筑 波 大 学

博 士 (医 学)学 位 論 文

Clinical research on the efficacy of medical devices in the area of emergency and critical care medicine

（救急医学および集中治療医学領域における医療機器の有効性に関する臨床研究）

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Abbreviations and acronyms

MD	medical device
REBOA	resuscitative endovascular balloon occlusion of the aorta
DCR	damage control resuscitation
PRF	pelvic ring fractures
ED	emergency department
ISS	injury severity score
RTS	revised trauma score
RBC	red blood cells
AKI	acute kidney injury
MOF	multiple organ failure
RIFLE	risk, injury, failure, loss of kidney function, and end-stage kidney disease
SOFA	sequential organ failure assessment score
OR	operating room
IR	interventional radiology
AIS	abbreviated injury scale
TAE	trans-arterial embolization
PRBC	packed red blood cell
SS	septic shock
ICU	intensive care unit
GNB	gram-negative bacilli
PMX	polymyxin B-immobilized fiber column
PMXHP	PMX hemoperfusion
P/F ratio	PaO2 / FiO2 ratio
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
DIC	disseminated intravascular coagulopathy
ACS	acute coronary syndrome

Summary

Medical device (MD) is a large number of types, more than 300, 000 products in Japan, so the evaluation of safety, efficacy, and effectiveness has a high diversity. There is a major difference of recognition in value of a MD among a manufacturing company and clinicians including doctors, nurse, and technician. Clinicians believe that the efficacy of MD is determined by the overall clinical outcome rather than the performance of the product itself. However, it is not required to overall clinical outcome for many of controlled MDs in the new registration. In this thesis, I examined the efficacy of two MDs in the area of emergency and critical care medicine by post-marketing study.

Summary of post-marketing study 1

Background: Resuscitative endovascular balloon occlusion of the aorta (REBOA) is one of the ultimately invasive procedures for managing a non-compressive torso injury. Since it is less invasive than resuscitative open aortic cross clamping, its clinical application is expected. Methods: We retrospectively evaluated the safety and clinical feasibility of REBOA (intra-aortic occlusion balloon; MERA, Tokyo, Japan) using the Seldinger technique to control severe hemorrhage. Of 5,230 patients admitted to our trauma center

in Japan from 2007–2013, we included 24 who underwent REBOA primarily. The indications for REBOA were a pelvic ring fracture (PRF) or hemoperitoneum with hemodynamically instability and impending cardiac arrest. Emergency hemostasis was performed during REBOA in all patients. Results: All 24 patients had a blunt injury, the median age was 59 (interquartile range, 41–71 years), median injury severity score was 47 (37–52), 30-day survival rate was 29.2% (n = 7), and median probability survival rate was 12.5%. Indications for REBOA were hemoperitoneum and PRF in 15 cases and overlap in 8. In 10 cases of death, the balloon could not be deflated in 5. In 19 cases in which the balloon was deflated, the median duration of aortic occlusion was shorter in survivors than in deaths (21 min vs. 35 min, P = 0.05). The mean systolic blood pressure was significantly increased by REBOA (from 53.1 ± 21 mmHg to 98.0 ± 26.6 mmHg, P < 0.01). There were 3 cases with complications (12.5%)—1 external iliac artery injury and 2 lower limb ischemias in which lower limb amputation was necessary in all cases. Acute kidney injury developed in all 3 cases, but failure was not persistent. Conclusions: REBOA appears to be feasible for trauma resuscitation and may improve survivorship. However, the serious complication of lower limb ischemia warrants more research on its

safety.

Summary of post-marketing study 2

The mortality rate associated with septic shock in an intensive care unit (ICU) remains high, with reported rates ranging from 30% to 50%. In particular, Gram-negative bacilli (GNB), which induce significant inflammation and consequent multiple organ failure, are the etiological bacterial agent in 40% of severe sepsis cases. Hemoperfusion using polymyxin B-immobilized fiber (PMX), which adsorbs endotoxin, is expected to reduce the inflammatory sepsis cascade due to GNB. However, the clinical efficacy of this treatment has not yet been demonstrated. Here, we aimed to verify the efficacy of endotoxin adsorption therapy using PMX through a retrospective analysis of 413 patients who received broad spectrum antimicrobial treatment for GNB-related septic shock between January 2009 and December 2012 in 11 ICUs of Japanese tertiary hospitals. After aligning the patients' treatment time phases, we classified patients in two groups regarding whether PMX hemoperfusion (PMXHP) therapy was or was not administered within 24 hours after ICU admission (PMXHP group: n = 134, conventional group: n = 279). The primary study endpoint was the mortality rate at 28 days after ICU admission.

The mean age was 72.4 (standard deviation: 12.6) years and the mean of Sequential Organ Failure Assessment (SOFA) scores at ICU admission was 9.9 (3.4), respectively. The infection sites included intra-abdominal (38.0%), pulmonary (18.9%), and urinary tract (32.2%), and two thirds of all patients had GNB-related bacteremia. Notably, the mortality at 28 days after ICU admission did not differ between the groups (PMXHP: 29.1% vs conventional: 29.0%, P = 0.98), and PMXHP therapy was not found to improve this outcome in a Cox regression analysis (hazard ratio = 0.878; 95% confidence interval, 0.61–1.24, P = 0.46). We conclude that PMX-based endotoxin adsorption did not have an effect on the mortality of patients with septic shock due to GNB.

As noted above, I believe that it was possible for re-evaluation of MD to select the appropriate study design depending on characteristics of the device in the real world. Clinical research of the post-marketing study performed in this thesis would contribute to the safety assurance of MDs in high-risk patients with a severe condition. The fair evaluation of MDs by health care worker is sufficiently possible, and it calls for a platform with an appropriate scale to resolve a number of clinical questions in the realistic medical field.

Chapter 1

Overall background

Medical device (MD) holds a large number of types, more than 300, 000 products in Japan, as compared to the drug in 17,000 products, therefore the evaluation of safety, efficacy, and effectiveness displays has a high diversity.

In general, except for a special bioabsorbable material, the shape of MD is universal and its action is either mechanical, and electrical, or physical. Therefore, evaluation of MD, unlike drugs, is carried out by determining the efficacy of the overall clinical outcome rather than the performance of the product itself. However, efficacy of MD is dependent on the user's experience and skill and it must be evaluated by incorporating a variety of factors. There is a major difference of recognition in value of a MD among manufacturing companies and clinicians including doctors, nurses, and technicians. Clinicians believe that the efficacy of MD is determined by the overall clinical outcome rather than the performance of the product itself. However, it is not required to overall clinical outcome for many of controlled MDs in the new registration.

In the clinical trials of MDs, some cases were evaluated only for product performance

rather than overall clinical outcome. For this reason, it is necessary to re-evaluate the true clinical value of a MD in post-marketing period. As pre-clinical trials were carried out only in a limited number of cases in a limited observation period, post-marketing study is carried out to confirm the safety. The post-marketing study collects clinical data in the realistic world to determine the validity of use for special cases or off-label cases. Medical professionals and patients can obtain long-term data and information about rare adverse events through the post-marketing study, which was not obtained through clinical trials. This process will improve the quality of information and ensure a highly transparent medical care provided to patients. In addition, it will also help in positioning of the treatment with the new MD by comparing it with the existing treatment. The following are the three advantages of the post-marketing study: (i) strengthening and re-evaluation of the evidence, (ii) confirming the clinical efficacy and safety with a high precision, and (iii) providing basic information to design clinical trials for the next generation of MDs. It proves to be important for the public health that such a post-marketing study is available to assure a highly effective treatment.

In this thesis, two post-marketing studies for the efficacy of MDs in the area of

emergency and critical care medicine were conducted and their validity was examined. The significance of re-evaluating the efficacy of the existing MDs is discussed throughout the study series.

Chapter 2

Evaluation of the Safety and Feasibility of Resuscitative Endovascular Balloon Occlusion of the Aorta

Background

Hemorrhagic shock is not controlled easily and is a leading cause of death in trauma patients worldwide [1]. Bleeding control, the maintenance of tissue oxygenation with fluid resuscitation, the correction of coagulopathy, and the management of normothermia remain therapeutic mainstays for critically injured patients with hemorrhagic shock. Recently, damage control resuscitation (DCR) brought a dramatic change to the resuscitation of severe trauma patients with hemorrhagic shock [2]. During DCR, if cardiac arrest is imminent because of an uncontrolled hemorrhage, open aortic cross clamping via resuscitative thoracotomy may be selected. In particular, this technique is used in patients with life-threatening penetrating injuries [3-5]. However, the procedure is extremely invasive, and the incidence of complications rises even if survival is possible. Conversely, several clinical reports on resuscitative endovascular balloon occlusion of

the aorta (REBOA) for trauma patients with difficult resuscitation due to hemorrhagic shock have demonstrated advances in endovascular technology [6-8]. The original method for REBOA was known as intra-aortic balloon occlusion [9] and was first reported during the Korean War in 1954 [10]. The aim of REBOA is to maintain the brain and coronary circulation and to control hemorrhaging from the injured organ temporarily by occluding it with balloon inflation of the aortic lumen.

Subsequently, some large animal experiments [11-15] and clinical series [6,7,9] on the effectiveness of REBOA have been reported. Recently, the effectiveness of aortic balloon occlusion in hemorrhage control of a cesarean section during placental presentation16 and endovascular treatment of ruptured abdominal aortic aneurysms [17,18] have been reported. Based on these studies, the possibility of using REBOA for non-compressive torso trauma has been suggested. A non-compressive torso trauma includes hemoperitoneum and pelvic ring fractures (PRF), in which hemostasis is difficult to achieve with simple manual compression. The general indications for REBOA are these aforementioned injuries and an unstable hemodynamic state.

REBOA is one of the invasive procedures for managing severe subphrenic non-

compressive torso injuries along with resuscitative open aortic cross clamping via resuscitative thoracotomy [19]. Nevertheless, the clinical feasibility and safety of REBOA is unclear; therefore, we aimed to evaluate its efficacy, safety, and clinical feasibility.

Methods

Study Setting

We conducted a retrospective study between January 2007 and December 2013 at the Shock and Trauma Center of Nippon Medical School Chiba Hokusoh Hospital, which is similar to a level 1 trauma center in the United States. This study was approved by the hospital's ethics committee.

Procedure for Resuscitative Endovascular Balloon Occlusion of the Aorta

The indications for REBOA were hemoperitoneum or PRF with impending cardiac arrest. In this study, the criteria for using REBOA included a state of no fluid responsiveness and a sustained systolic blood pressure of <90 mmHg. If there was no pulse, REBOA was prioritized over resuscitative thoracotomy even before the hospital

setting [19], because it is difficult to puncture the femoral artery. After resuscitative thoracotomy was rapidly performed, we converted to REBOA, because it was possible to finely adjust the endovascular occlusion. Thus, REBOA had primary and secondary uses. Typically, even if there has been circulatory failure, vascular access is preferred when using REBOA emergently.

Emergency hemostasis, including external fixation and retroperitoneal packing for PRF or urgent laparotomy to control bleeding, was performed during the REBOA procedure in all patients. If necessary, multiple hemostatic procedures (e.g., laparotomy and angiography) were used. Angiography was possible to restart the aortic blood flow to partly deflate the balloon. The device for REBOA was an aortic occlusion balloon, which contains the balloon catheter and sheath (intra-aortic occlusion balloon; MERA, Tokyo, Japan) (Figure 1). The size of the sheath is 10 French (Fr), and the insertable length of the catheter is 685 mm; it is reinforced by an internal metal wire. The length of the balloon tip is 65 mm with a maximum diameter of 30 mm. The insertion procedure was performed by trauma surgeons or emergency physicians. On occasion, ultrasound-guided or blind puncture and the cut-down method were optionally employed. The initial

position of the balloon catheter was placed blindly into Zone I [20], and then the position was adjusted by fluoroscopic angiography or portable radiography (Figure 2). In addition, intravascular placement was confirmed during hemostatic angiography or in the surgical field. Inflation of the aortic balloon was performed using 20 mL of normal saline, and the balloon was deflated gradually with careful hemodynamic monitoring. The sheath was removed after vascular repair by exposing the femoral artery when it was decided that REBOA was no longer necessary.

At our institution, there is no technical qualification regarding the implementation of REBOA; however, attending emergency physicians and surgeons in the emergency room are skilled in vascular puncture procedures. In addition, the anesthesiologist was contracted for the perioperative management of REBOA. For technique acquisition, he/she was skilled in femoral artery blood vessel puncture and was familiar with the anatomy of the large blood vessels in elective angiography. This experience is necessary for managing the aortic balloon based on aortic pathophysiology. Additionally, it is necessary to understand the massive transfusion protocol and hemostasis procedure. Along with such knowledge and experience, it is possible to use the REBOA system after

having hands-on training under a senior physician's supervision.

Data Analysis

Figure 3 shows the study flow chart. Inclusion criteria in this study were patients aged ≥18 years who underwent the implementation of REBOA. Of 5,230 trauma patients admitted during the study period, 52 who underwent REBOA for total resuscitation and 24 who underwent REBOA primarily were included in the analysis. Twenty-eight who underwent REBOA secondarily after open aortic cross clamping via resuscitative thoracotomy were excluded. Patients were divided into the 24 h survivor group (group 1: n = 14) and the non-survivor group (group 2: n = 10). Their clinical and laboratory data were retrieved from their medical records and were compared. The clinical assessment data included the patients' age, sex, mechanism of injury, initial vital signs on arrival to the emergency department (ED), injury severity score (ISS), site of injury, type of surgical procedure, time from hospital admission to balloon inflation, and duration of aortic occlusion with balloon inflation. The 24-h and 30-day survival rates were recorded and evaluated. Laboratory data included the base deficit and lactate, which were recorded on ED arrival. The probability survival rate was based on the previously described trauma-

related injury severity score methodology, and it was calculated and evaluated by the prediction formula [21,22].

Surgical hemostasis and the volume of red blood cells (RBC) within 24 h after admission were recorded. The time course associated with REBOA was calculated. Other outcome measures were the incidence of complication, vascular injury due to the insertion of REBOA, limb ischemia and amputation, spinal cord ischemia, acute kidney injury (AKI), and multiple organ failure (MOF). AKI was defined using the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) criteria [23]. MOF was defined using the sequential organ failure assessment score (SOFA) system [24]. The maximum SOFA score of each organ with ≥3 points was defined as organ failure, and MOF was defined as ≥2 organ failures.

Statistical Methods

The demographics and clinical parameters were assessed between the groups. Significant differences for the median and prevalence estimates were determined using the chi-squared test and the Kendall and Mann-Whitney U tests for categorical and continuous variables, respectively. P values <0.05 were considered significant. All the

statistical analyses were performed using SPSS, version 19.0 (IBM, Chicago, IL, USA).

Results

Table 1 shows all the patients' characteristics. All 24 patients had a blunt injury, the median age was 59 years (interquartile range, 41–71 years), and the median injury severity score was 47 (range, 37–52). The probability survival rate for all the patients was <0.5 with a median rate of 12.5%. The survival rate of >24 h from admission was 58.3% (n = 14), and the 30-day survival rate was 29.2% (n = 7). The indications for REBOA were hemoperitoneum and PRF in 15 cases, and 8 cases included both indications. Only one patient was a trauma flanked by instrument of pelvic. Initially, PRF was suspected, but it was a left femoral artery injury. Percutaneous puncture was used in 23 cases, while insertion techniques and surgical cut-down were performed in 1 case.

Table 2 compares the patients' characteristics, clinical data, and treatment and complications between groups 1 and 2. The ISS and the site of injury were similar in both groups. The proportion of traffic accidents and pedestrian injuries in group 1 was greater than that of group 2. The initial state of consciousness in group 1 was significantly better

than that in group 2. Other clinical findings at the time of ED arrival were almost similar between the groups. The type of hemostasis revealed no difference between the groups, and there was no statistically significant difference in the amount of PRBCs within 24 h after admission.

The time from ED arrival to inflate the aortic balloon and perform vascular puncture was 20 min in all the cases. The aortic balloon could not be deflated in 5 of 10 cases in group 2. In the remaining 19 cases in which the aortic balloon was deflated, the median duration of aortic occlusion, the time from inflation of the aortic balloon to deflation, was shorter in group 1 than that in group 2 (21 min vs. 35 min, $P = 0.05$), even though it was not significantly different (Table 2). Three patients arrested before the implementation of REBOA after ED arrival. One of these patients temporarily recovered, but all three patients died in the hospital.

With regard to systemic complications, there were nine cases of AKI. Only one case had AKI alone. Five of 9 cases had an AKI grade of failure according to the RIFLE criteria. There were also 9 cases of MOF (Table 2). Complications of the lower extremities associated with vascular puncture were observed in 3 cases—lower limb

ischemia in 2 and external iliac artery injury in 1, all of which required lower limb amputation. In one case of vascular injury, the 10 Fr sheath was inserted after multiple blind punctures in an obese male. When the angiography for PRF revealed a simultaneous vascular injury, its repair had been performed; however, lower limb ischemia that required amputation 2 days later was inevitable. One patient with ischemia had open bilateral femoral fractures with an extensive soft tissue injury that progressed to limb ischemia and resulted in amputation of the puncture side of the lower limb 3 days after admission. Another patient with ischemia had an open pelvic fracture, and the balloon catheter was inserted into the femoral artery directly through the damaged part of the groin. After emergent arterial embolization was performed for bleeding, the lower limbs were cut from the hip. AKI developed in all 3 cases, but failure was not persistent. None of the survivors had spinal cord ischemia or arterial thrombosis, and there were no complications related to sheath removal.

Discussion

With regard to damage control hemostasis and resuscitation for severe trauma patients

with hemorrhagic shock, several additional techniques have been sought to obtain temporary hemostasis. REBOA closely applies to this requirement, and the clinical probability of its effects is expected. In the present report, we described the complications and procedures associated with REBOA, and we showed its clinical safety and feasibility, which were insufficiently described in previous reports [6,7].

Since Holcomb proposed the concept of DCR in 2007 [2], aggressive plasma transfusion therapy using the massive transfusion protocol, permissive hypotension during hemostasis, and body temperature management have been accepted worldwide. Simultaneously, damage control surgery has also advanced, and the technique of temporary hemostasis has also been improved. Nevertheless, we still encounter many severe trauma patients whose hemorrhages cannot be easily controlled. It would be difficult to perform additional treatments (e.g., surgical hemostasis or arterial embolization with transfer to the operating room [OR] or interventional radiology [IR] room) despite unstable vitals. For such a situation, REBOA is a good approach with the possibility of solving this dilemma.

According to our findings, after temporary bleeding control using thoracotomy or

laparotomy with REBOA in the ED, 12 patients were stable enough to move to the IR room and 9 were stable enough to move to the OR. To avoid cardiac arrest during transport to the hospital, blood flow blocking on the central side from the bleeding point is the most effective method. By using REBOA, the 30-day survival rate greatly exceeded its predictions, as it was more than double the calculated probability of survival. However, although the 24 h survival rate was >50%, MOF in the intensive care unit after hemostasis procedures was still a serious issue. Two-thirds of the patients who survived >24 h in this study had MOF. If we overcome this, the clinical efficacy of REBOA will be evaluated as the ultimate procedure for obtaining a long-term survival. Therefore, to truly evaluate the effectiveness of REBOA, it would be reasonable to evaluate early survival (i.e., the survival rate of >24 h from admission) without the influence of MOF.

In this study, the main indication for REBOA was non-compressible torso trauma with impending cardiac arrest due to hemorrhagic shock. In particular, we recognized that unstable PRF with hemodynamic instability is an optimal target for REBOA. PRF cases accounted for about 60% in this study, and they were all multiple traumas. Although the effect of REBOA for temporal hemostasis is theoretically poor in thoracic trauma,

REBOA contributed to maintaining tissue perfusion of the brain and heart to avoid dysoxia. Even if there was no statistical significance in the base deficit and lactate between the groups, tissue perfusion after REBOA application in the 24-h survival group may have improved because of the change in systolic blood pressure (data not shown). As a result, it was reasonable to use the REBOA in patients with multiple traumas. However, the decision to employ it was always difficult, and if necessary, the earlier adoption of REBOA was better. The REBOA implementation required about 20 min to inflate the aortic balloon from the patients' arrival, but there were three cases of cardiac arrest before its employment. Therefore, the time until the decision for using REBOA is most essential. In addition, if we can recognize that the victim has obvious shock and massive transfusion is predicted [25], it will also be necessary to prepare the REBOA induction. The prophylactic use of this technique for specific injuries of hemorrhagic shock may be expected in the future, but we have to overcome the risk of excessive invasiveness. Given such an effectiveness of REBOA in this study, it would be clinically feasible to introduce REBOA for patients with severe hemorrhagic shock.

Insertion of the catheter for the occlusion balloon was performed in the ED. Primary

positioning was blindly performed with manual estimation, and the intravascular placement of the catheter was confirmed by portable radiography. We aimed the aortic balloon at Zone I initially; [20] however, the success rate was unclear because all the imaging findings could not be obtained. Our catheter was reinforced with metal and was devised to not bend. Typically, it is reasonable for it to be placed in Zone I; however, if the vessel is meandered by arteriosclerosis, the risk of arterial injury due to the implementation of REBOA may increase. We confirmed the running of the blood vessels with a guide wire in such cases. There was no damage to the aorta in our case series. However, there was one case of arterial injury in the pelvic cavity, which was considered to be caused by the multiple punctures required for placing the guide wire in an obese patient. In recent years, ultrasound-guided vascular puncture with echo has become a standard procedure because of the spreading and progress of small movable devices [26,27]. Because it was necessary to perform a quick puncture for REBOA employment just before cardiac arrest, the process of vascular identification by ultrasound was often omitted. Since a safe arterial access and balloon management are required to achieve a good outcome, endovascular skills should be learned through a well-designed course (e.g.,

the Endovascular Skills for Trauma and Resuscitative Surgery Course) [27]. However, there are no public qualifications for REBOA and the training course on the balloon catheter in Japan. Since the REBOA procedure is used, only the basic skills of arterial puncture are required, and if one has the additional knowledge and experience with balloon management, it is not difficult. However, it is necessary to perform hemostasis in parallel with REBOA, and all the resuscitation team members should be aware of this concept.

Our series had major complications, which included lower limb ischemia and AKI induced by systemic ischemia associated with REBOA. To avoid these complications, earlier deflation of the aortic balloon must be performed after immediate hemorrhage control via a surgical or interventional radiological approach. Fortunately, there were no cases of thromboembolic or spinal cord ischemia, which are a concern with open aortic clamping via resuscitative thoracotomy. However, the number of cases was small in this report, and a more comprehensive evaluation of these complications is warranted. The time from inflation to deflation of the aortic balloon in 24-h survivors was shorter than that in non-survivors. It was suspected that reperfusion injuries due to systemic ischemia

would lead to death. In experiments with swine, Morrison and colleagues reported that a longer aortic inflation time increased the release of interleukin-6, incidence of acute respiratory distress syndrome, and use of vasopressors [15]. In the present case series, 7 of 14 patients in the 24-h survival group died. The cause of death included persistent hemorrhage in 1, head injury in 1, and MOF in 5. In another experiment with swine [14], the survival threshold of aortic occlusion was 40 min, but this evaluation only described early death during the resuscitation period and MOF was not considered. Therefore, the simplistic adaptation to humans is dangerous, and it would be realistic that the median occlusion time of the 24-h survival group was about 20 min. Hemostasis in the golden time of 20 min has emerged as a challenge for the future.

There are some limitations to this study. First, the study was conducted at a single center with a small sample population, and the study design was retrospective. This is the result of careful patient selection, but the potential number of patients would have been more. Thus, there was obviously selection bias. In particular, there were many secondary implementations of REBOA, because it was a priority in resuscitative thoracotomy for open aortic clamping due to the time shortening and impending cardiac arrest. This

trauma care process has been implemented as a facility policy. For comparison, resuscitative thoracotomy and REBOA were considered inappropriate because the patients' conditions were significantly different between the two procedures. Fifteen patients who underwent REBOA secondarily after resuscitative thoracotomy (15/28, 53.6%) had cardiopulmonary arrest before the procedure. In contrast, among our study patients, only three patients (3/24, 12.5%) had prior cardiopulmonary arrest. This apparent difference can lead to erroneous conclusions. Since the background of the two groups in the present study was not the same, the number of cases would have been more necessary. Second, the balloon catheter sets are only sold in Japan. Therefore, it is unknown whether patients of different races and physique in other countries would be compatible with this balloon catheter. Third, we did not evaluate the skills of the operator. There were no criteria for skills in the implementation. In the current study, an attending trauma surgeon and emergency physician managed the REBOA. Since complications cannot be avoided even with experienced staff, the acquisition of standard procedures is extremely important [27]. The weakest point in the evaluation of feasibility of REBOA is that this technology has fallen into disuse once in the world. Since the 1980s [9,28], some

reports describe that it was left behind until endovascular treatment progressed. Fortunately, advances in trauma care have been achieved since this period, and the door to REBOA has remained open. There is always swingback in medical technology [29]. It takes decades for evidence to be established, and recommendations for treating critical patients change with the times. REBOA may also follow such a course; however, it is expected to be a real innovation for enhancing safety, because the technology encompasses a fairly simple theory.

In conclusion, REBOA was a feasible adjunct for supporting definitive hemostasis of non-compressive torso trauma in our series. However, it must be noted that potential complications of lower limb ischemia and vascular injury exist, and there is a high risk of MOF after deflation of the aortic occlusion. The safety implementation of REBOA will be established through rapid conduct for severe hemorrhagic shock, appropriate puncture and placing, and immediate balloon deflation. A future multicenter prospective study in a reasonable adaptation setting is needed to expand on this innovative approach.

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Tables and Figures

Table 1. All patient characteristics

Characteristics	Patients (n=24)
Age (years)	59 (41-71)
Male/ female	13 / 11
Injury severity score	47 (37-52)
Revised trauma score	4.41 (2.93-5.77)
Probability survival rate	12.5 (2-40)
Blunt trauma, no (%)	24 (100)
Hemoperitoneum, no (%)	15 (62.5)
Pelvic ring fracture, no (%)	15 (62.5)
Time from ED arrival to balloon inflation (min)	20 (13 – 72)
24 hours-survival rate	58.3 %
30 days-survival rate	29.2 %

Data are presented as median values with interquartile range or as number (%).

Table 2. A comparison of the patients' characteristics, clinical data, and treatment between groups 1 and 2

Variable	Group 1 (n = 14)	Group 2 (n = 10)	P value
Age (years)	65 (41–73)	47 (32–65)	0.16
Male/female	6/8	7/3	0.36
ISS	40 (34–50)	50 (45–54)	0.06
Site of injury, no (%)			
Head AIS ≥3	3 (21.4)	5 (50.0)	0.14
Chest AIS ≥3	6 (42.9)	8 (80.0)	0.06
Abdominal AIS ≥3	11 (78.6)	8 (80.0)	0.93
Extremities AIS ≥3	8 (57.1)	6 (60.0)	0.88
Hemoperitoneum	9 (64.3)	6 (60.0)	0.83
Pelvic ring fracture	7 (50.0)	8 (80.0)	0.13
Mechanism of injury, no (%)			
Traffic accident	6 (42.9)	1 (10.0)	0.31
Fall	0 (0)	4 (40.0)	
Pedestrian	6 (42.9)	2 (20.0)	
Other	2 (14.3)	2 (20.0)	
ED admission vitals and laboratory data			
Systolic blood pressure (mmHg)	75 (59–96)	57 (31–89)	0.13
Heart rate (bpm)	125 (83–150)	115 (84–147)	0.74
Glasgow coma scale	10 (6–14)	3 (3–6)	0.01
Base deficit (mmol/L)	-8.7 (-15.7 to -6.0)	-16.0 (-19.3 to -11.4)	0.09
Lactate (mmol/L)	6.9 (4.2–10.8)	9.4 (5.8–11.4)	0.21
Hemostasis procedures, no (%)			
Laparotomy	6 (42.9)	4 (40.0)	0.88
Retroperitoneal packing	2 (14.3)	0	0.21
TAE	8 (57.1)	5 (50.0)	0.79
Volume of RBC within 24 hr after admission (mL)	6,160 (3,360–8,680)	3,640 (1,400–8,400)	0.22
Duration of aortic occlusion (min)	21 (13–26)	35 (28–35)	0.05

Continuation of Table 2 Variable	Group 1 (n = 14)	Group 2 (n = 10)	P value
Complications, no (%)			
AKI: Risk/injury/failure	3 (21.3)/1 (7.1)/5 (35.7)	-	
MOF	9 (64.2)	-	
Lower limb ischemia	2 (14.2)	0	0.21
Arterial injury due to puncture	1 (7.1)	0	0.38
Lower limb amputation	3 (21.3)	0	0.11

Group 1 is the 24 h survivor group (n = 14), and group 2 is the 24 h non-survivor group (n = 10). The data are presented as median values with an interquartile range or as a number (%).

ISS, injury severity score; AIS, abbreviated injury scale; ED, emergency department; TAE, trans-arterial embolization; PRBC, packed red blood cell; AKI, acute kidney injury; MOF, multiple organ failure.

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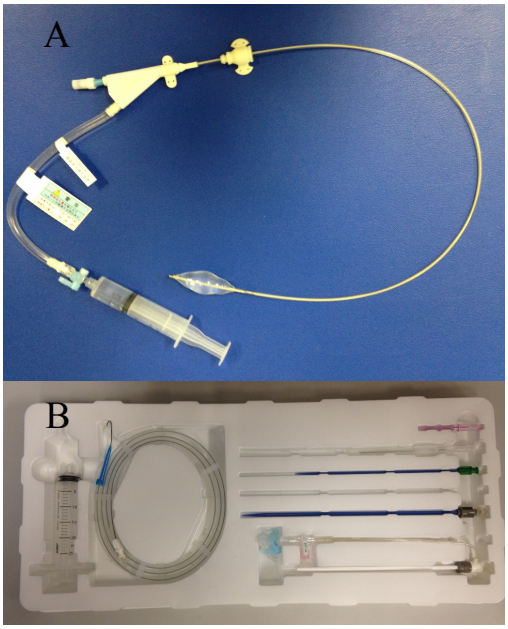

Figure 1. The device for resuscitative endovascular balloon occlusion of the aorta (REBOA) and the intra-aortic occlusion balloon (IABO; MERA, Tokyo, Japan).

The product is encapsulated in the IABO insertion set. A) The aortic balloon and the double-lumen catheter. B) The 10 French sheath, two dilators, guide wire, and seldinger needle. The inner lumen of the double lumen catheter is furnished with a stylet made of stainless steel. The cylindrical shaped balloon is made of a polyurethane material.

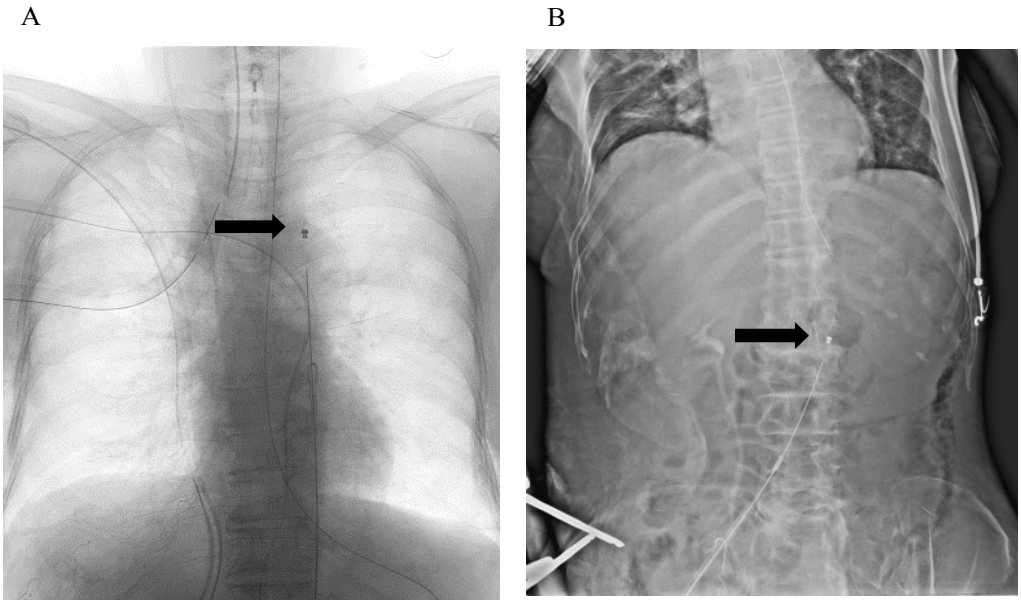

Figure 2. Position confirmation of the balloon catheter by fluoroscopy or portable radiography.

A) A case in which the catheter was placed in Zone I, and the position was confirmed at the start of angiography for the pelvic fracture after laparotomy. B) A case in which the catheter was placed in Zone III, and the position is confirmed in the emergency department during external fixation of the unstable pelvic ring fracture. The black arrows indicate the tip of the catheter.

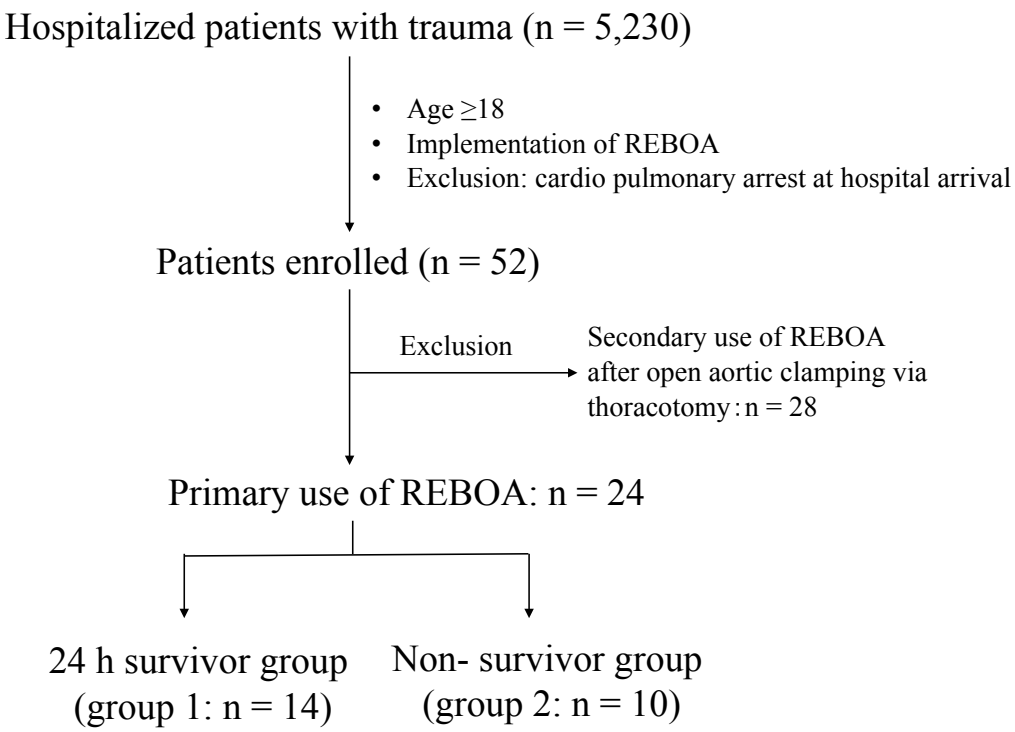

Figure 3. Study flow chart.

REBOA, resuscitative endovascular balloon occlusion of the aorta

Chapter 3

Efficacy of polymyxin B-immobilized fiber hemoperfusion for patients with septic shock caused by Gram-negative bacillus infection

Background

The incidence of septic shock (SS), a critical and potentially fatal illness characterized by an excessive biological reaction against an infections pathogenic microorganism, is increasing worldwide [1]. Since 2004, international guidelines for management of severe sepsis and septic shock (surviving sepsis campaign) have advanced the standardization of primary care for sepsis [2], and SS-related mortality rates have been steadily decreasing in intensive care units (ICUs) [3]. However, the clinical outcomes of SS vary widely, with reported 28-day mortality rates ranging from 30% to 50% [3].

Currently, Gram-negative bacilli (GNB) are the etiological bacterial agent in 40% of SS cases [1], and are known to cause excessive inflammatory reactions that may lead to multi-organ failure [4]. Unfortunately, GNB is also a major causative organism of nosocomial infections, and the resulting increase in drug resistance has led to treatment challenges [5]. The GNB outer membrane component endotoxin is a well-known, typical

pathogen-associated molecular component that can induce inflammation [6], and as early as a few decades ago, GNB-induced SS was described as endotoxin shock and considered to be a more critical condition [7, 8]. These findings have led to considerable research regarding the potential of endotoxin as a therapeutic target [9].

In the 1980s, this endotoxin-related research led to the development of a polymyxin B-immobilized fiber column (PMX: Toraymyxin®; Toray Medical Co., Ltd., Tokyo, Japan), which utilizes the ability of polymyxin B to bind lipid A within the major endotoxin effector site. The endotoxin adsorption efficacy of PMX, which has been used in clinical applications in Japan since 1994 [10, 11], has been demonstrated both in vitro and in vivo, and this material has since been used with the hope that it could suppress the GNB-related inflammatory cascade [10]. More recently, PMX has been used to treat intra-abdominal infection in several countries.

Although a high serum endotoxin levels is associated with a poor prognosis in patients with SS, there is no clear evidence regarding the clinical effect of endotoxin adsorption therapy with PMX hemoperfusion (PMXHP) on survival [7, 12, 13]. In a 2007 systematic review of PMXHP [11], Cruz et al. reported that the arterial pressure and pulmonary

oxygenation (PaO2 / FiO2 ratio; P/F ratio) were improved and the mortality was decreased with the implementation of PMXHP (odds ratio [OR] = 0.53, 95% confidence interval: 0.43–0.65). In contrast, recent publications by Cruz et al. in 2009[14] and Payen et al. in 2015 [15] reported no significant decreases in mortality among patients with abdominal sepsis. Similar results were observed among Japanese patients with lower gastrointestinal perforation in a propensity-matched analysis of nationwide inpatient insurance data [16]. However, the limitation of all of these previous reports was the lack of certainty regarding the GNB infection status in all target patients.

We conducted a multi-center study with the intent to verify the following hypothesis: after achieving infection site control and implementing broad-spectrum antibacterial treatment, the 28-day mortality rate would improve with the addition of PMXHP as an adjuvant therapy in patients with SS due to GNB.

Methods

Study setting

We conducted a retrospective study at 11 ICUs of Japanese tertiary hospitals. Before

data collection, the study protocol was reviewed and approved by the ethics committee of each institution. The trial was registered in the University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR ID: UMIN000012748).

Data collection

Each investigator was provided a comprehensive manual that described the data collection requirements and definitions of variables. Case report forms were uploaded to the study website via the internet. Case registration was mandatory to ensure correct alignment of the treatment order and time-phase and adjustment of confounding factors. Data management was performed by at an independent data center at the University of Tsukuba (CREIL Center, Ibaraki, Japan).

The inclusion criteria were patients admitted in ICUs from January 2009 to December 2012, an age ≥18 years and SS resulting from GNB, as detected from clinical specimens. Sepsis was diagnosed according to the 2008 Surviving Sepsis Campaign Guidelines. In addition, SS was defined as hypotension (systolic blood pressure <90 mmHg) at the start of the medical intervention or an elevated lactate level (>4 mmol/L). Microbial confirmation of GNB required the isolation of pathogens from any clinical culture. The

study excluded the patients of non-resuscitate status.

Patients received broad-spectrum antimicrobial treatment, if needed, surgical intervention for source control before ICU admission. After aligning each patient's treatment time phase, we classified patients into two groups depending on the administration of PMXHP treatment within 24 hours after ICU admission (PMXHP group: n = 134, conventional group: n = 279).

To compare patient's conditions before PMXHP therapy, the following information was collected: age, sex, severity of illness (e.g., APACHE [Acute Physiology and Chronic Health Evaluation II] II score [17], Sequential Organ Failure Assessment [SOFA] score [18]) pre-existing disease, comorbidities upon PMX session (e.g., all grades of acute respiratory distress syndrome [ARDS] defined according to the criteria of the Berlin definition [19], all grades of acute kidney injury [AKI] defined according to the RIFLE criteria [20], disseminated intravascular coagulopathy [DIC] diagnosed using the Japanese Association for Acute Medicine DIC scores [21], acute coronary syndrome [ACS]/stroke diagnosed a vascular lesion specialist, intraperitoneal abscess diagnosed from imaging findings), type of infection (e.g., community acquired, hospital acquired,

healthcare acquired), site of infection (e.g., pulmonary, intra-abdominal, urinary, soft tissue), vital signs, and laboratory data at the beginning of the medical intervention. Details of defined cultures were collected separately from blood and local samples. Information about treatment for comorbidities after ICU admission and specific drug usage was also collected.

Implementation of PMXHP therapy

Decisions regarding PMXHP therapy were left to each facility. Japanese public insurance allows the performance of 2-hour direct hemoperfusion sessions with heparin administration as a basic PMXHP protocol. In the current study, this protocol has been adjusted for anti-coagulant drugs and the duration of direct hemo-perfusion at each facility. In addition, further options could be added to a subsequent session of PMXHP after completing the initial session. Data regarding the implementation of PMXHP, vital signs, and laboratory data of the patient before and after the implementation PMXHP therapy, were collected.

Outcomes

The primary endpoint was the mortality rate at 28 days after ICU admission, and the

secondary endpoints were the mortality rate at hospital discharge, duration of mechanical ventilation, length of ICU stay, and length of hospital stay. In addition, outcome-free days (e.g., ventilator-free days, ICU-free days) were determined to minimize survivor bias. Comorbidities after PMX session, including ARDS, AKI, DIC, ACS, stroke, and intraperitoneal abscess, were also recorded as clinical outcomes.

Sample size and statistical methods

Based on previous studies [4, 11, 14], we assumed that in order to be clinically meaningful, the assumed mortality rate at 28 days for the target patient population, 40%, would need to be reduced to 25% after implementing PMXHP therapy. Assuming that PMX intervention was performed in one third of the target patients, the size needed to test an absolute reduction in mortality at 28 days of 15% (relative reduction of 37%) would be 390 patients (130 for PMXHP group and 260 for conventional group) to obtain a nominal two-sided p value of 0.05 and power of 85%.

The groups were compared with respect to demographic and clinical parameters. Significant differences in means, medians, and prevalence estimates were determined using the chi-square test for categorical variables, the t test or Mann–Whitney U test for

independent continuous variables, and the Wilcoxon signed rank test for paired continuous variables. P values <0.05 were considered significant. A Cox proportional hazards model adjusted for age, sex, and pre-treatment status was used for the multivariate analysis. All statistical analyses were performed using SPSS, version 23.0 (IBM, New York, IL, USA).

Results

Patient characteristics

The mean age of patients in this study was 72.4 years (standard deviation: 12.6), and the mean SOFA score upon ICU admission was 9.9 (3.4). Mechanical ventilation was performed in 72.9% of all patients, and a third of patients underwent surgery for source control. The infection sites were intra-abdominal, pulmonary, and urinary tract in 38.0%, 18.9%, and 32.2% of patients, respectively, and two thirds of all patients had bacteremia due to GNB.

Table 1 compares the patient characteristics, clinical data, and treatments of the PMXHP and conventional groups. Although the PMXHP group was younger than the

conventional group, this difference was not significant (P = 0.06). However, the frequencies of comorbid AKI and DIC at the time of ICU admission differed significantly between the two groups (P = 0.01 and <0.01, respectively), and the frequency of mechanical ventilation was significantly higher in the PMXHP group (87.3% vs. 65.9% for the conventional group).

Although the distribution of infection type was homogenous, the distribution of infection site was somewhat heterogeneous. For example, a large proportion of patients in the PMXHP group had intra-abdominal infection, whereas the proportion with pulmonary infection was relatively small. However, both groups had similar frequencies of bacteremia. Furthermore, surgery for source control was more frequently implemented in the PMXHP group relative to the conventional group. In addition, although the conditions prior to treatment were similar in both groups, the severity of illness, indicated by the SOFA score, was significantly higher in the PMXHP group than the conventional group. The administration of specific treatments, including continuous renal replacement therapy and recombinant thrombomodulin, after ICU admission also differed significantly between the two groups.

Outcomes

The primary endpoint, mortality rate at 28 days after ICU admission, did not differ between the two groups (PMXHP: 29.1% vs conventional: 29.0%, P = 0.98). For secondary outcomes, duration of mechanical ventilation and ventilator free days were better in the conventional group than that in the PMXHP group. The groups differed with regard to additional comorbidities after PMX session; specifically, DIC was more common in the PMXHP group, whereas ARDS and stroke were more common in the conventional group (Table 2). Figure 1 demonstrates that PMX treatment (hazard ratio = 0.87; 95% confidence interval, 0.61–1.24, P = 0.464) did not improve the study outcome measures, according to a multivariate Cox regression model analysis; in addition, no inter-group differences were observed at hospital discharge. Figure 2 additionally shows a post-hoc subgroup analysis in which we again did not observe differences in efficacy and interactions in any PMXHP subgroup.

Hemoperfusion practice

A total of 184 PMXHP sessions were conducted, and the actual median adsorbed time was 144 minutes. The standard 2 hours were not completed in 11 sessions (5.9%); in one

such case, the patient fell into cardiopulmonary arrest and died during PMX treatment. The overall mean arterial pressure increased after PMXHP relative to the pre-treatment value (before PMXHP: 68[57–80] vs. after PMXHP: 76 [65–87] mmHg, P <0.01); however, in the initial session, deterioration in blood pressure with or without additional catecholamine was observed at 42.5% (57/134). No improvements were observed in the P/ F ratio, lactate level, or base deficit (an indicator of circulatory failure; data not shown).

Discussion

In this study, which was conducted in tertiary care hospitals involved the current general level of sepsis practice in Japan, we did not observe an additional clinical benefit of adjuvant PMXHP therapy on mortality after the administration of broad-spectrum antimicrobial agents and source control among the patients with SS, in which more than 60% presented with GNB bacteremia. Moreover, no subgroup-related differences in efficacy were observed in a post-hoc analysis.

In Japan, PMXHP therapy has been used generally for approximately 20 years [10, 11], and protocols have been developed at a number of large-scale facilities. However, the use

of PMXHP therapy is left to the physician's preference because of its nature as a special and invasive adjunctive therapy. The present study demonstrates the lack of clinical efficacy of PMXHP when administered for typical SS caused by GNB. We suggest that the previously observed effect might be attributable to the Abilene paradox.

In 2015, Payen et al. [15] described a non-significant increase in mortality and no improvement in organ failure following PMXHP vs. conventional treatment for peritonitis-induced SS in the ABDOMIX trial, the latest multicenter randomized control trial in France. Although the results of our study were similar to those of the ABDOMIX trial, the trials differed in terms of focus, as the latter trial addressed SS due to peritonitis in contrast to our study. We note that although most previous reports targeted intra-abdominal infections, GNB infections occur at a much broader range of sites [11, 14, 22]. In principle, PMXHP is only valid for the treatment of bacteremia caused by GNB. Accordingly, we selected patients with SS caused by GNB with the prior expectation of a high probability of efficacy.

In the ABDOMIX trial, randomization was performed at 2 hours after surgery to recruit patients with prolonged SS due to peritonitis. Although we initially confirmed SS, this

classification included patients who had emerged from a state of shock at the time of ICU admission, according to resuscitation data from this study. However, 66.4% of patients in PMXHP group remained in a prolonged state of shock, defined as a mean arterial pressure of ≤65 mmHg or hyperlactatemia upon ICU admission. As a result, the mortality rate at 28 days after ICU admission in our intervention group was 29.1%, similar to that of the ABDOMIX study (27.7%).

We note that serum endotoxin values were not included among the considerations of this study, largely because few facilities have the ability to routinely measure serum endotoxin levels, and no standard method has been set for such measurements. We note that in this study, GNBs were detected in all patients, and GNB bacteremia accounted for approximately 67% of the sepsis cases. This proportion of bacteremia was sufficiently higher in comparison with previous reports to ensure that the target population would be appropriate even without a measured endotoxin level.

PMXHP therapy has not been subjected to a randomized trial in Japan or other developed countries. A fair evaluation has thus far been impossible because previous reports from Japan have tended to include considerable bias [11], and only the clinical

outcomes of intra-abdominal infection from a nationwide insurance database were reported. In 2014, Iwagami et al. [16] reported the mortality rate at 28 days in the presence or absence of PMXHP using a propensity score matching analysis. Although that report showed a national trend, biological patient information was lacking, and it was necessary to add a supplemental study. In contrast, our study presented clear information about the patients' medical treatment courses, including vital signs. Although the distributions of patient characteristics exhibited considerably heterogeneity, similar to the report by Iwagami, the time axis of treatment for SS was maintained in a linear manner. In particular, although the initial complications, infection site, and implementation of surgery varied, we did not observe a causal relationship between the outcomes after adjusting for heterogeneity. Furthermore, we were not able to identify any clinical efficacy of PMXHP, despite performing various stratified post-hoc analyses.

Previous reports [11] described improvements in oxygenation and blood pressure as short-term effects of PMXHP. In this study, although the mean arterial pressure increased after the initial PMXHP session relative to the pre-treatment value, the distribution of this effect was quite heterogeneous. Therefore, we could not determine whether the observed

changes were the result of PMXHP or other causes. Similarly, we did not obtain positive results regarding the P/F ratio and circulatory failure parameters, which raises concerns about the safety of PMXHP therapy.

This study has some limitations of note. First, the study design was observational, and a case-control design was adopted. Because PMX treatment is already commonly used for SS in Japanese healthcare settings, a randomized trial would present ethical challenges. To improve the quality of clinical research, however, the present study involved data collection and management by an independent clinical research organization to verify the likelihood of our interventions and outcomes. Although this was an observational study, the registration data at each facility were regularly monitored, and incompatibilities were coordinated via feedback as well as in a prospective manner. Second, the PMXHP execution rate varied among the participating institutions. However, the average rate of 32.4% (standard error: 9.7%; range: 0–100%) was acceptable. Although PMXHP itself was feasible at the participating hospitals, the policies regarding PMXHP therapy for SS ranged from completely negative to active affirmation. Although the overall result might have been acceptable, this variability is a source of potential selection bias. Third, the

mortality rate used to calculate the sample size [4, 14] differed from the actual number. Consequently, the number of samples in the PMXHP group was smaller than the expected, thus provided less preferred power. Since the elucidation of the pathophysiology of sepsis, the mortality rate associated with sepsis is decreasing [3], and a magic bullet in the form of a large difference in mortality might be already out of reach. Accordingly, the hurdles that must be overcome to prove the efficacy of a single adjuvant therapy have increased in size.

In conclusion, no difference in mortality was observed among patients with SS caused by GNB, regardless of the implementation of endotoxin adsorption therapy. Accordingly, reconfirmation of the efficacy and safety of PMX through a multicenter prospective study is essential.

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Tables and Figures

Table 1. Comparison between PMXHP group and Conventional group on patient characteristic

Variables	PMXHP group n=134	Conventional group n=279	P value
Age, years	70 ± 13	73 ± 12	0.06
Male / female	63 / 71	153 / 126	0.13
Pre-existing disease			
Chronic heart failure	11 (8.2 %)	27 (9.7 %)	0.62
Ischemic heart disease	15 (11.2 %)	25 (9.0 %)	0.47
Chronic obstructive pulmonary disease	3 (2.2 %)	13 (4.7 %)	0.23
Liver cirrhosis	9 (6.7 %)	13 (4.7 %)	0.38
Chronic renal failure	3 (2.2 %)	10 (3.6 %)	0.46
Diabetes	29 (21.6 %)	59 (21.1 %)	0.90
Cancer	10 (7.5 %)	35 (12.5 %)	0.12
Comorbidities before PMX session			
ARDS	21 (15.7 %)	42 (15.1 %)	0.87
AKI	100 (74.6 %)	173 (62.0 %)	0.01
DIC	80 (59.7 %)	115 (41.2 %)	<0.01
Type of infection			
Community acquired	100 (74.6 %)	197 (70.6 %)	0.39
Hospital acquired	30 (22.4 %)	63 (22.6 %)	0.96
Healthcare acquired	4 (3.0 %)	19 (6.8 %)	0.11
Site of infection			
Pulmonary	13 (9.7 %)	65 (23.3 %)	0.01
Intra-abdominal	68 (50.7 %)	89 (31.9 %)	<0.01
Urinary	37 (27.6 %)	96 (34.4 %)	0.16
Soft tissue / skin	6 (4.5 %)	12 (4.3 %)	0.93
Other / unknown	10 (7.5 %)	14 (5.0 %)	0.32
Positive blood culture	88 (65.7 %)	189 (67.7 %)	0.67
Pathogens			
E. coli	36 (26.9 %)	82 (29.4 %)	0.59

Pseudomonas aerginosa	5 (3.7 %)	14 (5.0 %)	0.55
Enterobactor spp.	8 (6.0 %)	11 (3.9 %)	0.35
Klebsiella spp.	22 (16.4 %)	34 (12.2 %)	0.24
Serratia spp.	4 (3.0 %)	5 (1.8 %)	0.43
Acinetobactor spp.	3 (2.2 %)	4 (1.4 %)	0.55
Citrobactor spp.	3 (2.2 %)	6 (2.2 %)	0.95
Gram-positive cocci	4 (3.0 %)	3 (1.1 %)	0.15
Surgery for infection control, Total	69 (51.5 %)	65 (23.3 %)	<0.01
Laparotomy	53 (39.6 %)	44 (15.8 %)	<0.01
Vital signs at beginning of treatment			
Mean arterial pressure, mmHg	60 ± 21	59 ± 23	0.98
Heart rate, beat/ minutes	114 ± 24	111 ± 27	0.35
Respiratory rate, breath/minutes	26 ± 7	26 ± 8	0.71
Glasgow coma scale, points	11 ± 4	11 ± 3	0.56
Laboratory data			
C reactive protein, mg/ml	16.5 ± 11.7	15.9 ± 11.8	0.64
Lactate, mmol/L	5.0 ± 3.8	4.7 ± 3.9	0.53
APACHE Ⅱ score	26 ± 9	25 ± 9	0.31
SOFA score, total score	10.5 ± 3.8	9.5 ± 3.2	<0.01
Treatment after ICU admission			
Mechanical ventilation	117 (87.3 %)	184 (65.9 %)	<0.01
Continuous renal replacement therapy	100 (74.6 %)	63 (22.6 %)	<0.01

Data are presented as median values with interquartile range or as number (%).

Pathogens were detected from blood cultures and contained duplications.

ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation; APACHE; acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; ECMO : extracorporeal membrane oxygenation.

Table 2. Primary and secondary outcome

	PMXHP group n=134	Conventional group n=279	P value
Primary outcome			
Mortality rate: 28 days after ICU admission	39 (29.1 %)	81 (29.0 %)	0.98
Secondary outcomes			
Mortality rate: Hospital discharge	51 (38.1 %)	69 (34.4 %)	0.68
Length of ICU stay, days	8 (4 – 16)	7 (3 - 13)	0.11
ICU free days	12 (0 – 20)	15 (0 – 22)	0.16
Length of hospital stay, days	26 (11 – 56)	25 (10 - 43)	0.35
Duration of mechanical ventilation, days	6 (2 – 13)	3 (0 – 9)	<0.01
Ventilator free days	16 (0 – 19)	19 (0 – 24)	0.03
Comorbidity after PMX session			
ARDS	27 (20.1 %)	27 (9.7 %)	<0.01
AKI	8 (6.0 %)	28 (10.0 %)	0.17
DIC	31 (23.1 %)	37 (13.3 %)	0.01
Acute coronary syndrome	1 (0.7 %)	9 (3.2 %)	0.12
Stroke	1 (0.7 %)	12 (4.3 %)	0.05
Intraperitoneal abscess	7 (5.2 %)	11 (3.9 %)	0.55

Data are presented as median values with interquartile range or as number (%).

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; DIC: disseminated intravascular coagulation.

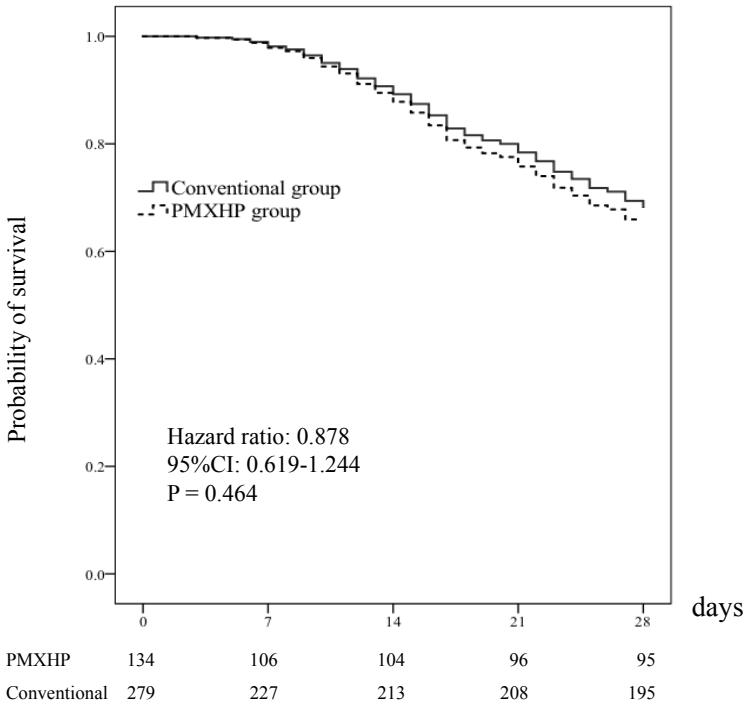

Figure 1. Multivariate Cox regression analysis.

Patients in the polymyxin B hemoperfusion (PMXHP) group received at least one session of direct PMXHP as adjuvant therapy for septic shock.

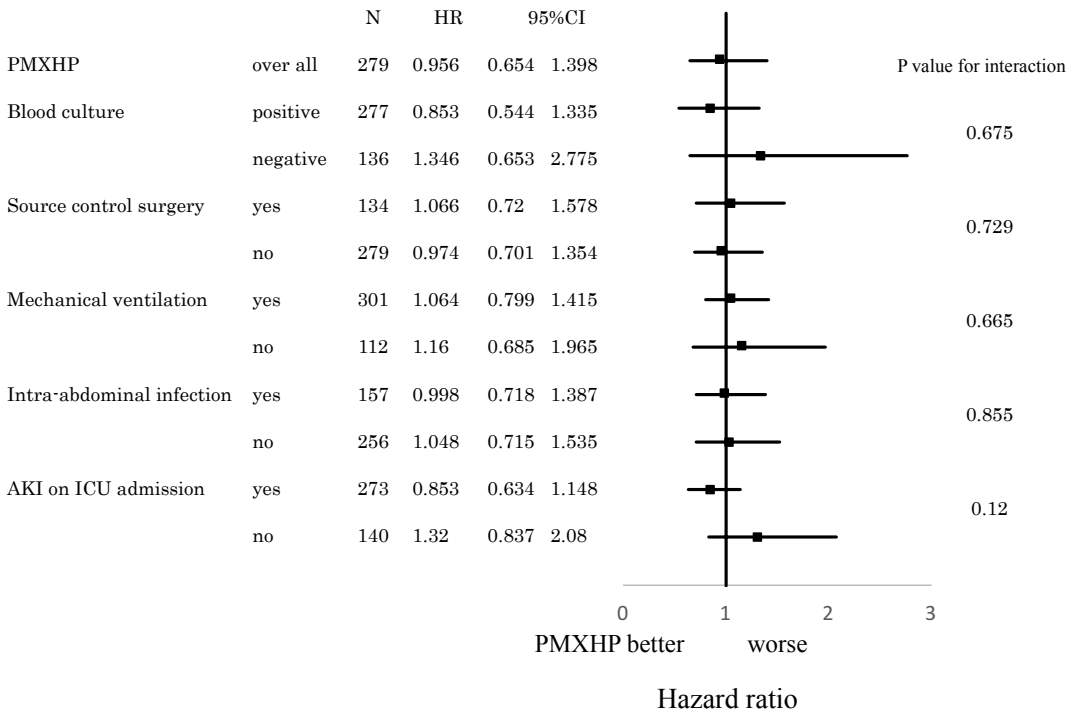

Figure 2. Post-hoc analysis.

The mortality rates at 28 days after ICU admission across the indicated subgroups were defined according to several baseline characteristics. PMXHP: polymyxin B immobilized fiber hemoperfusion, HR: hazard ratio, CI: confidence interval, AKI: acute kidney injury

Chapter 4

Overall discussion and conclusion

In this thesis, the post-marketing study for two medical devices (MDs) is described, whose clinical efficacy is skeptical for a long time. The research method used here is different for each of the MDs depending on their characteristics.

In Chapter 2, the safety and efficacy of the resuscitative endovascular balloon occlusion of aorta (REBOA) was examined. Although clinical trials for the catheter used in REBOA had been carried out previously, there was no information about the feasibility, efficacy, and safety of the therapeutic method. Randomized trial was not needed at the time of approval because patients with a severe trunk injury developing hemorrhagic shock were distributed to a facility, which could not provide high standard trauma care. Based on this background, it was justified that the rare injury is evaluated through advanced treatment with a specialized resuscitation team in a single high-volume trauma center. This report showed the feasibility of REBOA as a therapeutic strategy, which is the last resort for lethal trauma patients. However, we must be prepared for a variety of complications in the practice of REBOA. If this information reflected the realistic world of emergency

medicine, it would have been probably a fair result. On the other hand, facilities claim that the procedure of REBOA increases the risk. It is an undeniable fact that the procedure of REBOA depends on the resuscitation team and not on a single medical person. After this report, Inoue et al. reported that the result of the propensity score matched the analysis of the Japanese trauma registry data. It has been reported that there has been a serious impact on the hospital mortality [1]. Their report showed a relief that the difficulty of evaluation of MDs include the entire treatment strategy, which could not be determined by measuring only the performance of the product. In the actual resuscitation field, it is very difficult for such a progressive treatment to prove superior than the conventional method. This clinical report is a case series that proved to be the vanguard in this subject. I believe that it played an important role in the clinical evaluation of REBOA, which is the current hot topic [2].

In Chapter 3, a multicenter study of an expensive MD has been described; the treatment efficacy of this MD has not been proven yet. The history of polymyxin B-immobilized fiber hemoperfusion（PMXHP）therapy is very long and this therapy is highly popular in Japan. Unfortunately, there are only a few low-quality clinical single center reports

available for this therapy, and these clinical evaluations are biased. In view of such a past situation, I adopted a multicenter study format, with a focus on the general hospital. In addition, I had planned the study in partnership with independent clinical research centers to improve the quality of registration data, which usually had a major problem in the retrospective study. As a result, the efficacy of the PMXHP therapy with realistic world was completely negative. There have been a myriad of development of therapeutic drugs and treatments for sepsis till date. However, a potent treatment does not exist. Rapid fluid resuscitation, broad-spectrum antibiotics, and appropriate surgical drainage continue to be the main steps of sepsis treatment. Though bench data were excellent, these were not always effective in bedside. It is not necessary that PMXHP therapy is conducted only as part of the complicated septic pathology; in such cases, the clinical efficacy was not shown. Despite the observational study, it was possible to collect high-quality data from multicenters. I have proven that the medical professional-driven post-marketing study for MDs can be realized through this chapter. As these formats for post-marketing clinical trials are the most pragmatic ones, it is necessary to develop a platform that can be used with simple procedures and reasonable prices in the future.

It is obvious that the sales strategy of a MD changes over time with new improvements. Health care workers, including doctor, nurse, and technician, would begin to use a MD without a thorough understanding of the new value. This is a common problem. The performance of a MD might have become better, but the clinical effectiveness of the entire treatment compared to the conventional treatment is often unclear. Therefore, they are always confused in this regard. More than 300,000 MDs are approved in Japan, which is huge product pool. It is the responsibility of the hospital management to find the best one from this large product line.

Though economic analysis was not included in this thesis, I will proceed on the effectiveness of MD in the next step. There are many MDs that did not prove to be effective as an entire treatment in the area of emergency and critical care medicine. In particular, post-marketing study for invasive mechanical ventilator is still untouched despite being a device in critical care area. As this subject area is vast, this thesis did not have the scope to include all the clinical questions; hence, these will be considered in the future research after grasping the current situation.

In conclusion, clinical research of the post-marketing study performed in this thesis

would contribute to the safety assurance of MDs in high-risk patients with a severe condition. The fair evaluation of MDs by health care worker is sufficiently possible, and it calls for a platform with an appropriate scale to resolve a number of clinical questions in the realistic medical field.

Reference

1. Inoue, J., et al., Resuscitative endovascular balloon occlusion of the aorta might be dangerous in patients with severe torso trauma: A propensity score analysis. J Trauma Acute Care Surg, 2016. 80(4): p. 559-66; discussion 566-7.
2. Morrison, J.J., et al., A systematic review of the use of resuscitative endovascular balloon occlusion of the aorta in the management of hemorrhagic shock. J Trauma Acute Care Surg, 2016. 80(2): p. 324-34.

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