Institucionalne smernice Univerzitetnega kliničnega centra Maribor za uporabo angiotenzina II kot vazopresorja tretjega reda pri bolnikih z distributivnim šokom

University Medical Centre Maribor Institutional Guidelines for the Use of Angiotensin II as a Third-Line Vasopressor in Patients with Distributive Shock

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Izvleček

Namen: *Distributivni šok, še posebej septični šok, predstavlja življenje ogrožujoče stanje, za katerega sta značilna huda vazodilatacija in hipotenzija kljub ustreznemu tekočinskemu nadomeščanju in terapiji s konvencionalnimi vazopresorji. Umrljivost zaradi septičnega šoka je visoka. Angiotenzin II je sintetični analog endogenega vazokonstriktorja, ki ga je Ameriška uprava za hrano in zdravila (angl. Food and Drug Administration, FDA) 2017 odobrila za zdravljenje ali septičnega ali drugega distributivnega šoka. Visoka cena angiotenzina II trenutno omejuje njegovo širšo uporabo. Ta dokument vsebuje na dokazih podprta priporočila za ustrezno rabo angiotenzina II pri bolnikih*

Abstract

Purpose: *Distributive shock, particularly septic shock, is a critical medical condition characterized by severe vasodilation and hypotension that persist despite adequate fluid resuscitation and conventional vasopressor therapy. Septic shock is associated with a notably high mortality rate. In 2017, the Food and Drug Administration approved angiotensin II, a synthetic analogue of the endogenous vasoconstrictor, for treating adults with septic shock or other types of distributive shock. The relatively high cost of angiotensin II currently restricts its extensive clinical application. The institutional guidelines presented in this paper provide evidence-based recommendations for the appropriate use of angiotensin II in patients with vasodi-*

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z vazodilatatornim šokom. Opredeljuje kriterije izbire bolnikov, režim odmerjanja, zahteve za spremljanje, varnostne vidike in strategije za ukinjanje zdravila, usmerjene v optimizacijo kliničnega izida.

Metode: *Opravljen je bil pregled trenutno razpoložljive literature ter analiza lastnih kliničnih izkušenj z uporabo angiotenzina II.*

Rezultati: *Raziskava ATHOS-3 je pokazala, da je uporaba angiotenzina II v povprečju pomembno povečala odziv srednjega arterijskega pritiska po treh urah v primerjavi s placebom (69,9 % proti 23,4 %, p = 0.001) in zmanjšala potrebo po kateholaminih ob sprejemljivem varnostnem profilu.*

Kasnejše raziskave iz prakse so potrdile, da pribl. dve tretjini bolnikov hemodinamsko odgovorita na uporabo angiotenzina II, pri čemer odzivni bolniki kažejo zmanjšano 30-dnevno umrljivost.

Zaključek: *Angiotenzin II je namenjen za bolnike z distributivnim šokom, pri katerih vztraja hipotenzija kljub visokim odmerkom konvencionalnih vazopresorjev (noradrenalin ≥ 0,3 mcg/kg/min in vazopresin 0,03 IE/h). Potemtakem ta predstavlja tretji fiziološki mehanizem, ki dopolnjuje terapijo s kateholamini in vazopresinom.*

latory shock. They outline patient selection criteria, dosing regimens, monitoring protocols, safety considerations, and discontinuation strategies for enhancing clinical outcomes.

Methods: *A comprehensive narrative review of the current literature was conducted, and personal clinical experiences with angiotensin II were examined.*

Results: *The ATHOS-3 trial revealed that angiotensin II significantly increased mean arterial pressure response at 3 h compared to placebo (69.9% vs. 23.4%, p = 0.001) and reduced catecholamine requirements while maintaining an acceptable safety profile. Subsequent real-world studies confirmed that approximately two-thirds of patients demonstrate hemodynamic responsiveness to angiotensin II, with responders exhibiting a decrease in 30-day mortality rates.*

Conclusion: *Angiotensin II should be used exclusively for patients with distributive shock who remain hypotensive despite receiving high-dose conventional vasopressors (norepinephrine ≥0.3 μg/kg/min and vasopressin 0.03 IE/h), representing a third physiologic pathway to complement catecholamine and vasopressin therapies.*

INTRODUCTION

Background and Rationale

Distributive shock is the predominant type of shock observed in critical care settings, characterized by peripheral vasodilation, reduced systemic vascular resistance, and hypotension occurrence despite preserved or elevated cardiac output (1,2). The majority of cases of distributive shock are attributed to septic shock, while other etiologies include neurogenic shock, anaphylactic shock, and shock associated with cardiopulmonary bypass (3,4).

Patients with severe vasodilation and persistent hypotension despite receiving high doses of conventional vasopressors show a poor prognosis, with the 30-day all-cause mortality rate exceeding 50% and approaching 100% in patients who require norepinephrine-equivalent doses greater than 1 μg/kg/min (1). Historically, the therapeutic landscape for this condition has been limited to two classes of vasopressors: catecholamines (including norepinephrine, epinephrine, phenylephrine, and dopamine) and vasopressin analogues. Both these classes show narrow therapeutic windows with clinically relevant adverse effects at high doses, including tachyarrhythmias, myocardial ischemia, splanchnic hypoperfusion, and digital ischemia (1,2). The body's physiologic response to hypotension involves the activation of three major systems: the catecholamine system, the vasopressin system, and the renin-angiotensin-aldosterone system (RAAS) (1,5–7). Until recently, therapeutic interventions have primarily targeted the first two systems (8,9).

Recent research has identified angiotensin II, a potent endogenous vasoconstrictor and the primary effector of the RAAS, as a novel therapeutic agent that more closely mimics the body's intrinsic physiologic response to shock (1,10–14).

Mechanism of Action

Angiotensin II exerts its vasopressor effects primarily by binding to angiotensin II type 1 (AT1) receptors located on vascular smooth muscle cells, leading to vasoconstriction and an increase in systemic vascular resistance (5). Angiotensin II also stimulates aldosterone release from the adrenal cortex, which subsequently promotes sodium and water retention and enhances sympathetic nervous system activity. In distributive shock, the RAAS is dysregulated through multiple mechanisms, including downregulation of AT1 receptors by proinflammatory cytokines, excessive nitric oxide production, and increased activity of angiotensin-converting enzyme 2, which degrades angiotensin II (5).

The rationale for therapeutic administration of angiotensin II is based on restoring this deficient physiologic pathway and achieving synergistic effects with catecholamines and vasopressin, potentially allowing the use of lower doses of each agent and consequently reducing the likelihood for associated adverse effects (1,10,13).

Evidence Base

The Food and Drug Administration approved angiotensin II primarily based on the results of the ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock) trial, a multinational, double-blind, randomized, placebo-controlled phase 3 study (1). This trial enrolled 321 patients with vasodilatory shock who received high-dose vasopressors (norepinephrine equivalent >0.2 μg/kg/min). The primary endpoint—mean arterial pressure (MAP) response at 3 h was operationalized as either an increase of ≥10 mmHg or the attainment of MAP ≥75 mmHg without increasing background vasopressors—was successfully reached by 69.9% of angiotensin II-treated patients compared to 23.4% of placebo recipients (odds ratio (OR): 7.95, 95% confidence interval (CI): 4.76–13.3, p = 0.001) (1).

Secondary outcomes indicated a notable enhancement in cardiovascular Sequential Organ Failure Assessment scores at 48 h in the angiotensin II group (-1.75 vs. -1.28, p = 0.01) and a substantial reduction in catecholamine requirements (1). Although the 28-day mortality rate showed a favorable trend (46% vs. 54%, hazard ratio (HR): 0.78, 95% CI: 0.57–1.07), this observation was not statistically significant, probably because the study was underpowered for mortality outcomes (1).

Post-hoc analyses revealed that patients with elevated baseline renin concentrations (exceeding the study median) exhibited a significant reduction in the mortality rate following angiotensin II therapy (50.9% vs. 69.9%, HR: 0.56, 95% CI: 0.35–0.88, p = 0.012) (6). Real-world postmarketing data from 270 patients across five United States tertiary centers confirmed that 67% of patients demonstrated hemodynamic responsiveness, with responders showing a reduction in the 30-day mortality rate (HR: 0.50, 95% CI: 0.35–0.71, p = 0.001) (2). A similar outcome was noted in our retrospective cohort of patients (15).

PATIENT SELECTION CRITERIA

Indications

Angiotensin II is indicated for the management of hypotension in adult patients with distributive shock (14,16,17). Specific clinical scenarios appropriate for the initiation of angiotensin II therapy include the following:

Primary Indication:

- Distributive shock (septic, neurogenic, refractory anaphylactic, post-cardiopulmonary bypass or vasoplegia subsequent to major surgical interventions) accompanied by persistent hypotension
- No significant component of cardiogenic, hemorrhagic, and/or obstructive shock
- Adequate fluid resuscitation
- Receiving norepinephrine equivalent dose ≥0.3 μg/kg/min
- MAP at 65 mmHg or inability to achieve target MAP

Contraindications

Absolute contraindication is known hypersensitivity to angiotensin II or any component of the formulation.

Special Populations

Patients on chronic angiotensin converting enzyme inhibitors (ACEI):

- May show enhanced responsiveness to angiotensin II (18)
- Consider earlier initiation and potentially lower doses
- Monitor for exaggerated blood pressure response

Patients on chronic angiotensin receptor blockers (ARBs):

- May exhibit attenuated responsiveness to angiotensin II (18); however, a previous observational study by Pettit et al. revealed no difference regarding angiotensin II dose and treatment duration between patients receiving ARBs and those not treated with ARBs (19).
- May require higher doses to achieve hemodynamic targets
- Consider alternative vasopressor strategies if the patient shows inadequate response

Patients with acute kidney injury (AKI) receiving renal replacement therapy (RRT):

- Post-hoc analyses suggest potential mortality benefit in AKI patients receiving RRT (20)
- No dose adjustment required for renal dysfunction

DOSING AND ADMINISTRATION

Preparation

Formulation: Angiotensin II is supplied as a sterile solution requiring dilution prior to administration (16,17).

Dilution Instructions:

1. Dilute angiotensin II sterile solution in 250 mL of 0.9% normal saline only.
2. Visually inspect for any particulate matter and discoloration before administration.
3. Discard vial and any unused portion after initial use.

Storage (16,17):

- Undiluted vials: Refrigerate at 2–8°C
- Diluted solution: May be stored at room temperature (20–25°C) or refrigerated (2–8°C)
- Prepared solution: discard after 24 h

Initial Dosing (16,17):

Starting dose: 20 ng/kg/min through continuous intravenous (IV) infusion

Route of Administration:

- Administration through a central venous catheter is recommended and strongly preferred (17).
- Peripheral administration (IV access through the cubital fossa) may be considered if central access is unavailable (21).

Titration Protocol:

1. Assess blood pressure response approximately every 5 min.
2. Titrate by increments of 5–10 ng/kg/min to achieve target MAP every 5 min.
3. Do not exceed the maximum dose of 80 ng/kg/min.
4. Reduce background vasopressor doses during initial titration.
5. Prioritize weaning catecholamines to minimize adverse effects (immunosuppression, arrhythmia, cardiomyocyte injury, or myocardial stress) (17,22–24).
6. Titrate angiotensin II to the lowest effective dose while maintaining hemodynamic stability.
7. Reassess hemodynamic status and vasopressor requirements every 1–2 h.

Duration of Therapy

Standard Duration (1):

- Initial infusion period: Up to 48 h
- May be continued beyond 48 h if clinically indicated (maximum up to 7 days)

Discontinuation Protocol:

1. Begin weaning when underlying shock etiology is being resolved.
2. Reduce dose by decrements of around 5 ng/kg/min every 5–15 min according to blood pressure response (16).
3. If background vasopressor requirements increase to >0.1 µg/kg/min norepinephrine equivalent after discontinuation, consider resuming angiotensin II therapy (1).

MONITORING REQUIREMENTS

Hemodynamic Monitoring

Continuous Monitoring:
- Arterial blood pressure through an arterial line
- Heart rate and cardiac rhythm
- Oxygen saturation

Intermittent Assessment:
- MAP reading every 5 min during initial titration and every 15–30 min thereafter once the patient is stable
- Cardiac output/cardiac index (to be considered)
- Central venous pressure (to be considered)
- Mixed venous oxygen saturation (to be considered)

Laboratory Monitoring

Baseline (Prior to Treatment Initiation):
- Complete blood count
- Comprehensive biochemistry panel (electrolytes, renal function, liver function, and troponin level)
- C-reactive protein, procalcitonin, and interleukin-6 levels in patients with septic shock
- Lactate level
- Arterial blood gas analysis
- Coagulation studies
- Sample for renin concentration measurement to be collected immediately before angiotensin II infusion

Ongoing Monitoring:
- Standard Intensive Care Unit (ICU) laboratory examination
- Renin level measurement at 6 h after the initiation of angiotensin II infusion

Clinical Monitoring

Assessment for Adverse Effects:
- Cardiac: Tachyarrhythmias, atrial fibrillation, ventricular tachycardia, and myocardial ischemia
- Vascular: Digital ischemia, skin mottling, and peripheral cyanosis
- Thrombotic: Clinical signs of deep venous thrombosis or pulmonary embolism, signs of mesenteric ischemia, and signs of cardiac ischemia
- Respiratory: Bronchospasm and worsening oxygenation
- Neurologic: Altered mental status and focal deficits

Organ Perfusion Assessment:
- Urine output (target ≥ 0.5 mL/kg/h)
- Skin perfusion and capillary refill
- Mentation and neurologic status
- Gastrointestinal function (assessment for mesenteric ischemia)

SAFETY CONSIDERATIONS

Adverse Event Profile

The ATHOS-3 trial demonstrated that the safety profile of angiotensin II was comparable with that of placebo, with serious adverse events reported in 60.7% of angiotensin II-treated patients versus 67.1% of placebo-treated patients (1). Distinguishing between adverse effects attributable to the underlying critical illness and those related to angiotensin II therapy poses a considerable challenge.

Common Adverse Events (≥5%):
- Tachyarrhythmias (similar rates to placebo treatment)
- Atrial fibrillation (similar rates to placebo treatment)
- Hyperkalemia (monitor potassium levels closely)
- Thrombocytopenia

Serious Adverse Events of Special Interest:
- Venous and arterial thromboembolic event rates of 12.9% with angiotensin II therapy vs. 5.1% with placebo treatment were reported in the ATHOS-3 trial (1); however, these events occurred very rarely in the angiotensin II therapy group in subsequent observational studies (approximately 1.5%) (2,25).
- Arrhythmias: 10% occurrence rate in postmarketing study (2)

Rare but Serious Events (7):
- Exacerbation of heart failure in patients with left ventricular dysfunction
- Bronchoconstriction in patients with reactive airway disease
- Cerebral hemorrhage (one case reported in a systematic review article)

Drug Interactions

Other Vasopressors:

- Potential synergistic effects with catecholamines and vasopressin (1)
- Allows reduction of catecholamine dose, potentially decreasing toxicity
- No specific drug–drug interactions identified

INTEGRATION INTO VASOPRESSOR ALGORITHM

Recommended Vasopressor Sequence

First-Line Therapy:

Norepinephrine: Initial vasopressor of choice for treating distributive shock. Titrate to MAP ≥65 mmHg.

Second-Line Therapy (if norepinephrine ≥0.2 µg/kg/min): Add vasopressin at the fixed dose of 0.03 units/min.

Third-Line Therapy: Administer angiotensin II if MAP is 65 mmHg despite treatment with norepinephrine equivalent ≥0.3 µg/kg/min.

Combination Therapy Considerations

Angiotensin II is primarily recommended for use in combination with other vasopressors, not as monotherapy. The ATHOS-3 trial enrolled patients receiving a median of 2–3 vasopressors at baseline (1). Optimal combination strategies include the following:

- Angiotensin II + Norepinephrine + Vasopressin: Most frequently used combination, leveraging all three physiologic pathways
- Catecholamine-sparing approach: Use angiotensin II to reduce the doses of norepinephrine/epinephrine, which could minimize tachyarrhythmias, meet myocardial oxygen demand, and attenuate catecholamine-induced immunosuppression.

SPECIAL CLINICAL SCENARIOS

Septic Shock

Septic shock was reported in 91% of patients in the ATHOS-3 trial (1). Angiotensin II is a particularly appropriate treatment agent for septic shock patients with:

- Catecholamine-resistant hypotension;
- Elevated lactate levels with concern for catecholamine-induced tissue hypoperfusion; and
- Tachyarrhythmias limiting catecholamine escalation.

Post-Cardiopulmonary Bypass Vasoplegia

Vasoplegic syndrome following cardiac surgery affects 5–25% of patients and is associated with significant morbidity. Angiotensin II may be considered in post-cardiopulmonary bypass vasoplegia refractory to conventional vasopressors, particularly for patients receiving ACEI, if hyperreninemia is present, or in patients at risk for AKI and de novo atrial fibrillation (17–19), although data are limited to case series and observational studies (13).

Neurogenic Shock

Patients with neurogenic shock due to spinal cord injury, severe traumatic brain injury, or subarachnoidal hemorrhage may respond to angiotensin II therapy, although there is limited evidence. Treatment with angiotensin II could be considered in patients with refractory hypotension despite receiving adequate fluid resuscitation and conventional vasopressors.

AKI

Post-hoc analyses suggest potential benefit in patients with AKI, particularly those receiving RRT (20). Angiotensin II does not require dose adjustment for renal dysfunction and may help maintain renal perfusion pressure (17,26).

QUALITY ASSURANCE AND DOCUMENTATION

Required Documentation

Institutional angiotensin II use form should be completed for each patient receiving angiotensin II therapy.

COST CONSIDERATIONS

Angiotensin II is substantially more expensive than conventional vasopressors. Cost-effectiveness analyses of angiotensin II are limited, and its clinical

benefit compared to traditional agents has not been definitively established (3). Present institutional guidelines aim to balance currently available evidence of clinical benefit versus cost considerations:

- Potential benefits: reduced catecholamine toxicity, improved hemodynamics, and possible mortality benefits in select patients
- Costs: Drug acquisition costs substantially higher than those of norepinephrine, vasopressin, or epinephrine
- Resource utilization: Potential to reduce ICU length of stay if the patient shows more rapid resolution of shock

CONCLUSION

Angiotensin II is a novel therapeutic agent for patients with distributive shock. By targeting the RAAS, angiotensin II provides a third physiologic pathway to restore blood pressure and reduce catecholamine requirements. Evidence from the ATHOS-3 trial and real-world studies demonstrates that angiotensin II offers considerable hemodynamic benefits with an acceptable safety profile. These institutional guidelines provide a framework for appropriate patient selection, dosing, monitoring, and safety management, while considering the current cost of angiotensin II. Future research should focus on identifying biomarkers to predict response, optimal treatment initiation timing, and long-term outcomes to further refine the role of angiotensin II in the management of patients with distributive shock.

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