passive leg raising in septic shock patients. *Crit Care Med.* 2011;39(4):689–694. https://doi.org/10.1097/ccm.0b013e318206d2a3
3. Morimatsu H, Singh K, Uchino S, Bellomo R, Hart G. Early and exclusive use of norepinephrine in septic shock. *Resuscitation.* 2004;62(2):249–254. https://doi.org/10.1016/j.resuscitation.2004.03.016
4. Rahnema A, Jones J. Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER): A Randomized Trial. *J Emer Med.* 2019;56(6):729–730. https://doi.org/10.1016/j.jemermed.2019.05.004
5. Russell JA, Gordon AC, Walley KR. Early May Be Better: Early Low-Dose Norepinephrine in Septic Shock. *Am J Respir Crit Care Med*. 2019;199(9):1049–1051. https://doi.org/10.1164/rccm.201901-0083ed
6. Bai X, Yu W, Ji W et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care.* 2014;18(5):532. https://doi.org/10.1186/s13054-014-0532-y
7. Elbouhy MA, Soliman M, Gaber A, Taema KM, Abdel-Aziz A. Early use of norepinephrine improves survival in septic shock: earlier than early. *Archives of Medical Research.* 2019;50(6):325–332. https://doi.org/10.1016/j.arcmed.2019.10.003
8. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *J Am Board Fam Med.* 2004;17(1):59-67. https://doi.org/10.3122/jabfm.17.1.59

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