Report on study number 2007-005010-40 (Sponsor's protocol code number 30082007)

Arginin Vasopressin im fortgeschrittenen vasodilatorischen Schock: Ein Dosisvergleich 2 vs. 4 IU/h

Purpose: To compare the effects of two arginine vasopressin (AVP) dose regimens on the hemodynamic response, catecholamine requirements, AVP plasma concentrations, organ function and adverse events in advanced vasodilatory shock.

Methods: In this prospective, controlled, open-label trial, patients with vasodilatory shock due to sepsis, systemic inflammatory response syndrome or after cardiac surgery requiring norepinephrine >0.6 µg/kg/min were randomized to receive a supplementary AVP infusion either at 0.033 IU/min (n = 25) or 0.067 IU/min (n = 25). The hemodynamic response, catecholamine doses, laboratory and organ function variables as well as adverse events (decrease in cardiac index or platelet count, increase in liver enzymes or bilirubin) were recorded before, 1, 12, 24 and 48 h after randomization.

Randomization and study groups: Based on a computer-generated list, patients were randomly allocated to one of the two study groups. The first group received AVP at 0.067 IU/min, while AVP was infused at 0.033 IU/min in the second group. Clinicians and researchers were not blinded to the study group allocation.

Inclusion and exclusion criteria: Critically ill patients were considered eligible to participate in the study if they presented with vasodilatory shock due to sepsis, systemic inflammatory response syndrome (SIRS) or cardiac surgery and required norepinephrine doses >0.6 µg/kg/min to maintain MAP >60 mmHg. Patients <18 years, in a moribund state unlikely to survive >12 h, in whom intensive care therapy was withdrawn or limited in an end-of-life decision, who received AVP or any of its analogues because of other diagnoses than vasodilatory shock, participated in another clinical trial, were pregnant or refused written informed consent were excluded. Patients had to be included within 12 h after their norepinephrine demand exceeded 0.6 µg/kg/min or within 12 h after intensive care unit

admission (in case norepinephrine doses exceeded 0.6 µg/kg/min before intensive care unit admission). Sixty-one patients met the inclusion criteria during the observation period, of which 50 patients were enrolled.

Study endpoints: The primary endpoint was to compare the hemodynamic response to AVP at two doses (0.033 vs. 0.067 IU/min). Secondary endpoints included differences in organ function and laboratory variables, AVP and prolactin plasma levels as well as the rate of adverse events.

Statistical analysis: Normality distribution was assessed by the Kolmogorov–Smirnov test. In case the normality assumption was not fulfilled (aspartate and alanine aminotransferase, total bilirubin, troponin T, AVP, prolactin), variables were ln-transformed. All group comparisons were performed as intention-to-treat analyses. The unpaired Student's t (continuous) or Fisher's exact test (categorical) was used to compare demographic and clinical parameters as well as the rate of adverse events between groups.

Results: Heart rate and norepinephrine requirements decreased while MAP increased in both groups. Patients receiving AVP at 0.067 IU/min required less norepinephrine (P = 0.006) than those infused with AVP at 0.033 IU/min. Arterial lactate and base deficit decreased while arterial pH increased in both groups. During the observation period, AVP plasma levels increased in both groups (both P<0.001), but were higher in the 0.067 IU/min group (P<0.001) and in patients on concomitant hydrocortisone. The rate of adverse events and intensive care unit mortality was comparable between groups (0.033 IU/min, 52%; 0.067 IU/min, 52%; P = 1).

Conclusions: A supplementary AVP infusion of 0.067 IU/min restores cardiovascular function in patients with advanced vasodilatory shock more effectively than AVP at 0.033 IU/min.