CASE REPORT

Should the norepinephrine maximal dosage rate be greatly increased in late shock?

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SUMMARY

Any advanced shock eventually degenerates into vasoplegia, which responds weakly to vasopressors. The highest reported norepinephrine flow rate is 3 µg/kg/min. We present the case of a young explosion victim, who was transferred in late haemorrhagic shock. Apart from usual treatment (hydration, mass transfusion protocol), single-agent norepinephrine was used to maintain a mean arterial pressure (MAP) of >60–65 mm Hg. For several hours, norepinephrine flow was 7–10 times the aforementioned (highest reported) in order to achieve our goal; during which, further hydration or transfusion would not contribute to MAP elevation. Sequential Organ Failure Assessment (SOFA) severity score was 18 (expected mortality >99%). The patient survived without underperfusion-related damage. We conclude that norepinephrine dosages could potentially be greatly increased in late shock. We must resist giving up flow escalation based on its numerical value.

BACKGROUND

Shock is best classified based on its prevalent pathophysiology because this classification assists in management. The main types are hypovolaemic (ie, intravascular volume depletion), distributive (ie, arterial-to-venous and capillary redistribution, largely due to vasoplegia, eg, septic) and cardiogenic (which incorporates ‘obstructive’) shock. However, there are overlaps, coexistences and transformations between types in single patients. More importantly, all cases of shock involving delayed presentation or unsuccessful resuscitation will ultimately degenerate into distributive shock as a consequence of ischaemia-induced vasoplegia, the counteraction of which requires very high doses of vasopressors to maintain a minimal acceptable blood pressure. The latter is essential for organ perfusion, particularly the heart itself, until the cause of the shock is reversed. Norepinephrine (NA), an α-1/β agonist, is currently the drug of choice for distributive shock, due to its prevalently vasoconstrictive action.¹ In our review, the highest NA flow rate that has been reported in trials in adults is 3 µg/kg/min; yet the highest ‘typical’ value in prescription information is approximately 1 µg/kg/min. Indeed, the drug dosage sections of two of the most widely accessed medical resources worldwide include the following information: (1) “Indication, hypotension, acute dose [weight-based dosing]: 0.02–1 µg/kg/min IV [...]; Info: pts w/septic shock may require higher doses.” (Epocrates); and (2) “Sepsis and septic shock (weight-based dosing): Range from clinical trials: 0.01–3 µg/kg/min

(Hollenberg, 2004)[...]” (Up To Date).^{2 3} The evidence, criteria and reasoning for withholding further escalation of the dose (when the blood pressure continues to respond to increases in NA flow) are poorly described,⁴ and the relevant clinical data guiding practice are weak. A treating physician might wonder why further dosage escalations should not be attempted for a patient in whom the arterial pressure is maintained at an acceptable level with only increases in NA dosage, and who would otherwise certainly die. We present a case in which we increased the flow far beyond ‘traditional’ limits, under the guidance of a consistent arterial pressure response, which is not an unusual phenomenon in our practice. This endeavour was lifesaving for this patient.

CASE PRESENTATION

A 36-year-old man with no medical history was transferred intubated from the emergency room to our intensive care unit (ICU) in late haemorrhagic shock (mean arterial pressure (MAP) <40 mm Hg). The patient’s condition resulted from a bomb explosion approximately 5 h earlier. Clinical studies and a whole-body CT were remarkable (only) for a massive posterior nasal bleeding. His Sequential Organ Failure Assessment (SOFA) severity score was 18, APACHE-II score was 43, and he had undergone hydration and a mass transfusion protocol⁵ (red blood cells, platelets and plasma in approximately 1:1:1 ratio, Hgb maintained at >8 g/dL; and tranexamic acid). No cardiogenic, no neurogenic, no hypovolaemic (tested with dynamic indices) and no other components were present in his state of shock. Hence, over this acute period, further hydration or transfusion would cause neither additional benefit nor blood pressure improvement. Single-agent NA was used to maintain the MAP within the range of 60–70 mm Hg. NA was initiated at a flow of 2.7 µg/kg/min (maintained for 1 h) and rapidly escalated to and remaining in the range 22–30 µg/kg/min during the subsequent 4 h (maintained at the peak of 30 µg/kg/min for 1 h). During these 4 h, the patient’s lactate level ranged between 13 and 17 mmol/L, the pH was 7.09–7.15, the pCO₂ was approximately 40, the SpO₂ was approximately 90% and the HCO₃ was approximately 11 mmol/L (as mentioned in the Discussion section, these values were associated with a 100% mortality in a series in which lower NA doses were used). Over the subsequent 3 h, NA was decreased to 5 µg/kg/min and again decreased to 1.2 µg/kg/min 4 h later (figure 1, which details the NA dose of our case vs the typical maximum

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Figure 1 Norepinephrine dose (hours, in our case) versus maximal dose per drug information.

per the drug information). The patient's extremities remained underperfused (cold). Throughout this period, minimal NA reductions (ie, by 3%) caused rapid decreases in the MAP to <55 mm Hg. Hence, the entire management was not predefined but, rather, guided by the bedside haemodynamic responses. After posterior nasal tamponade, the bleeding subsided.

OUTCOME AND FOLLOW-UP

The patient survived the episode, and, by day 28, he was stable and removed from acute care with minimal deficits due to the explosion, and no underperfusion-related organ damage.

DISCUSSION

We present a case in which the NA dose was exceeded by 10-fold of the maximal dose that has been reported in clinical trials because no clear evidence contraindicated the dose escalation attempt. The principle of 'do no harm' needs to be balanced against the need to rescue blood pressure that would otherwise collapse instantly. The maximal NA dose is not incontrovertibly defined.^{2–4} Remarkably, the drug information source notes that patients in septic shock may require higher doses. However, because vital organs generally tend to be less injured in hypovolaemic shock (a state in which the cytokine storm is less evident and so has a better prognosis) compared with septic shock, it may be worth considering retaining hope and exceeding the defined NA limits (to the extent that they are defined) for septic shock. Moreover, these experiences and related suggestions should be openly shared, to at least allow physicians to defend their lifesaving efforts.

Hence, it is possible that there should be no predefined maximal NA dose for patients with any form of late shock (including hypovolaemic shock during the angioparalysis phase in which the responsiveness to NA is very weak due to endothelial ischaemia-induced vasoplegia).⁶ Furthermore, the position of not giving up on care based on dosage numbers when the vital organs may be not severely injured is supported.

In a review of 113 consecutive patients in shock and receiving NA at a flow rate of 0.9–2.9 µg/kg/min, the dose and duration were found to have no prognostic significance. APACHE-II scores of >40, HCO₃ levels <9 mmol/L and epinephrine co-treatment at >0.25 µg/kg/min were associated with 100% 28-day mortality. Other prognostic factors included oliguria, lactate level and prothrombin time.² In another cohort, an NA flow >3.8 µg/kg/min resulted in 100% mortality (17 of 17 patients).⁷ Moreover, Abid *et al*⁸ found that, with delayed NA treatment, an SOFA score >12 was associated with 100% mortality (100 of 100 patients). We make no assumptions about the possible survival benefits that might have been observed if the traditional NA limits had been exceeded in these series, because randomised controlled studies are required to resolve this issue. However, we feel compelled to report our 36-year-old patient who survived despite an APACHE-II score of 43 (94% mortality

when the general APACHE-II is considered as the sole prognosticator and 100% when the above NA flow-adjusted data are considered), an SOFA score of 18 and a HCO₃ of just 11 mmol/L (despite the fact that he had received NaHCO₃).

Until further research sheds light on the management of advanced/distributive shock based on comparisons of different doses, and vasopressor types and combinations, it appears appropriate to prevent the MAP from declining below a sensible limit at which coronary underperfusion will eliminate any remaining cardiac compensatory resource. We suggest that, as long as blood pressure response is noted, the NA rate, regardless of the specific value, should continually be increased until the MAP target (approximately 60–65 mm Hg, or, in certain situations, eg, in preoperative management of massive bleeding in the absence of cerebral injury, this target might be somewhat lower⁹) is met or exceeded.

The technique of increasing or decreasing the NA flow rate to a target MAP is guided by the immediate response of blood pressure—typically within <30 s. Hence, small steps of 0.1–0.2 µg/kg/min, repeated accordingly every few seconds (for inappropriately low MAP) or every 1–2 min (for MAP above the target range), is a typical practice we employ in our ICU. Our principle remains to never allow an MAP <55 mm Hg at any time, as this will cause unacceptably low perfusion of the coronary vessels to the point that the heart will have such severe energy deficiency that it will be unable to handle the cardiovascular compromise, a condition that typically causes further drop of MAP and increase of the cardiac hypoxemia—a vicious cycle that tends to lead to asystole within minutes or hours.

Learning points

- ▶ Any type of shock eventually degenerates to vasoplegia (distributive type) in which the responsiveness to norepinephrine is weak. In this case, the norepinephrine flow may need to be continually increased, regardless of its numeric value, until a minimum mean arterial pressure target, approximately 60–65 mm Hg, is achieved.
- ▶ Prognostic haemodynamically based indices in the early phase of resuscitation should not avert a further dosage escalation of norepinephrine, as vital organs may be viable.

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