Impact of Morphine Administration Timing on Lipopolysaccharide-Mediated Lethal Shock in Mice

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Introduction: Sepsis is a severe condition characterized by systemic inflammation, organ dysfunction and failure, and cytokine storm. Morphine, which is routinely used to treat perioperative pain, is a potent immunomodulator.
We recently reported that morphine administration before shock improved the survival rate in a murine model of lipopolysaccharide (LPS)-mediated lethal shock (2012 ASA annual meeting). In this study, we examined whether the timing of morphine administration affects the survival rate and cytokine production in LPS-mediated lethal shock.

Materials and Methods

1. **Induction of LPS-mediated lethal shock**
   All animal procedures and protocols were approved by the Ethics Committee on Animal Experimentation of Tokyo Women's Medical University. Mice (female C57BL/6; age: 6-8 weeks; weight: 20-25 g) were injected intraperitoneally with LPS after a subcutaneous injection of α-galactosylceramide (α-GC).
2. **Effect of morphine on the survival rate of mice with LPS-mediated lethal shock**
   Mice were subcutaneously administered 0.8 mg/mouse morphine, or phosphate buffered saline (PBS) 30 min before or after an inducing LPS-mediated lethal shock. The survival rate was recorded every 1-12 h.
3. **Effect of morphine on cytokine production *in vivo* and histological changes**

in mice with LPS-mediated lethal shock

Cytokine levels were measured over time, and various organs were removed, and stained using hematoxylin-eosin (HE).

Results

1. **The survival rate of mice with LPS-mediated lethal shock**

   Morphine administration before shock improved the survival rate. However, morphine administration after shock significantly deteriorated the survival rate (Figure).

2. **Cytokine production *in vivo***

   Compared with PBS administration, morphine administration before shock inhibited the production of tumor necrosis factor (TNF)-α, interferon (IFN)-γ, monocyte chemotactic protein-1 (MCP-1), and interleukin (IL)-12. However, morphine administration after shock increased the production of TNF-α and did not inhibited the production of other cytokines.

3. **Histological changes**

   Morphine administration before shock inhibited the accumulation of a large number of infiltrates consisting of polymorphonuclear leukocytes and mononuclear cells in the lungs. However, morphine administration after shock did not inhibit the accumulation of infiltrates.

Discussion and Conclusions: The effect of morphine on the immune system changes with shock condition. Morphine administration before shock inhibited cytokine production and improved the survival rate of mice with LPS-mediated lethal shock, which is consistent with the clinical features of severe septic shock. On the other hand, morphine administration after shock enhanced cytokine production and deteriorated survival. Morphine is a double-edged sword; therefore, it is necessary to consider the timing of administration while using morphine.

Summary: In mice with LPS-mediated lethal shock, morphine completely changes the survival rate and cytokine production, and the effects differ depending on the timing of administration.

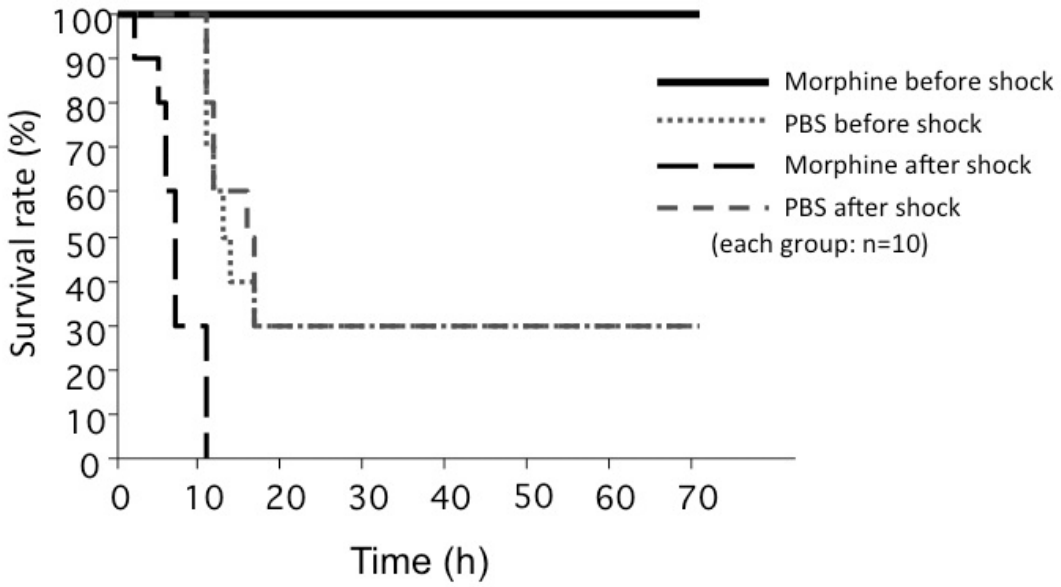

Fig. Survival rate of mice with LPS-mediated lethal shock