USE OF VASOPRESSIN IN SEPTIC SHOCK

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1. INTRODUCTION

Septic shock is a commonly managed condition in Intensive Care Units (ICUs). At present, mortality rates associated with septic shock remain high, despite the wide variety of developed early intervention strategies. These include tailored identification of critically ill patients, culture collection and initial fluid resuscitation, among others.

According to 2017 data [1], there were 48.9 million cases of septic shock and 11 million deaths directly attributable to it that year — accounting for 19.7% of all deaths worldwide.

In Spain, the estimated incidence of septic shock ranges from 27 to 31 cases per 100,000 individuals, with associated mortality rates from 32.6% to 54.3% [2] Septic shock imposes a significant burden on the national healthcare system, with costs ranging from €11,000 k to €15,000 per admission per patient [3].

The main clinical signs of septic shock include arterial hypotension, abnormal tissue perfusion, and increased serum lactate levels. Hypotension is primarily associated with a loss of vascular smooth muscle reactivity and, to a lesser extent, with hypovolemia and cardiac dysfunction [4].

Currently, the most common first-line management strategy for septic shock involves fluid resuscitation, followed by the administration of noradrenalin (NAD) to reverse hypoperfusion and achieve adequate arterial pressure. Progressive increase in NAD doses is usually required.

A state-of-the-art line of research in septic shock management focuses on the potential use of a second vasopressor agent. Current efforts aim to determine which drug should be used and the optimal timing for its initiation.

In line with this, the Surviving Sepsis Campaign 2021 clinical guidelines [5] recommends **considering vasopressin-arginine (VAP) as a second-line vasopressor when norepinephrine (NAD) doses exceed 0.25 µg/kg/min**, although this suggestion is based on limited evidence and remains weak. The Spanish Agency of Medicines and Healthcare Products (AEMPS) approved VAP for use in adult septic shock patients with catecholamine-resistant hypotension.

A neurohypophyseal hormone, VAP is synthesized in the neurosecretory cells of the supraoptic and paraventricular nuclei. Under physiological conditions, two types of stimuli trigger its release.

- When serum osmolality rises above 290 mOsm/kg.
- When blood volume decreases.

VAP acts on the human body in two ways: inducing vasoconstriction — and thus, increasing blood pressure— and increasing water reabsorption in the kidneys —

decreasing diuresis and increasing blood volume. As a collateral effect, VAP administration also leads to a reduction in NAD requirements [6].

Paradoxically, a diuresis increase was also observed in some VAP-treated septic shock patients, due to mechanisms —not yet well understood— that could be related high serum plasma hormone levels [7] [8].

Previous clinical literature has already addressed different aspects of VAP administration in septic shock adult patients.

- In the VANISH trial [9], early VAP use did not increase the number of renal failure-free days, compared with NAD-treated patients. However, the confidence interval suggests a potential benefit, with indices pointing to vasopressin helping to prevent further organ dysfunction.
- The VASST trial [10] suggests that VAP may improve clinical outcomes when initiated at intermediate NAD doses (0.2–0.5 μg/kg/min) in less severe patients. Early onset (<12 h) is associated with better outcomes. Vasopressin could also improve renal function and reduce the need for renal replacement therapy in selected patients. With a dose of 0.03 U/min appearing to be safe.
- The OVISS trial [11] shows how a reinforcement learning algorithm recommends earlier vasopressin initiation at lower norepinephrine doses and SOFA scores. The more closely clinicians adhered to the rule, the lower the in-hospital mortality and the reduced need for kidney replacement therapy, without increasing mechanical ventilation requirements.

2. BACKGROUND AND RATIONALE

The “Hospital General Universitario Gregorio Marañón" — the institution to which the promoters of this study belong — is a Spanish public hospital located in Madrid.

In recent years, significant efforts have been undertaken by the hospital’s intensive care unit to improve and tailor septic shock detection and management. Several strategies were implemented, in line with global septic shock handling trends. These includes early antibiotic onset, improvements at fluid resuscitation procedures, bacterial culture collection and NAD early administration.

In addition, a new protocol was implemented in 2021 at hospital’s ICU. The aim of it was to set a course of action for second vasopressor administration in septic shock patients, in accordance with state-of-art clinical evidence.

As previously stated, there is no conclusive evidence regarding **which is the best moment for VAP initiation in adult septic shock patients**. Further research is also needed to determine **the effects of VAP use in patient septic shock prognoses and progression**, especially concerning its impact on **renal function**.

The hypothesis of this study relies on the evidence-based possibility that early initiation of vasopressin, **defined by the norepinephrine dose (µg/kg/min) at which it is started**, may have a prognostic impact by reducing mortality in patients with septic shock.

3. OBJECTIVES

The main objective of this work is to **analyse routine clinical practice in the use of vasopressin in critically ill, ICU-admitted adult patients with septic shock**. In addition, some complementary objectives are also defined.

- To analyse the prognostic impact, in terms of all-cause mortality, of **early VAP initiation** in patients with septic shock.
- To evaluate **the impact of VAP use as a second vasopressor (adjunct to NAD) on renal function** in patients with septic shock.
- To evaluate the **impact of VAP use as a second vasopressor on the progression of organ dysfunction** in patients with septic shock.

Renal function will be assessed using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for acute kidney injury (AKI). KDIGO stages range from 0 (no AKI) to 3 (severe AKI), with higher stages indicating worse renal function. KDIGO classification will be recorded at 24, 48, and 72 hours after vasopressin initiation, as well as the highest stage reached during the entire ICU stay.

Organ dysfunction will be measured using the Sequential Organ Failure Assessment (SOFA) score, which ranges from 0 (no organ dysfunction) to 24 (severe multi-organ failure). Higher scores indicate worse outcomes. SOFA score will be recorded at 24, 48, and 72 hours after vasopressin initiation, as well as the maximum SOFA score obtained during the ICU stay.

4. STUDY DESIGN AND POPULATION

The study is defined as an **observational**, **prospective**, **non-interventional drug study** conducted on patients diagnosed with septic shock and admitted to the ICUs of the participating hospitals over a **two-year** period. The clinical study will be conducted in the following phases.

- Recruitment and case collection: 10/2025 — 10/2027.
- Data analysis: 11/2027 — 12/2027.
- Result dissemination through scientific publication: Q1 2028.

4.1. Inclusion and exclusion criterio

Eligible patients for this study must comply with the following requirements.

- ICU admission with a septic shock diagnosis.
- Age 18 years or above at ICU admission.
- Use of vasopressin as an adjunct of norepinephrine.

For the purposes of this study, septic shock is defined by full compliance with the following criteria.

- Sustained arterial hypotension or serum lactate above 2 mmol/L.
- Adequate but unsuccessful fluid resuscitation.
- Vasopressor usage to maintain a mean arterial pressure above 65 mmHg.
- Probable or proven infectious etiology.

Patients with some of the following conditions will be automatically excluded.

- Pregnancy.
- Ischemic cardiogenic shock.
- Acute intestinal ischemia.
- Readmission to the Intensive Care Unit.

4.2. Study design

Once recruited and until the end of follow-up, patients will be **evaluated every morning**. Variables of interest will be collected using **REDCap** —a specialized application for managing clinical research databases and clinical trials. More precisely, a REDCap instance hosted at Gregorio Marañón Hospital server will be used. The follow-up period will extend **from the patient's ICU admission until 30 days have elapsed or until hospital discharge/death occurs**.

For security reasons, only authorized personnel will be granted access, using a personal and non-transferable user account.

To safeguard patients' rights and ensure compliance with the data protection regulations currently in force within the European Union, any extraction of data from the study database to external devices for research or analytical purposes **will be pseudonymized**. Medical Record Numbers (MRN) will be encrypted using a hash algorithm. For each patient, all clinically relevant dates related to hospital admission will be uniformly shifted by a random number of days.

Furthermore, only clinical data strictly relevant to the research will be collected. Personal identifiers not pertinent to the study—such as names, surnames, or other personal IDs different than MRN—will be excluded.

Responsibility for the custody of the study database and for ensuring compliance with the regulations will rest with the study sponsor.

4.3. Study sample size

The sample size was determined based on the reported annual incidence of septic shock in Spain (31 cases per 100,000 inhabitants) and an estimated mortality of 40%. Using the Cochran sample size equation, a total of 1,200 patients was deemed necessary to achieve a 95% confidence level with a 3% margin of error, accounting for an anticipated 15% dropout rate.

4.4. Clinical database schema

In line with the study objectives and previously outlined guidelines, a database will be developed to support data collection. This resource will be implemented on the hospital's REDCap server. A comprehensive breakdown of all collected variables is provided in **Annex I**.

5. STATISTICAL DATA ANALYSIS

Once the data gathering phase is completed, collected clinical data will be statistically analysed, using SPSS statistics.

5.1. Descriptive analysis

The Kolmogorov–Smirnov test will be applied to evaluate whether the continuous quantitative variables follow a normal distribution.

- Quantitative variables following a normal distribution will be featured using its mean and standard deviation.
- If they do not follow a normal distribution, median and interquartile range will be used.
- Dichotomous, and categorical variables will be described using percentages.

5.2. Univariate analysis

Normally distributed continuous variables will be analysed using mean comparisons through the Student's t-test, after confirming variance homogeneity using Levene's test. For variables that do not meet the assumption of normality, the Mann–Whitney U test (non-parametric) will be applied.

Additionally, univariate logistic regression will be performed to assess the strength of association between each variable and the primary outcome, expressed as Odds Ratios (OR) with their corresponding 95% CI.

Categorical variables will be recoded into dichotomous variables to facilitate analysis. Associations will be examined using the Chi-square (χ^2) test or Fisher's exact test when expected cell counts fall below five. Relative Risks (RR) with 95% confidence intervals will also be calculated to quantify the magnitude of these associations.

5.3. Multivariate analysis

To determine whether early vasopressin use—defined as the norepinephrine dose (µg/kg/min) at initiation—acts as an independent prognostic factor for mortality, a multivariable logistic regression analysis will be performed. Variables significant in the univariate analysis will be included, along with others that, although not statistically significant, are clinically relevant.

If early vasopressin use proves to be an independent prognostic factor, the optimal cut-off point for discriminating mortality risk will be identified. Based on this threshold, patients will be stratified into two groups, and survival will subsequently be assessed using Cox regression.

6. ETHICAL COMPLIANCE AND PATIENT RIGHTS

The study has been formally backed by the Research with Drugs Ethics Committee of the Gregorio Marañón University Hospital, which ensures full compliance with all required ethical standards and safeguards the confidentiality of recruited patients.

The study will be conducted in accordance with the Declaration of Helsinki guidelines. Study deployment will strictly follow the approved protocol and the applicable standard operating procedures (SOPs) to ensure compliance with Good Clinical Practice (GCP), as described in the ICH Harmonised Tripartite Guideline for GCP (1996). Established guidelines for Good Epidemiological Practice will be also followed.

6.1. Risk-benefit assessment

The proposed study relies on an observational, non-intervention approach. Given that, **no risk is posed to patient integrity**. Moreover, potential benefits regarding septic shock handling could be derived from this work.

6.2. Data confidentiality

The study will be conducted in accordance with European Union legislation on personal data, specifically Organic Law 3/2018 of December 5th, on the Protection of Personal Data and the Guarantee of Digital Rights, Royal Decree 1720/2007, Law 41/2002 of November 14th, which regulates patient autonomy and the rights and obligations related to clinical information and documentation, as well as the General Data Protection Regulation (GDPR) (EU) 2016/679.

Each patient will be assigned a numeric code, known only to the study sponsor. No personally identifiable information will be recorded in REDCap. The study sponsor is responsible for safeguarding and retaining the study data.

Only authorized researchers and the Drugs Ethics Committee board members of the Gregorio Marañón University Hospital have data access rights. In addition, data access must be granted to the Spanish health authorities, if it is required as part of an inspection.

Only the pseudonymized database will be used for data analysis. Researchers will commit to maintaining complete confidentiality regarding any data they may come across during the work.

Collected data will not be copied or used for purposes other than those specified, nor will it be disclosed to third parties, even for storage purposes. These duties will remain in effect after the authorized access period has expired. The study's results may be presented at conferences, meetings, and published in scientific journals, always ensuring the confidentiality of personal data.

6.3. Informed consent

Given the observational nature of the study, the absence of clinical intervention during follow-up, and the difficulty in obtaining explicit consent due to the severity of the condition being studied, and the possibility of retrospective inclusion of clinical cases, an exemption from informed consent has been requested from the Research Ethics Committee for Studies with Drugs.

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