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Intravenous immunoglobulin use in septic shock patients after emergency laparotomy

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Summary *Objectives:* The role of intravenous immunoglobulin (IVIG) as an adjunctive treatment for abdominal sepsis remains controversial.
Methods: Mechanically ventilated septic shock patients following emergency laparotomy for perforation of the lower intestinal tract were identified in the Japanese Diagnosis Procedure Combination inpatient database from July 2010 to March 2013. The effect of IVIG use on 28-day mortality was evaluated using propensity score and instrumental variable analyses.
Results: Eligible patients (n = 4919) treated at 845 hospitals were divided into IVIG (n = 2085) and control (n = 2834) groups. Propensity score matching created a matched cohort of 1081pairs with and without IVIG treatment. Although significant mortality differences existed between the IVIG and control groups in the unmatched analysis (20.6% vs. 18.3%; difference, 2.3%; 95% confidence interval [CI], 0.07–4.5), there were no significant differences in the propensity score-matched analysis (20.4% vs. 19.3%; difference, 1.1%; 95% CI, −2.3–4.5). Analysis employing the pattern of hospital IVIG use as an instrumental variable showed that IVIG use was not associated with reduced mortality (difference −2.5; 95% CI, −6.5–1.6).
Conclusions: There may be no significant association between IVIG use and mortality in mechanically ventilated septic shock patients after emergency laparotomy.

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Introduction

Emergency laparotomy is a high-risk surgical procedure with a high mortality rate of 15%–20%.[1–7] Sepsis is one of the most frequent causes of death after such surgery, especially with emergency laparotomy for intestinal perforation.[6] The mainstream treatment for abdominal sepsis involves controlling the infection source, i.e., surgery or drainage, and using appropriate antibiotics along with initial resuscitation.[8,9] For several decades, efforts have been made to find effective additional therapies to reduce the high mortality rate.[3,9] Owing to the broad potential activity of intravenous immunoglobulin (IVIG) against both bacterial products and host cytokines, it has been suggested that IVIG may be advantageous as an additional therapy in severe sepsis. The effectiveness of IVIG in sepsis models has been evaluated, and it has demonstrated positive effects in several experimental studies using cecal ligation and puncture models[10–14]—one of the gold standard experimental models for abdominal sepsis.[15,16]

However, previous studies indicate that there is still insufficient evidence to support the use of IVIG in septic patients because a number of the preceding studies both supported the use of IVIG and were associated with no mortality benefit.[17–23] Werdan et al.[24] conducted the largest randomized trial of IVIG use for sepsis (n = 653) and found that IVIG use did not reduce 28-day mortality. In addition, some meta-analyses found no benefit on mortality for IVIG use for severe sepsis and septic shock patients.[19,25] Thus, the latest Surviving Sepsis Campaign guidelines[8] (international guidelines for severe sepsis and septic shock) do not suggest the use of IVIG in patients with severe sepsis and septic shock (grade 2B). Conversely, several meta-analyses of randomized trials have reported that IVIG use decreased mortality in sepsis patients compared with placebo or no IVIG.[17,19,26,27] Accordingly, the Japanese Guidelines for the Management of Sepsis suggest that IVIG use "may be considered" in patients with sepsis (grade 2C).[28] The Japanese Ministry of Health, Labour and Welfare has approved the clinical use of IVIG for sepsis at 5 g/day for 3 days, and IVIG is widely used clinically in Japan. The role of IVIG as an adjunctive treatment for severe sepsis or septic shock, including septic shock patients after emergency laparotomy, is therefore still controversial.

We hypothesized that IVIG is effective in the treatment of septic shock patients after emergency laparotomy for intestinal perforation because the causative insults and pathophysiology may resemble those in cecal legation and puncture models.[15,16] The purpose of this study was to evaluate our hypothesis using a large nationwide database.

Materials and methods

Ethics statement

This study was approved by the institutional review board of The University of Tokyo, which waived the requirement for informed patient consent because of the anonymous nature of the data.

IVIG use in Japan

The Japanese Ministry of Health, Labour and Welfare has approved the clinical use of polyclonal IVIG no more than 5 g/day for 3 days, while IgM-enriched IG [10–12] is not available in Japan.

Data source

The Japanese Diagnosis Procedure Combination database includes administrative claims and discharge abstract data for all inpatients discharged from over 1000 participating hospitals in Japan, including 92% (244/266) of all tertiary-care emergency hospitals.[29–35] The baseline patient information in the database includes the following: age; sex; and primary diagnosis, comorbidities on admission, and post-admission complications coded using the International Classification of Diseases, 10th Revision codes and written in Japanese. Complications that occurred after admission are clearly differentiated from comorbidities already present on admission. All interventional and surgical procedures are coded using original Japanese codes. The database also includes the following details: dates of hospital admission and discharge; surgery; bedside procedures; drugs and blood products administered; and discharge status (dead or alive), recorded using a uniform data submission format. To optimize the accuracy of recorded diagnoses, the responsible physicians are obliged to record them with reference to medical charts. In addition, the diagnostic records are linked to a payment system, and attending physicians are required to report objective evidence for disease diagnosis for reimbursement of treatment. The DPC is an administrative database with information input when patients are discharged. Thus, patient follow-up began on the day of admission and ended on the hospital discharge date (either to home, transfer to other hospital, or death). We could not follow up the patients after discharge from hospital as the information was not available in this discharge database.[29–32,34,35]

Patient selection

We identified mechanically ventilated septic shock patients who underwent emergency open laparotomy for perforation of the lower intestinal tract from July 1, 2010 to March 31, 2013. The inclusion criteria for the current analysis were as follows[1]: aged 15–89 years[2]; confirmed diagnosis of perforation of the lower gastrointestinal tract on admission (coded in the primary diagnosis or comorbidities on admission)[3]; undergoing open abdominal laparotomy, except exploratory laparotomy on days 0 or 1[4]; septic shock, defined as the use of vasopressors (noradrenaline and/or dopamine) and antibiotics started on days 0 or 1; and[5] requiring mechanical ventilation after surgery on days 0 or 1. We excluded from this analysis patients who began receiving IVIG after day 1 and cases of IVIG being used at more than the approved dose for sepsis in Japan.

Variables and end points

In addition to the baseline characteristics on admission, several other variables were evaluated in the present