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Inflammatory mediators in sepsis and antiinflammatory effects of ketamine

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Sepsis is characterized by both the criteria of SIRS and the clinical or microbiological evidence of infection. Severe sepsis associated with either hypotension or organ hypoperfusion. Septic shock is a subtype of severe sepsis and is defined as sepsis-induced hypotension despite adequate fluid resuscitation. Along with the presence of perfusion abnormalities sepsis may include, but is not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Until now, no reliable diagnostic or prognostic marker exists for either sepsis or certain systemic injury in sepsis. However, numerous studies investigating potential markers of the outcome of sepsis have contributed greatly to our understanding of the pathogenesis of sepsis. In the present study potential mediators and modulators of inflammation are described, which may be important markers for the outcome of sepsis.

Patients with severe sepsis have a high mortality. In the present study, 14 of the 26 patients with severe sepsis and septic shock died during the 28 day observation interval with a mortality rate as high as 54%, similar to the death rate reported by other researchers (Brun-Buisson et al 1995, Eisele and Lamy 1998). Most of the non-survivors died in the first week after onset of severe sepsis. The pathogenesis leading to death was mainly MOF, especially circulatory and respiratory decompensation.

Since sepsis is based on host inflammatory disturbances indicated by either SIRS or CARS, plasma levels of some key cytokines (TNF-α, IL-6) and adhesion molecules (L-, P-, E-selectin; ICAM-1) were investigated with enzyme-linked immunosorbent assay and analysed for their correlation with the outcome of sepsis. In addition, clinical variables were analysed to characterize the extent of systemic deterioration.

The imbalance of the patients' inner milieu caused by tissue hypoperfusion and cytokine cascade in sepsis was indicated by electrolyte and acid-base imbalances, abnormal blood-gas results, acidosis, hyperglycemia, low excretion of creatinine and blood urea nitrogen. However, only initial blood pH values were significantly different between survivors and non-survivors.

Anaemia appeared and worsened in patients despite blood transfusion. Hematocrit was significantly lower in the non-survivors than in the survivors. DIC tendency was more pronounced upon patients' inclusion but tended to ameliorate. Liver function as indicated by GOT and total bilirubin was more apparently impaired in non-survivors and their individual total bilirubin levels distributed in a pattern clearly different to that of survivors. Total bilirubin levels were slightly correlated with sICAM-1 levels.

The individual values of PaO_2/FiO_2 and $AVDO_2$ were not significantly different between survivors and non-survivors. However, these oxygenation parameters were all worsened and were more severe in non-survivors suggesting impaired pulmonary oxygen exchange and decreased tissue oxygenation. The hemodynamic variables revealed typical changes in sepsis such as decreased vascular resistance and compensatory increase of cardiac work. The results also suggested that cardiac function was more severely impaired in non-survivors than survivors. Some variables such as MPAP, RVSW, RCW and LCW showed not only stable

tendency to compensate septic shock, but also significant differences between survivors and non-survivors. Other hemodynamic parameters varied greatly in values and therefore could not be considered as outcome indicators.

Our results suggest that neither sTNF-α nor its soluble 55 kDa receptor correlates closely with survival, although both parameters were increased. The survivors had relatively higher sTNF-α levels and relatively lower sTNFR-55 levels than non-survivors, a phenomenon which might be explained by the character of TNF release, i.e., a rapid decline to undetectable levels. However, the level of IL-6 increased sharply on the inclusion of patients into the study but decreased gradually and slowly afterwards. Non-survivors had higher IL-6 levels than survivors but the difference was not statistically significant.

Adhesion molecules mediate intercellular and intracellular activation of leukocytes and endothelial cells. In the present study, selectins, whether expressed on leukocytes (L-selectin) or on endothelial cells (E-selectin, P-selectin) failed to indicate mortality, although different tendencies of the values could be seen between survivors and non-survivors. However, sICAM-1 levels were found to be an outstanding indicator for mortality. In non-survivors sICAM-1 levels demonstrated a significant difference to that in survivors including a cut-off level of 800 ng/mL at admission. At the level of 600 ng/mL at admission the sensitivity and specificity of sICAM-1 to indicate non-survival were 58.3% and 82.8%, respectively. This may be due to its long half life after peak expression.

To test the predictability of the outcome of sepsis with some parameters at the patients' admission, variables with great differences in values between survivors and non-survivors were collected. These variables include blood pressure, hematocrit, serum total bilirubin, pH, $AVDO_2$, PaO_2/FiO_2, sICAM-1, SIRS parameters (heart rate and respiratory frequency, body temperature and WBC) and hemodynamic parameters (MPAP, RVSW, RCW, LCW). This mortality predicting score system (MPSS) was set up to include the systemic changes in sepsis for outcome prediction.

In conclusion, the mortality of patients with severe sepsis is predictable with some outstanding factors of survival such as sICAM-1 levels. A mortality prediction scoring system based on these factors could be helpful in differentiating the death risk of patients with severe sepsis predictively. However, it must be mentioned that this investigation was based on a limited number of subjects and variables. Studies with a greater number of patients are required to build up a more widely applicable and more advanced system.

Septic patients require individual analgesia and sedation to reduce and moderate the stress response to endogenous and exogenous stressors. The main goals are the absence of cardiocirculatory depression or, if at all, cardiocirculatory stabilization, absence of negative pulmonary, renal, hepatic and immunological side effects. Ketamine has therefore been preferred due to its sympathomimetic activities as well as its anti-inflammatory activities.

Cytokine production, neutrophil adhesion to endothelial cells, and release of reactive oxygen species are thought to be critical events in sepsis or ischemia/reperfusion. Modulation of leukocyte responses by anesthetics may have an important role in limiting tissue injury under these conditions. Therefore, the effect of ketamine on the expression of CD18, CD62L and oxygen radical production of human neutrophils in vitro, and on interleukin-6 production was investigated in endotoxin-stimulated human whole blood. Ketamine inhibited both the FMLP- and PMA-induced up-regulation of CD18 and shedding of CD62L determined by flow cytometry, in a concentration-dependent manner. Ketamine also caused a significant suppression of oxygen radical generation of isolated human neutrophils. In addition, there was a significant decrease in endotoxin-stimulated interleukin-6 production in human whole blood. The inhibitory effects were similar for racemic ketamine and its isomers S(+)-ketamine and R(-)-ketamine suggesting that inhibition of stimulated neutrophil function is most likely not mediated through specific receptor interaction.