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RESEARCH ARTICLE

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Slow 0.9% NaCl Bolus Administration Reduces ANP, MMP-2, and Syndecan-1 Shedding in Septic Shock Rabbit Models

I Nyoman Budi Hartawan[1], Made Wiryana[2], I Made Jawi[3], I Nyoman Mantik Astawa[4], I Made Bakta[5], Ida Bagus Subanada[1], Ida Bagus Suparyatha[1], Dyah Kanya Wati[1]

[1]*Department of Pediatric, Faculty of Medicine, Universitas Udayana-Ngoerah Hospital, Denpasar, Indonesia*
[2]*Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Udayana-Ngoerah Hospital, Denpasar, Indonesia*
[3]*Department of Pharmacology and Therapy Department, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia*
[4]*Immunology Laboratory, Faculty of Veterinary, Universitas Udayana, Denpasar, Indonesia*
[5]*Internal Medicine Department, Faculty of Medicine, Universitas Udayana-Ngoerah Hospital, Denpasar, Indonesia*

Background: The optimal rate for fluid bolus administration in septic shock remains a critical and unresolved question. Rapid bolus administration is commonly practiced but has been linked to elevated levels of atrial natriuretic peptide (ANP), matrix metalloproteinase-2 (MMP-2), and syndecan-1 shedding, potentially exacerbating endothelial glycocalyx damage and increasing vascular permeability. However, the physiological and clinical implications of slower bolus rates have not been thoroughly investigated. This study was conducted to identify safer fluid management practices and improve patient outcomes in septic shock.

Materials and methods: A randomized post-test-only control group design was employed, involving 36 male New Zealand rabbits with lipopolysaccharide-induced septic shock. The treatment group received 0.9% NaCl boluses (20 mL/kg body weight) over 20 minutes per bolus (slow bolus), while the control group received the same volume over 5 minutes per bolus (rapid bolus). ANP, MMP-2, and syndecan-1 levels were measured using ELISA 10-15 minutes post-intervention.

Results: The median ANP levels in the treatment group (92.86 ng/mL) were significantly lower (p<0.05) than those in the control group (367.32 ng/mL). The mean MMP-2 levels in the treatment group (10.26 ng/dL) were lower than those in the control group (11.43 ng/dL). The median levels of syndecan-1 were also lower in the treatment group (4.31 ng/mL) compared to the control group (5.94 ng/mL).

Conclusion: Slow fluid boluses appear to mitigate endothelial damage by reducing ANP, MMP-2, and syndecan-1 shedding. These findings suggest that slower infusion rates may offer a protective advantage in fluid resuscitation, paving the way for updated clinical guidelines.

Keywords: *fluid bolus, ANP, MMP-2, syndecan-1*

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Corresponding Author:
I Nyoman Budi Hartawan
Department of Postgraduate Biomedical Science, Faculty of Medicine
Universitas Islam Sultan Agung
Terboyo Kulon, Semarang 50112, Indonesia
e-mail: drekosetiawan@unissula.ac.id

Cell and Biopharmaceutical Institute

Introduction

Fluid bolus administration is one of the treatments for septic shock. The 2012 surviving sepsis campaign algorithm states that fluid boluses are given at 20 mL/kg body weight (BW) within 5-10 minutes, three times consecutively, or until signs of fluid overload, such as edema, microvascular dysfunction, and changes in oxygen distribution, develop.[1] The fluid bolus rate and the volume of fluid given are still debated, given the risk of fluid overload, which causes increased atrial natriuretic peptide (ANP) release from the heart. Atrial natriuretic peptide eventually damages endothelial glycocalyx (EG), which further worsens patients' outcomes.[2-5] A previous study[6] found that administration of albumin labelled with radioactive compounds within 15 minutes will result in a smaller increase in plasma volume compared to slower fluid administration in rats. Research on elective surgical patients with good cardiopulmonary conditions showed that a 6% hydroxyethyl starch (HES) bolus of 20 mL/kg body weight (over 15 minutes, at a rate of 90 mL/minute) resulted in increased levels of ANP, EG (syndecan-1 and hyaluronan).[7]

As part of the management of septic shock, fluid bolus administration has two sides. Rapid fluid boluses may cause several disadvantages compared to slower boluses. The aim of this study was to verify that ANP, MMP-2 and syndecan-1 levels are lower in slow fluid bolus than with rapid ones. This study was conducted to evaluate whether slow fluid bolus administration (20 minutes per bolus) results in lower levels of ANP, MMP-2, and syndecan-1 compared to rapid bolus administration (5 minutes per bolus) in septic shock rabbit models. The hypothesis suggests that slower bolus rates will reduce atrial stretch and vascular damage, as evidenced by lower levels of these biomarkers. Rapid fluid bolus administration is associated with fluid overload, increased atrial stretch, and elevated levels of biomarkers such as atrial natriuretic peptide (ANP), matrix metalloproteinase-2 (MMP-2), and syndecan-1, which indicate endothelial glycocalyx (EG) shedding and vascular damage. In contrast, studies in animal models and clinical observations suggest that slower infusion rates can mitigate these effects by reducing atrial distension, stabilizing plasma volumes, and preserving vascular integrity, offering a safer approach to fluid resuscitation in septic shock.[7]

Despite the widespread use of rapid fluid bolus administration in septic shock management, its potential to exacerbate endothelial damage through increased ANP release, MMP-2 activation, and syndecan-1 shedding raises significant concerns. Emerging evidence suggests that slower infusion rates may reduce the physiological stress on the vasculature, thereby preserving endothelial glycocalyx integrity and mitigating fluid overload complications. However, the relationship between infusion rate and these biomarkers remains insufficiently explored, particularly in septic conditions. By investigating this relationship, this study was conducted to provide critical insights into the protective effects of slower fluid bolus administration, with the goal of informing safer and more effective resuscitation practices in septic shock.

Materials and methods

Study Design

This study was a laboratory experimental study using male New Zealand rabbit (*Orictolagus cuniculus*) and employed a randomized post-test only control group design to evaluate the effects of different fluid bolus administration rates on septic shock. Ethical approval was granted by the Animal Ethics Commission of the Faculty of Veterinary Medicine, Universitas Udayana (No. 22/UN14.2.9/PT.01.04/2021), and the study was authorized for implementation by the Integrated Biomedical Laboratory Unit (No. 856/UN14.2.2.VII.6/LT/2021).

Animal Model

Thirty-six male New Zealand rabbits, aged 1.5 to 2 months, weighing 1000-2500 grams, were induced with septic shock and randomly divided into control group (n=18) and experimental group (n=18). In the control group, a bolus of 0.9% NaCl (20 mL/kg BW) was administerd three times in a row, each within 5 minutes (rapid bolus). In the experimental group, a bolus of 0.9% NaCl (20 mL/kg BW) was administerd three times in a row, each within 20 minutes (slow bolus).

Sepsis Induction

Septic shock in rabbits was induced by administering lipopolysaccharide (LPS), standard preparation LPS from *Escherichia coli* 055:B5- TLR4 and TLR2 ligand) (Invivo Gen, San Diego, California, US). The dose of LPS was 6 µg/kg BW. Rabbits were anaesthetized using ketamine at a dose of 35 mg/kg BW, administered intramuscularly.

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Marginal ear vein catheterization was performed, and the vein was connected to an infusion of 0.9% NaCl. Arterial catheterization was performed and connected to a blood pressure and heart rate monitor.

Following LPS injection, clinical signs of sepsis, including anorexia and lethargy, were observed. Blood pressure was continuosly monitored until the rabbits developed septic shock, defined as mean arterial pressure (MAP) < 65 mmHg, or a decrease in MAP ≥ 40 mmHg from baseline, and/or lactate levels ≥ 3 mmol/L, which indicates septic shock. Blood samples were collected from contralateral ear artery to determine lactate levels and base deficit. These were measured using i-STAT Analyzer (#41573, Abbott Point of Care Inc., Singapore).

Fluid Bolus Administration

The rabbits in the intervention group received a bolus of 0.9% NaCl via the marginal ear vein, with a volume of 20 mL/kg BW, administered three times consecutively over 20 minutes per bolus using a 50 mL syringe and an infusion pump. Blood samples were collected from the contralateral marginal ear vein to determine the levels of ANP, syndecan-1, and MMP-2, 10 to 15 minutes after the fluid bolus infusion.

The rabbits in the control group received a bolus of 0.9% NaCl via the marginal ear vein with the same volume of 20 mL/kg BW. However, the bolus was administered three times consecutively over 5 minutes per bolus using 50 mL syringe and an infusion pump. Blood samples were collected from the contralateral marginal ear vein to measure the levels of ANP, syndecan-1, and MMP-2, 10 to 15minutes after the fluid bolus infusion. Eexperimental animals were sacrificed 6 hours after LPS injection.

Rabbit ANP ELISA kit (Finetest, Wuhan, China) was used to quatify ANP serum levels quantitatively *in vitro*. The rabbit MMP-2 ELISA (Finetest) was used to quantify MMP-2 levels, and Rabbit Syndecan-1 ELISA kit (BT Lab) was used to measure syndecan-1 levels.

Data Analysis

Data were analyzed using SPSS 24.0 for Windows. Normality test was performed using Shapiro-Wilk test. A Mann-Whitney U test was used to compare the levels of ANP and syndecan-1 between groups. MMP-2 levels were compared using an independent t-test. Statistical significance was set at a $p<0.05$, and the results were evaluated with a 95% confidence interval.

Results

Slow 0.9% NaCl Bolus Administration Reduced ANP Levels

ANP levels in treatment group were significantly lower compared to control group (Table 1, Figure 1). This suggested a notable reduction in ANP secretion following the slow fluid bolus administration.

Slow 0.9% NaCl Bolus Administration Reduced MMP-2 Concentrations

MMP-2 levels in treatment group were significantly lower than those in control group (Table 2). The results showed a noticeable difference in mean values of distribution of MMP-2 levels between groups (Figure 2).

Slow 0.9% NaCl Bolus Administration Reduced Syndecan-1 Levels

Syndecan-1 levels were significantly reduced in treatment group compared to control group (Table 3, Figure 3).

Discussion

Various studies have shown that the degree of ANP secretion depends on the degree of atrial distention.[8-10] This study demonstrated that ANP levels were higher in rapid boluses compared to slow boluses. This suggest that there is an increase in atrial pressure, as well as atrial muscle stretching, in rapid boluses compared to slow boluses. Consequently, ANP secretion is higher in rapid boluses.

Previous studies have shown that fluid bolus volumes in septic shock rabbits are significantly correlated with ANP levels.[8-9] Research with LPS-induced septic shock rabbits that were given fluid boluses demonstrated that the highest ANP levels were obtained in boluses with a fluid volume of 30 mL compared to 10 mL. As the fluid bolus

Table 1. Macroscopic and microscopic characteristics of bacterial isolates.

Variable	Group		*p*-value
	Control (Median±IQR)	Treatment (Median±IQR)	
ANP (ng/mL)	367.32±153.75	92.86±148.67	0.001*

IQR: Inter quartile range. *Significant (Mann-Whitney test, $p<0.05$).

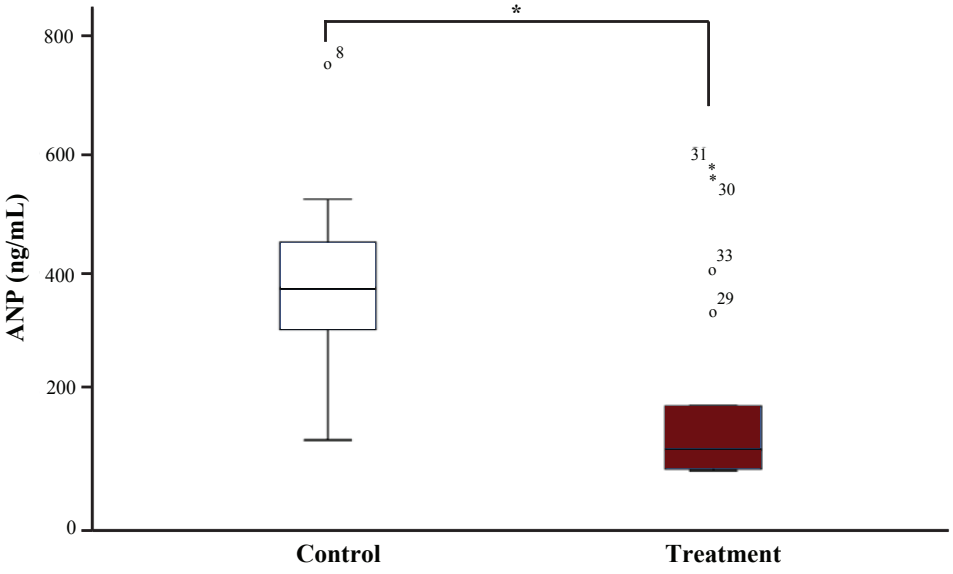

Figure 1. Slow 0.9% NaCl bolus administration reduced ANP levels. The central line represented the median, the box showed the IQR, and the whiskers indicated the range of data, excluding outliers. *Significant (Mann-Whitney test, p<0.05).

volume increased, the higher the increase in ANP. Another study.[8] did not specify the speed or duration of fluid bolus administration but showed that fluid boluses can increase ANP levels in septic shock.

A previous studies in children with septic shock have shown children receiving fluid boluses over 5-10 minutes each had a higher risk of intubation and poorer outcome than those receiving boluses over 15-20 minutes each.[10,11] The septic shock also has 55.7% mortality rate in the children population.[12] This study led to the formation of a new hypothesis: rapid boluses may result in increased levels of ANP, which can increase vascular permeability and tissue edema.

A study investigated the effect of changes in plasma volume in septic rats (by ligation and incision of the cecum, followed by abdominal closure) three hours after a bolus of 12 mL/kg BW of albumin and 48 mL/kg BW of 0.9% NaCl within 15 minutes or 3 hours. A fluid bolus for 15 minutes resulted in a minor increase in plasma volume (expansion effect) compared to a slower fluid bolus (within 3 hours), and the effect of plasma albumin expansion was more significant than that of 0.9% NaCl.[6] Albumin itself is the most abundant protein produced in liver that decrease the shedding of endothelial glycocalyx.[13] This suggests that fluid boluses cause a brief increase in capillary pressure due to a transient increase in systemic arterial pressure, accompanied by a decrease in precapillary resistance and a decrease in haematocrit level. All of these events lead to intravascular fluid loss, due to the release of ANP and BNP after the bolus, resulting in increased urinary excretion and increased vascular permeability. This is consistent with current study, which demonstrated that rapid bolus significantly caused higher ANP levels than slow bolus. The results of this study further strengthen the theory that rapid bolus causes a greater increase in ANP levels and greater vascular permeability compared to slow bolus. Rapid boluses cause more significant atrial distension, resulting in higher ANP secretion.[9]

This study found that the MMP-2 level in the slow bolus group was significantly lower in the rapid bolus group. A previous study demonstrated that the higher the fluid bolus volume, the higher the MMP-2 expression.[8] The difference in resuscitation volume results in different expression levels of MMP-2 in rabbits' kidneys.

Table 2. The comparison of MMP-2 concentrations in control and treatment groups.

Variable	Group		Mean Difference	95%CI	p-value
	Control (Mean±SD)	Treatment (Mean±SD)			
MMP-2 (ng/mL)	11.43±1.74	10.26±1.73	1.17	0.005-2.35	0.001*

SD: Standard deviation. CI: Confidence interval. *Significant (Independent t-test, p<0.05).

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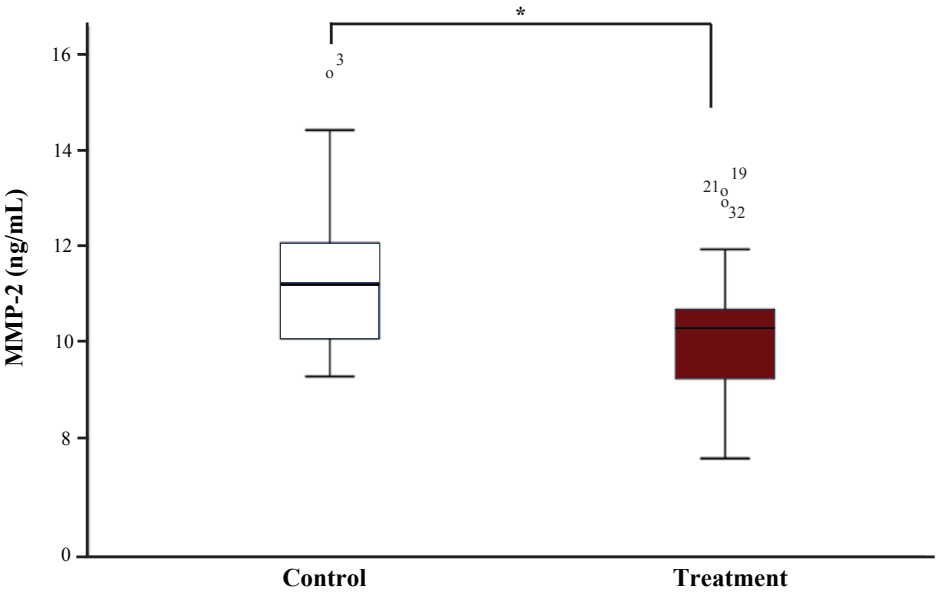

Figure 2. Slow 0.9% NaCl bolus administration reduced MMP-2 concentrations. The central line represented the median, the box showed the IQR, and the whiskers indicated the range of data, excluding outliers. *Significant (Independent t-test, $p<0.05$).

This study is supported by research investigating the association of various neurohormones (BNP, ANP, endothelin-1, angiotensin-II, epinephrine, and norepinephrine) with MMP-2, MMP-9, and TIMP-1 in adult patients with chronic heart failure.[14,15] In this study, there was a positive correlation between ANP and MMP-2, indicating that an increase in ANP levels is also accompanied by an increase in MMP-2 levels. This study also demonstrated a positive correlation between BNP and MMP-2.

Previous studies have examined the response of cardiac mast cells to ANP, which is secreted in large quantities during fluid overload in patients with heart failure. Atrial natriuretic peptide (225 pg/mL) was injected into the bloodstream in the rat's heart, followed by measurement of MMP-2 levels. The study demostrated that ANP did not increase the secretion of MMP-2 by the heart. The study was an *in vitro* study on a rat's heart and did not involve vascular endothelium.[15,16] This is in contrast with *in vivo* results from this study. The increase in MMP-2 can come not only from the heart but also from other sources such as vascular endothelium, fibroblasts and keratinocytes.

This study demonstrated that syndecan-1 levels after rapid fluid bolus were significantly higher than slow fluid boluses in septic shock rabbits. In conditions of sepsis and septic shock, there is a very severe inflammation. Rapid boluses have been shown to cause high levels of ANP, so in sepsis, syndecan-1 shedding is not only due to systemic inflammation but also induced by rapid bolus, which increases ANP level. Other studies have shown that even in good cardiopulmonary conditions (healthy patients), fluid boluses (HES 6% 20 mL/kg body weight for 15 minutes) can increase the syndecan-1 and hyaluronan shedding.[7] Thus, fluid boluses have been shown to increase syndecan-1 shedding. Other studies also concluded there was an increase in syndecan-1 levels with an increase in fluid balance (syndecan-1 increased accordingly with the increase in fluid balance).[17] This is consistent with this study, high levels of syndecan-1 in fluid bolus administration.

Previous research showed highest bolus volumes obtained highest levels of ANP and syndecan-1.[8] Larger fluid boluses resulted in an increase in ANP and higher syndecan-1 compared to smaller volume boluses. This is

Table 3. The comparison of syndecan-1 level in control and treatment groups.

Variable	Group		*p* -value
	Control (Median±IQR)	Treatment (Median±IQR)	
Syndecan-1 (ng/mL)	5.94±1.8	4.31±2.61	0.019*

IQR: Inter quartile range. *Significant (Mann-Whitney test, $p<0.05$).

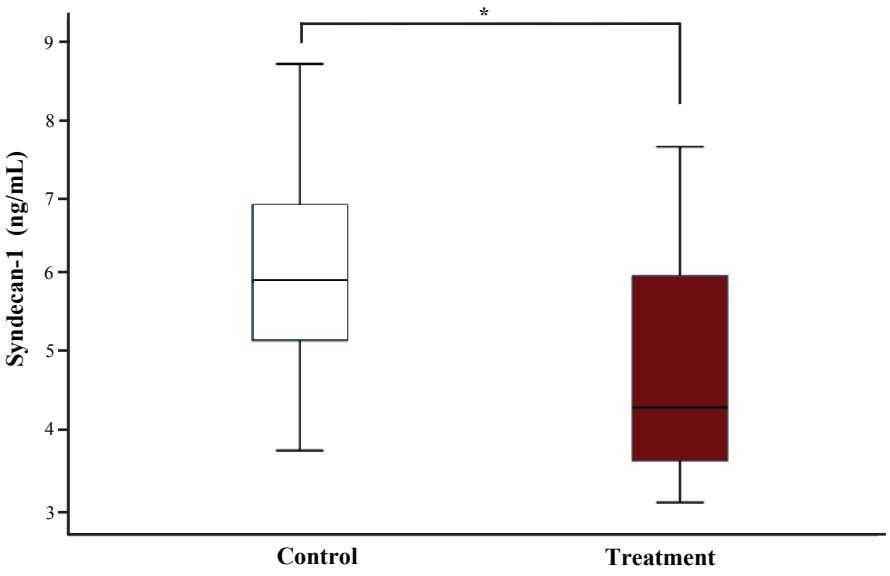

Figure 3. Slow 0.9% NaCl bolus administration reduced syndecan-1 levels. The central line represented the median, the box showed the IQR, and the whiskers indicated the range of data, excluding outliers. *Significant (Mann-Whitney test, $p<0.05$).

consistent with this study, which demonstrated high levels of ANP in rapid boluses were followed by high levels of syndecan-1. These studies reinforce the theory that ANPs are involved in syndecan-1 shedding.

A fluid bolus study in healthy term pregnant women who will undergo cesarean section (previously given spinal anaesthesia), with 750 mL of RL administered within 15 minutes demonstrated an increase in the levels of syndecan-1 and heparan sulphate but was not accompanied by an increase in ANP.[17] This demonstrates that fluid bolus can increase syndecan-1 shedding.

In good cardiopulmonary conditions and without fluid boluses, blood flow through the endothelium will result in fluid shear stress. Fluid shear stress causes local NO secretion in the endothelium, resulting in vasodilation of blood vessels. Under shear stress conditions, after a short fluid bolus, there is shedding of syndecan-1. Excessive fluid shear stress in rapid boluses can damage syndecan-1.[8] The higher the rate of infusion, the greater the injury. Research has shown that shear stress will be higher if the speed of fluid bolus administration is faster and the diameter of the catheter is smaller.[19] Shear stress is also able to stimulate inflammation, which in turn causes endothelial dysfunction, endothelial glycocalyx sloughing, and leukocyte adhesion to the endothelium. The release of proteases and lyases is thought to impair syndecan-1 after high fluid shear stress.[20,21] In this study, very high fluid shear stress occurred in the endothelium and glycocalyx. Fluid shear stress was higher in rapid bolus group compared to the slow bolus group, as evidenced by higher syndecan-1 levels in the rapid bolus.

Despite these findings, this study has several limitations. First, the study utilized an animal model, which, while informative, may not fully replicate the physiological responses seen in human septic shock. Second, the sample size was relatively small, and while statistical significance was achieved, larger studies are needed to confirm these results. Third, the study focused solely on biomarkers (ANP, MMP-2, and syndecan-1) and did not assess clinical outcomes such as survival rates or organ function recovery. Finally, the exclusive use of 0.9% NaCl restricts generalizability to other fluid types that may have different effects on endothelial glycocalyx integrity.

Future studies should focus on validating these findings in human populations, particularly in pediatric and critical care settings, where fluid bolus administration is crucial. Investigating the impact of different fluid types, such as balanced crystalloids or colloids, on biomarkers and clinical outcomes will provide a more comprehensive understanding of fluid therapy in sepsis. Longitudinal studies are also needed to assess the long-term effects of slow versus rapid fluid bolus administration on patient recovery and survival. Additionally, exploring the molecular mechanisms behind the protective effects of slow bolus administration could uncover new therapeutic targets for reducing endothelial damage in septic shock. Overall, further research is essential to fully understand the relationship between infusion rates and biomarkers in septic conditions, ultimately improving resuscitation practices.

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Conclusion

In conclusion, while rapid fluid bolus administration is common in septic shock management, it may exacerbate endothelial damage through increased ANP release, MMP-2 activation, and syndecan-1 shedding. Slower infusion rates may help preserve endothelial glycocalyx integrity and reduce complications associated with fluid overload.

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Authors' Contributions

INBH was involved in the study conception. INBH, MW, and IMJ were involved in the study design. INBH, INMA, IMB, IBSub, IBSup, and DKW were involved in data collection. IMBH, INMA, and IBSub analyzed and interpreted the results. IMBA, MW, and IMJ drafted the original manuscript. INBH, MW, IMJ, INMA, IMB, IBSub, IBSup, DKW, and IMBH participated in providing critical revisions to the manuscript and approved the final version.

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