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Clinical research article

Evaluating the impact of obesity on safety and efficacy of weight-based norepinephrine dosing in septic shock: A single-center, retrospective study

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ABSTRACT

Objective: Norepinephrine is the first-line vasopressor recommended for patients in septic shock. Weight-based dosing may increase drug exposure and the risk of adverse effects in obese patients. The objective was to evaluate the safety and efficacy of weight-based norepinephrine dosing using actual body weight in the morbidly obese compared with normal weight patients.
Methods: This was a single centre, retrospective study of adult patients admitted with septic shock requiring norepinephrine for at least 12 hours. The primary endpoint was the incidence of tachycardia within 48 hours after norepinephrine initiation. Secondary endpoints included timing and dosing of norepinephrine when adjunctive agents were added.
Results: The incidence of tachycardia was similar between groups. Total norepinephrine exposure was significantly greater in obese patients on day 1 ($p = 0.02$). Obese patients were more likely to be started on vasopressin ($p < 0.001$) and steroids at a lower weight-based norepinephrine dose ($p = 0.016$).
Conclusions: Weight-based norepinephrine dosing using actual body weight did not result in more tachycardia in the morbidly obese compared to normal weight patients, despite greater total exposure. These results were limited by the low doses used and a small cohort. However, use of actual body weight in morbidly obese patients appears to be safe.

Implications for Clinical Practice

- This study suggests that there is no difference in outcomes when using actual body weight for dosing norepinephrine in morbidly obese patients despite theoretical concerns for risks associated with overall greater norepinephrine exposure. The small cohort and low doses in this study limit broad application of this data.
- Recognition of relative doses of norepinephrine associated with weight-based dosing in obese patients is important in determining when to consider addition of adjunct therapy.
- Critical care nurses are ideally positioned to alert the medical team of relative doses of norepinephrine and potentially initiate the process of adding therapy.

Introduction

Norepinephrine is recommended as the first-line vasopressor for the management of haemodynamic instability in patients with septic shock (Dellinger et al., 2013). Exhibiting primarily α-adrenergic activity, norepinephrine acts at adrenergic receptors on smooth muscle lining the vasculature to cause vasoconstriction, exerting haemodynamic effects. Norepinephrine also possesses β-adrenergic activity, acting at β_1 receptors on cardiac tissue to produce a chronotropic effect. Thus, the appropriate dosing of norepinephrine balances these effects and is vital to meeting

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haemodynamic goals and optimising patient outcomes. However, both flat-dose and weight-based dosing strategies have been described in the literature and drug references, with no particular strategy being recommended over the other (Annane et al., 2007; Jung et al., 2014; Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically.; Russell et al., 2008). Rationale for using a weight-based dosing regimen assumes a linear relationship between patient weight and amount of norepinephrine required to achieve haemodynamic goals. However, the correct dosing weight is unclear, specifically in the obese patient population. As body weight increases in these patients, the tissue composition changes to increasingly greater amounts of adipose tissue, with an accompanying change in the distribution of the vasculature and adrenergic receptors (Gu and Xu, 2013). While adipose tissue is highly vascularised and can regulate local vascular tone, its relative vasopressor requirements during septic shock are unclear. Vasopressors, including norepinephrine, have a low volume of distribution and escalation of doses based on increases in weight due to adipose tissue may be inappropriate (Kane-Gill et al., 2013). Indeed, a previous study noted that obese patients had fewer haemodynamic disturbances and required significantly lower doses of norepinephrine, based on mcg/kg/minute (Arabi et al., 2013).

Compared to flat-dosing, weight-based dosing using actual body weight in obese patients has the potential to increase overall drug exposure, particularly in morbid obesity, defined as a body mass index (BMI) $\geq$40 kg/m^2, delivering supratherapeutic doses of norepinephrine (Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults, 1998). Given norepinephrine's β-adrenergic activity, this increased drug exposure may lead to a greater incidence of tachycardia. Additionally, using an inappropriate dosing weight may affect the time to attainment of target mean arterial pressure (MAP). Finally, clinicians may fail to recognise the true norepinephrine exposure associated with a weight-based regimen in the morbidly obese. In doing so, they may miss the ideal timeframe to escalate therapy, delaying the addition of adjunctive therapy, such as a second vasopressor and stress-dose steroids. Despite this, the appropriate dosing weight for norepinephrine in the critically ill obese patient population remains unclear. At our institution, standard of practice is to use weight-based dosing of norepinephrine. The purpose of this study was to evaluate the safety and efficacy of weight-based dosing of norepinephrine using actual body weight in morbidly obese patients compared with normal weight patients.

Methods

This was a single centre, retrospective cohort study conducted on patients admitted to our institution from January 1, 2011 to December 31, 2014. A patient list was obtained from a University HealthSystem Consortium (UHC) database. This list was used for screening and identification of patients for inclusion, extracting patients with septic shock based on ICD-9 and Diagnosis-Related Group codes. After identification, patient data was collected from the electronic medical record (EMR). Patients were included if they were 18 years or older and admitted to the medical intensive care unit (ICU) with septic shock requiring norepinephrine for at least 12 hours. Patients were also included and grouped based on body mass index (BMI). Patients with a BMI 18.5–24.9 kg/m^2 were categorised as normal weight and those with a BMI $\geq$40 kg/m^2 as morbidly obese (Clinical Guidelines, 1998). Those patients with a BMI between 25 kg/m^2 and 39.9 kg/m^2 were not included to maximise the degree of effect seen, if any, that obesity may have on using a weight-based approach (using actual body weight) with norepinephrine. Patients admitted for surgical or cardiac reasons were excluded. This study was approved by the institutional review board on December 8, 2014 under protocol number 14-0883-P2H.

The University of Kentucky Medical Center is a tertiary, academic medical centre with 945 licensed beds. During the study, the medical ICU services averaged approximately 180 admissions per month across 50–60 beds. Standard of practice for patients in septic shock included first-line use of norepinephrine to maintain a mean arterial presuure (MAP) goal of greater than 65 mmHg, as recommended by the Surviving Sepsis Guidelines (Dellinger et al., 2013). Norepinephrine was titrated by bedside nurses to a maximum of 0.4 mcg/kg/min. Further management, including addition and timing of a second vasopressor and stress-dose steroids, was at the discretion of the treating physician.

The primary endpoint examined the incidence of tachycardia within 48 hours after norepinephrine initiation. Due to norepinephrine's higher relative affinity for α-receptors compared to β-receptors, tachycardia primarily manifests with high doses of norepinephrine. Tachycardia can thus serve as a marker for excessive exposure to norepinephrine and was chosen as the primary safety outcome. Vital signs and doses of norepinephrine (in mcg/kg/min) were recorded at least hourly by bedside nurses and documented manually in the EMR. Tachycardia was defined as a heart rate (HR) $\geq$110 beats per min (bpm) in any rhythm and stratified as follows: 110–119, 120–129, 130–139, and >140 bpm. In this study, tachycardia included both normal rhythms (i.e. sinus tachycardia) and irregular rhythms (i.e. atrial fibrillation). A threshold of $\geq$110 bpm was chosen to account for intrinsic increases in HR related to the stress response during septic shock. Number of tachycardic readings and total HR readings were collected for the 48 hours after norepinephrine initiation and divided into the first and second 24 hours of the infusion. Secondary efficacy endpoints included time to goal MAP, in-hospital mortality and ICU and hospital length-of-stay (LOS). Other secondary endpoints were the time to and norepinephrine dose at which a second vasopressor and stress-dose steroids were added. Baseline demographics were also recorded for both groups. Actual body weights were used for all dosing. The goal MAP was defined as $\geq$65 mmHg. Stress-dose steroids were defined as hydrocortisone 200–300 mg/day.

Data analysis was conducted using IBM SPSS (version 22, 2013). Continuous data were analysed using the *t*-test and categorical data with the Chi-squared test and Fisher's exact test with an α set at 0.05 for statistical significance.

Results

A total of 415 patients were screened for inclusion, with 33 patients meeting inclusion criteria, of which 20 patients were in the normal weight group and 13 in the morbidly obese group. Two hundred fifty-eight patients were excluded for not meeting the BMI criteria (Fig. 1). A number of patients received <12 hours of norepinephrine or were inadvertently started on flat dosing of norepinephrine and were thus excluded from the analysis. Baseline characteristics were similar between groups (Table 1). The mean age of included patients was 56.3 years and approximately half were men. Morbidly obese patients were significantly more likely to have a reported history of arrhythmias prior to admission. Predicted mortality estimates were provided by UHC and similar between groups.

There was no significant difference in the incidence of tachycardia 48 hours after norepinephrine initiation between treatment groups (Table 2). Rates of tachycardia were similar between the morbidly obese and normal weight groups on days 1 (18.4% vs.

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