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A New Approach: Chronotherapy in Acute Blood Purification for Septic Shock

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Abstract

Circadian rhythms are daily oscillations of multiple biological processes. Recently, relationships between circadian rhythms and immune functions have also been described. In a mouse sepsis model, the death rate due to lipopolysaccharide (LPS)-induced endotoxic shock was found to be dependent on LPS administration as determined by circadian time. In humans, a pronounced inflammatory response to endotoxemia differs depending on whether it is daytime or night-time: Levels of tumor necrosis factor-alpha and interleukin-6 were higher during the night. Therefore, it is reasonable to assume that circadian rhythms influence not only organ dysfunction and the prognosis induced by LPS, but also the therapeutic effect of anti-LPS therapy such as Polymyxin-B direct hemoperfusion. We herein postulate the concept that it is important to discuss septic shock treatment in terms of whether or not the treatment is adjusted for the optimal time window as determined by circadian rhythms.

Keywords

Chronotherapy, PMX-DHP, Septic Shock

1. Text

Toll-like receptor (TLR) families on monocytes/macrophages are involved in the initiation of a chain reaction in response to an infection. More specifically, TLR2 and TLR4 are related to the recognition of gram-positive and gram-negative bacteria, respectively [1]. In sepsis, mononuclear cells/macrophages are activated via TLR to release early mediators such as interleukin-6 (IL-6) and IL-8, which further stimulate mononuclear cells/macrophages. The cells also release a late lethal mediator, High Mobility Group Box 1 (HMGB1) [2]. Once endothelial cells are injured, they also release excessive HMGB1 into the bloodstream. Ac-

cordingly, in septic shock, it is obvious that the regulation of pro-inflammatory cytokines is of the utmost importance in addition to the treatment of causative disorders. We have previously reported that combination therapy with Polymyxin-B direct hemoperfusion (PMX-DHP) and recombinant thrombomodulin (rTM) is effective in septic shock that is accompanied by disseminated intravascular coagulation (DIC), and that this was expected to improve patient survival rates through HMGB1 regulation [3]. Moreover, early induction of PMX-DHP was found to be associated with amelioration of hemodynamic derangement and mortality in patients with septic shock [4].

Circadian rhythms are daily oscillations of multiple biological processes, typical examples being cellular or animal activities such as feeding behavior and the cell cycle, which are driven by an endogenous clock [5]. A protein heterodimer composed of CLOCK and BMAL1 is the core transcriptional regulator of the circadian clock and facilitates the transcription of *Period2* (*Per*2) and *Period1* (*Per*1) circadian genes [6] [7]. In the past, we have described the influence of circadian rhythms on cell junctions in the rat [8]. We also reported on the relationship between the parathyroid hormone (PTH) circadian rhythm and calcium-phosphorus metabolism in non-dialyzed, chronic kidney disease (CKD) patients [9].

Recently, relationships between circadian rhythms and immune functions, including those of macrophages [10], T cells [11], dendritic cells, and B cells [12], have been described. TLR9, one of the HMGB1 receptors, is controlled by BMAL1 and CLOCK binding to its promoter. Daily variations in TLR9 responsiveness were found to influence disease severity in a TLR9-dependent cecal ligation and puncture (CLP) mouse model of sepsis [13]. In another mouse sepsis model, the death rate due to lipopolysaccharide (LPS)-induced endotoxic shock was found to be dependent on the LPS administration time [14] [15]. *Per*2-deficient mice were also found to be more resistant to LPS-induced endotoxic shock than control wild-type mice [14]. On the other hand, LPS was reported to downregulate *Per*1 and *Per*2 gene expression [16]. In humans, a pronounced inflammatory response to endotoxemia differs depending on whether it is daytime or nighttime: levels of tumor necrosis factor (TNF)-alpha and IL-6 were found to be higher during the night [17]. Therefore, with regard to the pathophysiology in response to septic shock, it is reasonable to assume that the circadian rhythm influences not only organ dysfunction and the prognosis induced by LPS, but also the therapeutic effect of anti-LPS therapy in humans.

Studies of chronotherapy with regard to the circadian rhythm in the treatment of chemotherapy or hypertension have recently been increasing [18]. However, to the best of our knowledge, a study of the influence of chronotherapy in acute blood purification to treat septic shock is lacking. PMX-DHP has been widely used in Japan as treatment for septic shock. PMX-DHP therapy is designed to remove endotoxin through direct adsorption and is generally administered for 2 h. If, however, chronotherapy is relevant to acute blood purification for septic shock, we hypothesize that PMX-DHP would show an improved or even optimal

therapeutic performance in time periods when LPS is most strongly toxic and organ dysfunction becomes more severe. Namely, as shown in **Figure 1**, the therapeutic effect of PMX-DHP may differ between time periods ① and ②.

Currently ongoing is the EUPHRATES study, a randomized, double-blind controlled, clinical trial undertaken throughout the US and Canada that compares standard of care versus standard of care plus PMX-DHP using Spectral's EAA™ Endotoxin Activity Assay [19]. The results have not been completely published, but, in future, we may have to reconsider such results from the point of view of chronotherapy as described above. Recently, a duration longer than the conventional 2 h of PMX-DHP therapy was expected to improve the hemodynamics and pulmonary oxygenation capacity of patients with septic shock [20]. The longer duration of PMX-DHP may not only allow an improvement in the total removal of endotoxin, but may also be undertaken in time period ① (**Figure 2**).

Therefore, we herein put forward the concept that it is important to discuss septic shock treatment in terms of not only how prompt PMX-DHP is initiated after septic shock, but also whether or not the treatment is adjusted for the optimal time window as determined by circadian rhythms, with the purposes of improving patient prognoses and investigating a more valid treatment for septic shock patients.

2. Conclusion

We postulate a concept that it is important to discuss septic shock treatment in terms of not only how prompt PMX-DHP is initiated after septic shock, but also whether or not the treatment is adjusted for the optimal time window of circadian rhythm.

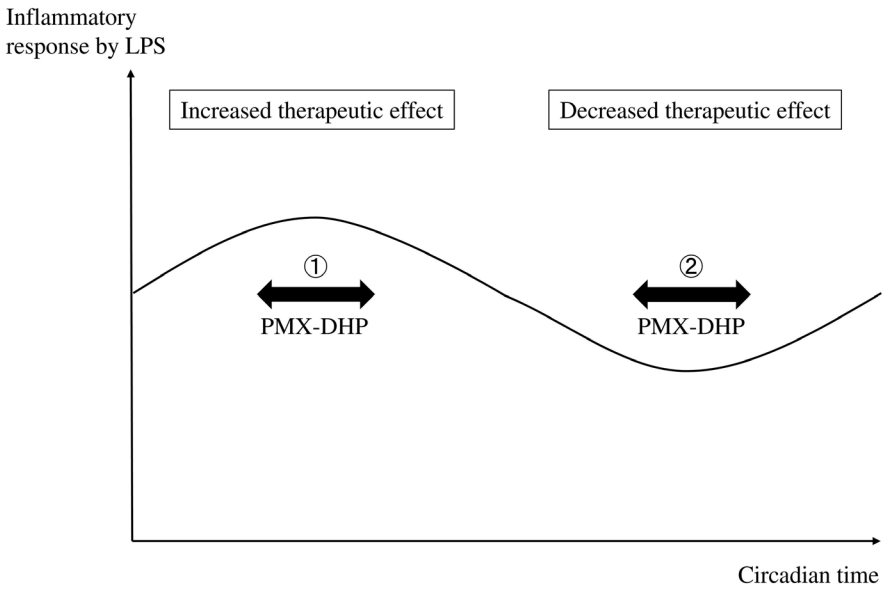

Figure 1. The therapeutic effect of PMX-DHP may differ between time periods ① and ②.

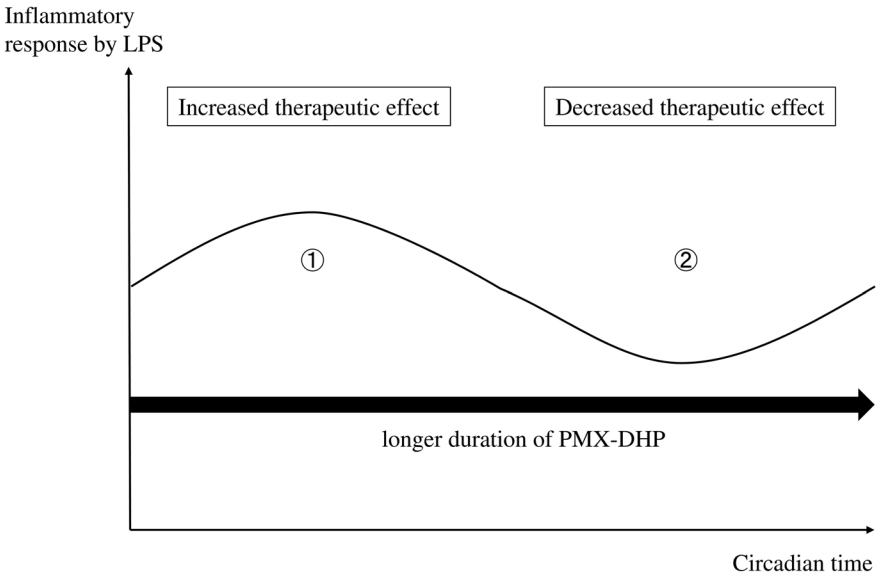

Figure 2. The longer duration of PMX-DHP may not only allow an improvement in the total removal of endotoxin, but may also be undertaken in time period ①.

Declaration of Interest

The authors have no conflicts of interest to disclose.

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