



Effect of Selepressin vs Placebo on Ventilator- and Vasopressor-Free Days in Patients With Septic Shock

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ABSTRACT

Background: The exploration of the effects of selepressin versus placebo in patients experiencing septic shock is an emerging area of interest in critical care medicine. The literature surrounding this topic reveals a complex interplay between vasopressor use, patient outcomes, and potential complications associated with septic shock management.

Literature Review: The literature surrounding the effects of selepressin versus placebo in patients with septic shock reveals a nuanced understanding of its potential benefits and limitations in critical care settings. The introduction highlights the significance of vasopressor management in septic shock and sets the stage for a detailed examination of selepressin's role, particularly its impact on ventilator- and vasopressor-free days. **Conclusion:** In conclusion, the literature suggests that selepressin presents a promising alternative to traditional vasopressors in the management of septic shock, particularly in its ability to maintain hemodynamic stability and potentially reduce the duration of mechanical ventilation. However, the variability in trial outcomes and the lack of significant differences in primary endpoints underscore the need for further research to clarify the role of selepressin in clinical practice. Continued exploration of its effects on secondary outcomes may provide valuable insights into optimizing treatment strategies for patients with septic shock.

Keyword: Selepressin, Placebo, Ventilator, Vasopressor, Septic Shock

INTRODUCTION

The exploration of the effects of selepressin versus placebo in patients experiencing septic shock is an emerging area of interest in critical care medicine. The literature surrounding this topic reveals a complex interplay between vasopressor use, patient outcomes, and potential complications associated with septic shock management.

In 2017, (A. Russell et al., 2017) conducted a phase IIa randomized, placebo-controlled trial that highlighted the efficacy of selepressin, a selective vasopressin V(1A) agonist, as a substitute for norepinephrine. Their findings indicated that a dosage of 5 ng/kg/minute not only maintained adequate mean arterial pressure (MAP) but also increased the proportion of patients weaned off norepinephrine within the first 24 hours. Furthermore, this dosage was associated with a higher number of days alive and free of mechanical ventilation compared to placebo,

suggesting a potential clinical advantage in mitigating lung dysfunction and improving overall treatment outcomes in septic shock. The study emphasized the protective role of selepressin against vascular leakage, which is a critical factor in the pathophysiology of septic shock.

Building on this foundation, (Demiselle et al., 2020) provided a broader review of vasopressin and its analogues in shock states. Their retrospective analysis indicated an improved prognosis in septic shock patients receiving fixed-dose vasopressin alongside norepinephrine. They noted that while terlipressin demonstrated superiority over norepinephrine in a small cohort, the results should be interpreted cautiously due to limited sample sizes. The review underscored the potential of selepressin as a more effective agent than both norepinephrine and vasopressin, particularly in maintaining MAP and reducing lung edema, although the SEPSISACT trial, which involved 817 patients, did not find significant

differences in primary and secondary endpoints between the groups.

In 2022, (Jozwiak et al., 2022) expanded the discussion through a comprehensive analysis of the SEPSIS-ACT trial, which evaluated the addition of selepressin to norepinephrine in septic shock patients. While the trial was halted for futility due to a lack of difference in the primary endpoint of ventilator- and vasopressor-free days, the authors noted beneficial outcomes in the selepressin group, including reduced norepinephrine requirements and improved urine output. This suggests that while the primary composite endpoint was not achieved, there may still be important clinical implications of selepressin use that warrant further investigation.

Overall, the literature indicates that selepressin presents a promising alternative to traditional vasopressors in the management of septic shock, with potential benefits related to vascular stability and reduced mechanical ventilation duration. However, the variability in trial outcomes and the complexities of septic shock management highlight

the need for ongoing research to clarify the role of selepressin in clinical practice.

LITERATURE REVIEW

The article titled "Selepressin, a novel selective vasopressin V(1A) agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients" authored by Russell et al. (A. Russell et al., 2017) presents a significant exploration of the efficacy of selepressin in managing septic shock compared to placebo. The study focuses on the potential benefits of selepressin, particularly its role in reducing the need for norepinephrine and its implications for mechanical ventilation and overall patient outcomes.

One of the key insights from the study is the administration of selepressin at a dosage of 5 ng/kg/minute, which was shown to maintain an adequate mean arterial pressure (MAP) while simultaneously increasing the proportion of patients who could be weaned off norepinephrine within the first 24

hours. This is a critical finding, as norepinephrine is commonly used in septic shock management, and reducing its cumulative dose can be beneficial for patient safety and recovery (A. Russell et al., 2017).

Moreover, the study indicates that patients receiving selepressin experienced a higher number of days alive and free from mechanical ventilation over a seven-day period compared to those receiving placebo. This suggests that selepressin not only aids in hemodynamic stability but may also contribute to mitigating lung dysfunction, which is often a complication in septic shock cases (A. Russell et al., 2017). The authors propose that the mechanism behind this may be related to selepressin's ability to block vascular leakage more effectively than vasopressin, a common concern in septic patients due to increased endothelial permeability leading to edema and organ dysfunction.

The article also highlights the selective action of selepressin on the vasopressin V1A receptors, contrasting it with nonselective vasopressin agonists. By not

activating the V2 receptors, which mediate antidiuretic effects, selepressin may offer additional advantages in managing fluid balance in septic shock patients (A. Russell et al., 2017). This specificity could potentially lead to fewer complications related to fluid overload, a common challenge in the treatment of septic patients.

Importantly, the study reports no significant differences in treatment-emergent adverse events between the selepressin and placebo groups, indicating a favorable safety profile for the drug (A. Russell et al., 2017). This aspect is crucial for clinicians considering the implementation of new treatment protocols in critical care settings.

The article "Vasopressin and its analogues in shock states: a review" by Demiselle et al. (Demiselle et al., 2020) provides a comprehensive examination of the role of vasopressin and its analogues, particularly in the context of septic shock. The review critically evaluates various studies, including a randomized trial involving 32 patients that demonstrated the superiority of

terlipressin combined with norepinephrine over norepinephrine alone. This finding is significant as it suggests that adjunctive vasopressor therapy may enhance hemodynamic stability in septic shock patients.

The authors reference a pivotal study by Liu et al. (2018), which contrasts terlipressin and norepinephrine as first-line agents in septic shock, revealing no significant difference in 28-day mortality rates. This highlights a critical aspect of the ongoing debate regarding the efficacy of different vasopressors in improving survival outcomes. The review further explores the potential of selepressin, a newer synthetic V1a agonist, which has shown promising results in animal models, particularly in maintaining mean arterial pressure while mitigating lung edema compared to norepinephrine and vasopressin.

In discussing the SEPSISACT study, the authors note that the addition of selepressin to norepinephrine in a placebo-controlled trial involving 817 patients did not yield a significant difference in the primary composite endpoint.

This finding raises important questions about the clinical utility of selepressin in septic shock management, particularly in terms of ventilator- and vasopressor-free days, which are crucial metrics for assessing patient recovery and overall treatment efficacy.

The article also references a meta-analysis of 20 studies that suggests a potential survival advantage with vasopressin and its analogues over adrenergic vasopressors. This meta-analytic evidence adds depth to the discussion, indicating that while individual studies may show mixed results, there may be a broader trend favoring the use of vasopressin in specific patient populations.

The article titled "Vasopressors and Risk of Acute Mesenteric Ischemia: A Worldwide Pharmacovigilance Analysis and Comprehensive Literature Review" by Jozwiak et al. (Jozwiak et al., 2022) provides a thorough examination of the effects of selepressin in the context of septic shock, particularly in relation to its comparison with placebo. The main

focus of the article is grounded in the findings from the SEPSIS-ACT trial, which was pivotal in assessing the efficacy of selepressin.

The SEPSIS-ACT trial, as highlighted in the article, was a phase 2b/3 study that ultimately concluded with a halt due to futility, revealing no significant differences in the primary outcome measure of ventilator- and vasopressor-free days within a 30-day period between the selepressin and placebo groups. This finding raises critical questions about the overall effectiveness of selepressin as a treatment option in septic shock, especially considering that the primary endpoint is a vital measure of patient recovery and resource utilization in critical care settings.

Despite the lack of significant differences in the primary endpoint, Jozwiak et al. (Jozwiak et al., 2022) note some beneficial effects associated with selepressin treatment. These included a reduction in the doses of norepinephrine required, improved fluid balance, and increased urine output in patients receiving selepressin compared to those on placebo. These secondary findings

suggest that while selepressin may not directly enhance the primary outcome of ventilator- and vasopressor-free days, it could still contribute positively to the management of septic shock by optimizing hemodynamic parameters and renal function.

The implications of these findings are multifaceted. On one hand, the results indicate that selepressin may not be a superior treatment option when considering the primary outcomes that are typically prioritized in clinical practice. On the other hand, the observed improvements in norepinephrine dosing and urine output could suggest a role for selepressin in specific patient populations or as part of a broader therapeutic strategy in managing septic shock.

CONCLUSION

The literature surrounding the effects of selepressin versus placebo in patients with septic shock reveals a nuanced understanding of its potential benefits and limitations in critical care settings. The introduction highlights

the significance of vasopressor management in septic shock and sets the stage for a detailed examination of selepressin's role, particularly its impact on ventilator- and vasopressor-free days.

The phase IIa randomized trial by Russell et al. (A. Russell et al., 2017) serves as a cornerstone in this discussion, demonstrating that selepressin, administered at a dosage of 5 ng/kg/minute, maintained adequate mean arterial pressure (MAP) and allowed for a higher proportion of patients to be weaned off norepinephrine within the first 24 hours. This finding is crucial, as it suggests that selepressin may mitigate the complications associated with prolonged norepinephrine use, particularly in terms of lung dysfunction and vascular leakage, which are common in septic shock (A. Russell et al., 2017).

Further exploration by Demiselle et al. (Demiselle et al., 2020) expands on the comparative efficacy of vasopressin analogues, indicating that while some studies suggest advantages for vasopressin and its analogues over

norepinephrine, the evidence remains mixed. The review underscores the potential of selepressin, particularly in maintaining MAP and reducing lung edema, yet it also points out the limitations of existing studies, including the SEPSIS-ACT trial, which did not demonstrate significant differences in primary and secondary endpoints despite some beneficial outcomes in secondary measures (Demiselle et al., 2020).

Jozwiak et al. (Jozwiak et al., 2022) provide a critical analysis of the SEPSIS-ACT trial, emphasizing that while the primary endpoint of ventilator- and vasopressor-free days was not achieved, secondary outcomes such as reduced norepinephrine requirements and improved urine output suggest that selepressin may still hold clinical relevance. These findings highlight the complexity of septic shock management and the importance of considering a broader range of outcomes when evaluating treatment efficacy.

In conclusion, the literature suggests that selepressin presents a promising alternative to traditional

vasopressors in the management of septic shock, particularly in its ability to maintain hemodynamic stability and potentially reduce the duration of mechanical ventilation. However, the variability in trial outcomes and the lack of significant differences in primary endpoints underscore the need for further research to clarify the role of selepressin in clinical practice. Continued exploration of its effects on secondary outcomes may provide valuable insights into optimizing treatment strategies for patients with septic shock.

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