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LETTER

Preliminary results of synergy between norepinephrine and terlipressin during septic shock

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Dear Editor,

We congratulate Dr. Liu and colleagues for their impressive randomized clinical trial (RCT). The authors compared terlipressin and norepinephrine as first-line vasopressor in septic shock [1]. They reported a similar result in both groups. In an insightful editorial, Drs. Mårtensson and Gordon questioned the benefit of simultaneously using the two drugs, instead of monotherapy [2].

In a previous observational study, we showed that a dose of norepinephrine above 1 µg/kg/min was associated with a mortality rate above 90% [3]. As a result of this finding, we introduced terlipressin in our local protocol as standard of care in septic shock patients receiving norepinephrine above 0.5 µg/kg/min. Of note, the patients with a central venous oxygen saturation ($ScvO_2$) below 70%, reflecting an inappropriate cardiac output, were excluded. Terlipressin was administered as an initial bolus (0.25 mg over 30 min) followed by a fixed continuous infusion (0.01 µg/kg/min), in addition to norepinephrine. The norepinephrine was titrated according to the hemodynamic goals defined by the Surviving Sepsis Campaign. For vasopressor withdrawal, terlipressin infusion was kept constant until norepinephrine was weaned.

From January 2016 to June 2017, 26 patients receiving norepinephrine and terlipressin were retrospectively compared to an historical cohort (2013–2015) including 86 patients treated with norepinephrine at a dose above 0.5 µg/kg/min. The patients requiring a second-line catecholamine and those with a $ScvO_2$ below 70% were excluded (Supplemental Figure). Our primary objective was to assess the rate of patients with a 3-point or more decrease of Sequential Organ Failure Assessment (SOFA) score between the onset of norepinephrine infusion at 0.5 µg/kg/min and day 3. If norepinephrine was still infused at day 3, the cardiovascular SOFA score was 3 (<0.1 µg/kg/min) or 4 (≥ 0.1 µg/kg/min). If norepinephrine was stopped at day 3 but terlipressin was continued, the cardiovascular SOFA score was 3. Regarding terlipressin, the weaning protocol consisted in halving the rate of infusion every 3 h after the norepinephrine interruption. In the case of hypotension in the 24 h after the vasopressor (norepinephrine or terlipressin) weaning, norepinephrine was reintroduced. We evaluated the lactate clearance at 24 h, the incidence of complications (including myocardial, intestinal, limb and digital infarctions) during the intensive care unit (ICU) stay, and the number of survival days without ICU need. The study received the approval of our ethics committee (IRB 00010254–2018–147).

In the univariate analysis, the baseline severity of patients was increased in the terlipressin group (Supplemental Table). After adjustment on the baseline SOFA score and Simplified Acute Physiology Score 2, the plasma lactate concentration (measured at 0.5 µg/kg/min) and the fluid volume (measured from the onset of shock to the time at which a dose of 0.5 µg/kg/min of norepinephrine was infused), the multivariate analysis showed that the 3-point or more decrease in SOFA score was more prominent in the terlipressin group than in the control group ($p<0.001$). The maximal

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Endpoint (qualitative)	OR*	95% CI	*p*-value	Adjusted Odds ratio Plot (log scale)
Δ SOFA ≥ -3 (point)	6.1	2.1 ; 20.0	0.001	
Complications	0.6	0.2 ; 1.6	0.3	
				0.05 0.1 0.2 0.5 1 2 5 10 20
Endpoint (quantitative)	**Beta***	**95% CI**	***p*-value**	**Adjusted Beta Plot**
Δ SOFA (%)	-40.8	-61.1 ; -20.5	<0.001	
Δ SOFA (point)	-4.3	-5.9; -2.6	<0.001	
Δ Lactate (%)	-14.4	-40.2; 11.4	0.3	
Δ Lactate (mmol/L)	-0.7	-1.9 ; 0.5	0.2	
ICU Free days (days)	0.9	-3.7 ; 5.6	0.7	
				-60 -45 -30 -15 0 15

OR: Odds Ratio; *SOFA*: Sequential Organ Failure Assessment; *ICU*: Intensive Care Unit. * Adjusted Odds ratio and Beta.

Fig. 1 Forest plot reports the results for the synergy group as compared to the norepinephrine group

dosage of norepinephrine was similar in the two groups ($p = 0.06$), as was the duration of vasopressor infusion ($p = 0.1$) (Supplemental Table). The incidence of complications ($p = 0.3$), the 24-h lactate clearance ($p = 0.3$) and the number of ICU-free days ($p = 0.7$) were similar in both groups (Fig. 1).

From our experience, the use of low-dose terlipressin in combination with norepinephrine in septic shock patients with $ScvO_2$ above 70% was associated with a more rapid progression toward organ dysfunction resolution. This is in line with experimental data showing a synergy between norepinephrine and vasopressin [4]. We have to acknowledge several limitations, including the retrospective design of the study and the relatively small number of patients. This is a pilot study suggesting the feasibility of future prospective studies. In addition, the study design does not make it possible to identify the variables associated with the SOFA score reduction reported in the synergy group [5]. One can suggest an improvement in the renal function, in line with a previous study. The plasma creatinine concentrations decreased in the synergy group (from 143 ± 80 to 119 ± 62 µmol/L, $p = 0.05$), while they were stable in the norepinephrine group (from 133 ± 99 to 130 ± 126 µmol/L, $p = 0.6$). Another explanation could be a decreased use of high-dosage norepinephrine. To confirm these findings, we initiated an RCT (NCT03336814) to evaluate the effect of terlipressin infusion versus placebo in the early stage of septic shock in patients with $ScvO_2$ above 70%.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
ML discloses conflicts of interest with Aguettant, Amomed, MSD, Octapharma Pfizer (Lectures). GD, MC, SM, and NR do not disclose any conflict of interest. GD assumes responsibility for the data.

Ethical approval
The study received the approval of our ethics committee (IRB 00010254–2018–147).

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