Feasibility and Safety of Angiotensin II Administration in General Ward Patients during COVID-19 Pandemic. A Case Series

Online Appendix

This appendix was part of the submitted manuscript and has been peer reviewed. It is posted as supplied by the authors.

Supplementary Methods

Patient monitoring

All patients were monitored with continuous 3-lead electrocardiography (ECG), continuous pulse oximetry, and intermittent non-invasive blood pressure (every 30 minutes for the first 2 hours and then every 2 hours). Monitors were placed in the individual rooms with telemetry monitoring linked to the ward central nurse desk.

Before starting the study, medical and nursing staff were instructed on AngII preparation, management and potential side effects. Flyers with study drug preparation, dosing scheme, common side effects, and safety instructions were hanged both in the drug preparation area and in patients' room. All patients were reviewed at least twice daily by an anesthesiologist/intensivist of the Medical Emergency Team, who discussed with the home team the need to continue or discontinue AngII. Of note, our hospital already had extensive experience in norepinephrine administration on normal ward for patients requiring vasopressor support but who are not candidate for ICU.

Angiotensin II preparation, administration and dosing

Angiotensin II (Giapreza, La Jolla Pharmaceutical Company, San Diego, California, USA) was diluted as 2.5 mg in 100 mL of normal saline, to obtain a final concentration of 25 μg/mL.

AngII was administered, to the first five patients, in a central vein through a dedicated CVC lumen with no other drugs or infusion running on the same lumen, to reduce the risk of inadvertent bolus administration. The last two patients received Ang II through a dedicated peripheral venous catheter.

The starting dose was 5 ng/kg/min (0.8 mL/h in a 70-kg patient). Dose could be reduced to 1.25 ng/kg/min or increased up to 9 ng/kg/min according to blood pressure. If a patient required a dose ≥ 10 ng/kg/min to maintain adequate blood pressure, admission to ICU for vasopressor support was considered.

AngII administration was started with an anesthesiologist/intensivist present who monitored the patient for the first 30 minutes.

Data collection and follow-up

Data were collected from medical records by trained investigators not involved in patients management.

We collected data on baseline and demographic clinical characteristics including comorbidities, laboratory values, and symptoms at presentation. Furthermore we collected the following hemodynamic and ventilatory variables: blood pressure, heart rate, urine output, need for and dose of concomitant vasopressors, dose of AngII, PaO_2/FiO_2 ratio, lactate, use of non-invasive ventilation (NIV), positive-end expiratory pressure (PEEP) for patients on NIV.

Hemodynamic and ventilatory variables were collected before AngII administration and at 1, 2, 4, 6, 12, 24 and 48 hours after AngII start.

Study outcomes

For this study, patients were followed up until day 28 after start of angiotensin II administration.

The primary outcome was the clinical improvement at day 28, defined as an improvement of two points or more on a six-category ordinal scale compared to baseline. The outcome of clinical improvement was recommended by the WHO R&D Blueprint expert group.[1,2] The six-category ordinal scale consisted of the following categories: 1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 5, hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 6, death.

Secondary outcomes included mortality at day 28, need for ICU admission at day 28, and need for

invasive mechanical ventilation at day 28.

Safety outcomes were drug extravasation, limb or bowel ischemia, arrhythmias, or uncontrolled hypertension during angiotensin II administration.

Statistical analysis

All data were stored in an electronic database. Categorical data were univariately analyzed with a χ^2 tests when the minimum number of observations in a category was greater than 5; otherwise, the Fisher's exact test was used. Student's *t* test was used to analyze continuous variables that had normal distribution, while the Mann-Whitney U test was used for variables that had non-normal distribution. Dichotomous and categorical variables were expressed as numbers and percentages, while continuous variables were expressed as means ± standard deviations (SD) in case of normal distribution, or median and interquartile range (IQR) in case of non-normal distribution. A p-value lower than 0.05 was considered statistically significant.

Given the small sample size and the study design, we performed only a descriptive analysis.

Supplementary Table 1. Baseline characteristics

Variable	N = 7
Age, years – median (IQR)	60 (57 – 65)
Sex, female – no. (%)	2 (28.6)
History of hypertension, number – no. (%)	0 (0.0)
Time between symptom onset and start of angiotensin II, days – median (IQR)	11 (10 – 13.5)
Six-category ordinal scale value	3 (3 – 3)

IQR: interquartile range

Supplementary Table 2. Hemodynamic and respiratory parameters over time

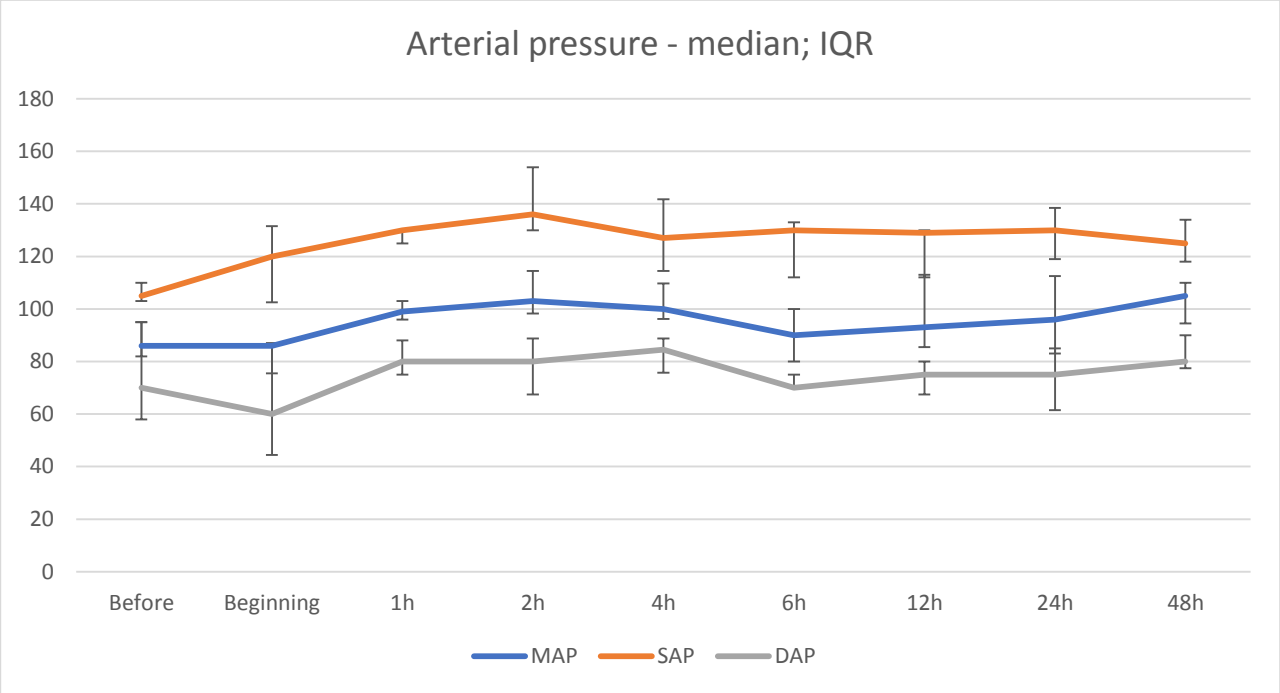
Parameter	Value	Missing data
Angiotensin II dose, ng/kg/min – median (IQR)		
➢ Before	N/A	
➢ Beginning	N/A	
➢ 1 h	5 (5 – 5)	0
➢ 2h	5 (5 – 5)	0
➢ 4h	5 (5 – 5)	0
➢ 6 h	5 (5 – 5)	0
➢ 12 h	5 (5 – 5)	0
➢ 24 h	5 (5 – 5)	0
➢ 48 h	5 (5 – 7.5)	0
Systolic arterial pressure, mmHg – median (IQR)		
➢ Before	105 (103 – 100)	2
➢ Beginning	120 (103 – 132)	0
➢ 1 h	130 (125 – 130)	2
➢ 2h	136 (130 – 154)	1
➢ 4h	127 (115 – 142)	1
➢ 6 h	130 (112 – 133)	2
➢ 12 h	129 (112 – 130)	0
➢ 24 h	130 (119 – 139)	0
➢ 48 h	125 (118 – 134)	0
Diastolic arterial pressure, mmHg – median (IQR)		
➢ Before	70 (70 – 78)	2
➢ Beginning	60 (58 – 70)	0
➢ 1 h	80 (75 – 88)	2
➢ 2h	80 (68 – 89)	1
➢ 4h	85 (76 – 89)	1
➢ 6 h	70 (70 – 75)	2
➢ 12 h	75 (68 – 80)	0
➢ 24 h	75 (62 – 85)	0
➢ 48 h	80 (78 – 90)	0

Mean arterial pressure, mmHg – median (IQR)		
➢ Before	82 (80 – 86)	2
➢ Beginning	86 (75 – 87)	0
➢ 1 h	97 (92 – 100)	2
➢ 2h	100 (94 – 104)	1
➢ 4h	97 (94 – 103)	1
➢ 6 h	90 (80 – 94)	2
➢ 12 h	91 (85 – 95)	0
➢ 24 h	97 (83 – 99)	0
➢ 48 h	93 (91 – 103)	0
Heart rate, bpm – median (IQR)		
➢ Before	89 (80 – 90)	2
➢ Beginning	87 (80 – 91)	0
➢ 1 h	88 (87 – 94)	2
➢ 2h	95 (89 – 99)	2
➢ 4h	92 (85 – 95)	3
➢ 6 h	75 (74 – 88)	2
➢ 12 h	75 (68 – 76)	0
➢ 24 h	83 (81 – 88)	0
➢ 48 h	81 (76 – 85)	1
PaO_2/FiO_2 – median (IQR)		
➢ Before	113 (104 – 113)	2
➢ Beginning	139 (124 – 160)	0
➢ 1 h	103 (92 – 165)	3
➢ 2h	106 (98 – 124)	1
➢ 4h	133 (117 – 164)	3
➢ 6 h	105 (99 – 156)	1
➢ 12 h	137 (137 – 151)	2
➢ 24 h	160 (121 – 200)	0
➢ 48 h	143 (130 – 151)	0
FiO_2, fraction – median (IQR)		
➢ Before	0.7 (0.7 – 0.7)	1
➢ Beginning	0.7 (0.675 – 0.7)	0

➢ 1 h	0.7 (0.7 – 0.7)	1
➢ 2h	0.7 (0.6 – 0.7)	0
➢ 4h	0.7 (0.7 – 0.7)	1
➢ 6 h	0.7 (0.65 – 0.7)	0
➢ 12 h	0.7 (0.7 – 0.7)	1
➢ 24 h	0.7 (0.6 – 0.7)	0
➢ 48 h	0.6 (0.55 – 0.7)	0

FiO_2: fraction of inspired oxygen; IQR: interquartile range; PaO_2: partial pressure of oxygen in arterial blood; PEEP: positive end-expiratory pressure

Supplementary Figure 1. Arterial pressure over time. Median values expressed as mmHg



IQR: interquartile range; DAP: diastolic arterial pressure; MAP: mean arterial pressure; SAP: systolic arterial pressure

Supplementary References

1. Wang Y, Fan G, Salam A, et al. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. *J Infect Dis* 2020;221:1688-1698. doi: 10.1093/infdis/jiz656.

2. Coronavirus disease (COVID-2019) R&D. Geneva: World Health Organization (http://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/. opens in new tab).