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Effects of shorter activated coagulation time on hemorrhage during venoarterial extracorporeal membrane oxygenation

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ABSTRACT

BACKGROUND

Extracorporeal membrane oxygenation (ECMO) has been used for decades, but optimal anticoagulation control remains unknown. This study aimed to compare shorter target activated coagulation time (ACT) criteria with the usual target ACT criteria in terms of complications.

METHODS

We retrospectively identified patients who received ECMO between 1 January 2013 and 31 December 2018 in an acute tertiary care hospital. Patients were divided into two groups: (I) those whose target ACT was 160–180 sec and (II) those whose target ACT was 180–220 sec. Cox proportional hazard models and Fine–Gray models adjusted for propensity score to account for the competing risk of death were used to compare the incidence of hemorrhage during ECMO between the groups.

RESULTS

We identified 74 patients, 25 of whom were managed with target ACT 160–180 sec, and 49 of whom were managed with target ACT 180–220 sec. In crude analysis, the proportions of patients with hemorrhage in the under 180-sec group were significantly more than those in the over 180-sec group [60.0% (15/25) vs. 28.6% (14/49), p = 0.009]. Shorter target ACT was not associated with hemorrhage during ECMO in either Cox regression (hazard ratio, 1.67; 95% confidence interval, 0.59–4.80; p = 0.336) or Fine–Gray model (hazard ratio, 1.58; 95% confidence interval, 0.64–3.91; p = 0.324).

CONCLUSIONS

The shorter ACT target was not associated with improved hemorrhage and inappropriate coagulation than the usual target ACT criteria. This study is the first to compare the ACT target of patients with ECMO.

KEY WORDS

Extracorporeal membrane oxygenation, activated coagulation time, monitoring anticoagulation

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INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) has been used for decades in the setting of severe cardiac and respiratory failure in the intensive care unit (ICU) [1, 2]. Because ECMO circuits are artifacts, anticoagulants are needed to prevent blood clotting. However, anticoagulants also tend to induce bleeding. Therefore, maintaining an appropriate level of anticoagulation is important. Anticoagulants such as unfractionated heparin, direct thrombin inhibitors, and nafamostat mesylate have been used during ECMO support for preventing blood clots [3, 4]. Unfractionated heparin is the current international standard anticoagulant during ECMO. However, the ideal strategy for monitoring anticoagulation is unknown [5].

The Extracorporeal Life Support Organization (ELSO) guidelines recommend that the doses of anticoagulants are controlled using activated clotting time (ACT) [1]. A previous survey investigating the current practices in anticoagulation during ECMO showed that the most preferred method for anticoagulation monitoring is the serial measurement of ACT. The most commonly reported target ACT range is 180–200 seconds [6]. A previous study reported an ACT range of 250–299 seconds during carotid stenting was associated with lower combined events (death, stroke, or acute myocardial infarction) and reduction of major bleeding events compared with an ACT range of 300–350 seconds [7]. Another study reported that the appropriate ACT for peripheral artery intervention remains unknown [8].

ELSO recommends the use of unfractionated heparin and targeting the ACT of 180–220 seconds [1]. The recommendation was made depending on limited evidence and expert opinions [9, 10]. The appropriate targeted ACT remains unknown.

This study aimed to compare two target ACT settings concerning complications: under 180 seconds and over 180 seconds.

METHODS

DATA SOURCE

This was a retrospective cohort study. We obtained patient data from electronic health records at Asahi General Hospital in Chiba Prefecture, Japan. Asahi General Hospital is an acute tertiary care hospital.

Because of the retrospective nature of the study, the need for obtaining patient consent was waived. Informed consent was obtained in the form of an opt-out option on the website.

This study was approved after the review of the institutional boards of Asahi General Hospital.

PATIENT SELECTION

We included patients aged ≥18 years who received ECMO due to cardiogenic shock in the ICU from 1 January 2013 to 31 December 2018. All patients received unfractionated heparin for anticoagulation. The ACT was measured every 3 hours and adjusted according to the dose of unfractionated heparin as per protocol. ECMO was managed in accordance with ELSO guidelines.

We excluded patients whose ACTs were not measured or whose records were incomplete. There were no patients whose source of bleeding was present at the start of ECMO. Patients that had hemorrhage were excluded.

Patients were divided into two groups: (I) Group with a target ACT of 160–180 second (the under 180-second group) and (II) Group with a target ACT of over 180–220 seconds (the over 180-second group). Because ACTs were measured using hemochron®, the appropriate ACTs recommended by the ELSO guidelines are 180–220 seconds.

BASELINE CHARACTERISTICS AND OUTCOMES

Baseline characteristics were age and sex; etiology, history of hypertension, hypercholesterolemia, and diabetes mellitus; receipt of anticoagulants, antiplatelet agents, and proton pump inhibitors; transfusion of red blood cells, fresh-frozen plasma, and platelet concentrate; use of intra-aortic balloon pumping; and receipt of continuous renal replacement therapy before the target ACTs were set.

The primary outcome was the occurrence of hemorrhage during ECMO, defined as hemorrhage caused by the introduction of ECMO, gastrointestinal bleeding, trunk bleeding (intrathoracic bleeding, intraabdominal bleeding, or retroperitoneal bleeding), airway bleeding, or intracranial hemorrhage during ECMO support. The secondary outcome was the complication by inappropriate coagulation, defined as ECMO circuit exchange due to coagulation, or thrombosis of the extremities.

STATISTICAL ANALYSIS

We generated a propensity score to adjust for individual variables [11]. We used the following variables to derive the propensity score: age, sex, etiology, history of hypertension, hypercholesterolemia, and diabetes mellitus; smoking status; use of proton pump inhibitors, H2-blockers, or antiplatelet agents; transfusion of fresh-frozen plasma, red blood cell, or platelet concentrates;

and receipt of continuous renal replacement therapy, use of intra-aortic balloon pumping.

We compared the incidence of hemorrhage between the target ACT in the under 180-second group and the target ACT in the over 180-second group using three survival analyses: log-rank test, Cox proportional hazard models adjusting for propensity score, and Fine–Gray models.

Fine–Gray models were used for determining nonfatal study outcomes to account for the competing risk of death, which is high in this population [12–14]. The absence of a violation of the proportional hazard assumption was determined using Schoenfeld residuals and found no violation of the proportional hazard assumption.

We conducted a sensitivity analysis without blood transfusions, drug administration, or any performed procedures. Subgroup analysis with or without antiplatelet therapy was conducted to determine the effect of platelet drugs.

Data of the baseline characteristics of the study population were described using proportions for categorical variables and means with SDs for continuous variables. Differences between groups were tested using the chi-square test for categorical variables and t-test for continuous variables, depending on the nature of the distribution. A P value of less than 0.05 was considered to indicate statistical significance. All analyses were performed using STATA 16.0 (STATA Corp, College Station, TX, USA).

RESULTS

We included 74 patients who received venoarterial (VA)-ECMO, including 25 patients whose target ACT was 160–180 seconds and 49 patients whose target ACT was 180–220 seconds. All patients were Japanese.

To determine the difference between target and actual ACTs, actual ACTs were calculated in both groups. The actual ACT in the under 180-second group in days 1 and 2 were 189 [interquartile range (IQR), 161–236] and 175.5 seconds (IQR: 152.7–191.7), respectively. The actual ACT in the over 180-second group in days 1 and 2 were 214.6 (IQR, 174.8–240.5) and 187.4 seconds (IQR, 168.9–203.7), respectively.

Table 1 shows patients' baseline characteristics. There were no differences between the two groups in terms of age (62.9 ± 15.8 vs. 63.4 ± 16.5), etiology (acute myocardial infarction 47% vs. 48%, arrhythmia 26% vs. 20%, heart failure 8% vs. 12%, pulmonary embolism 2% vs. 0%, myocarditis 4% vs. 8%, and others 12% vs. 12%), use of antiplatelet drugs (55% vs. 68%), use of anticoagulant drugs (12% vs. 16%), use of intra-aortic balloon pumping (86% vs. 84%), transfusion of red blood cells [92% (23/25) vs. 82% (40/49)], transfusion of fresh frozen plasma [56% (14/25) vs. 61% (30/49)], transfusion of platelet concentrates [12% (3/25) vs. 27% (13/49)], and perfusion at a temperature below 36°C by target temperature management [88% (22/25) vs. 69% (34/49)]. None of the baseline characteristics differed significantly between the groups. **Table 2** shows the number of cases in each type of bleeding and the time from ECMO induction to bleeding.

In the crude analysis, the proportions of patients with hemorrhage in the under 180-second group were significantly more than those of patients in the over 180-second group [60.0% (15/25) vs. 28.6% (14/49), p = 0.009]. The incidence of complications by inappropriate coagulation in the under 180-second group was one, and that in the over 180-second group was zero (4.0% vs. 0.0%, p = 0.472) (**Table 3**). There was no difference in mortality between the groups (84.0% vs.79.6%, p = 0.647). The log-rank test showed that there was no difference in the rate of hemorrhage between the groups (log-rank p = 0.076).

Cox regression adjusted using propensity score showed that there was no difference in the rate of hemorrhage [hazard ratio (HR), 1.67; 95% confidence interval (CI), 0.59–4.80; p = 0.336] (**Table 4**). Fine–Gray models adjusted using propensity score demonstrated that there was no difference in the rate of hemorrhage (HR, 1.58; 95% CI, 0.64–3.91; p = 0.324) (**Table 4**). There was no significant difference in the proportions of complications of hemorrhage and inappropriate coagulation between the two groups.

Sensitivity analysis without blood transfusions, drug administration, or performed procedures showed no significant differences between the two groups in either the Cox regression (HR, 1.53; 95% CI, 0.66–3.57; p = 0.474) or Fine–Gray (HR, 1.55; 95% CI, 0.70–3.43; p = 0.215) models. Furthermore, Cox analysis with antiplatelet therapy demonstrated no significant differences (HR, 0.88; 95% CI, 0.29–2.75; p = 0.83), while subgroup analysis without antiplatelet therapy demonstrated a significant difference (HR, 105.0; 95% CI, 0.39–28139.82; p = 0.03, 14 cases).

DISCUSSION

This study investigated the incidence of hemorrhage and inappropriate coagulation in patients with ECMO in the under 180-second group and the over 180-second group.

Table 1 Baseline characteristics of the study population

	ACT 160–180 sec (n = 25)	ACT 180–220 sec (n = 49)	p
Age, years (SD)	63.4 (16.5)	62.9 (15.8)	0.89
Sex (male), n (%)	20 (80.0)	34 (69.4)	0.33
Etiology, n (%)			0.91
Acute myocardial infarction	12 (48.0)	23 (46.9)	
Arrhythmia	5 (20.0)	13 (26.5)	
Heart failure	3 (12.0)	4 (8.2)	
Pulmonary Embolism	0 (0.0)	1 (2.0)	
Myocarditis	2 (8.0)	2 (4.1)	
Others	3 (12.0)	6 (12.2)	
Hypertension, n (%)	8 (32.0)	21 (42.9)	0.37
Diabetes mellitus, n (%)	10 (40.0)	25 (51.0)	0.37
Dyslipidemia, n (%)	15 (60.0)	29 (59.2)	0.95
Smoking status, n (%)	15 (45.5)	18 (24.4)	0.06
Use of proton pump inhibitors, n (%)	24 (96.0)	45 (91.8)	0.50
Use of H2 blockers, n (%)	3 (12.0)	3 (6.1)	0.38
Use of antiplatelet drugs, n (%)	17 (68.0)	27 (55.1)	0.29
Use of anticoagulant drugs, n (%)	4 (16.0)	6 (12.2)	0.66
Use of continuous renal replacement therapy, n (%)	17 (68.0)	27 (55.1)	0.29
Use of intra-aortic balloon pumping, n (%)	21 (84.0)	42 (85.7)	0.85
Transfusion of red blood cell, mL (SD)	1394 (990)	2006 (2354)	0.24
Transfusion of fresh frozen plasma, mL (SD)	1560 (1056)	1828 (2143)	0.66
Transfusion of platelet concentrates, mL (SD)	267 (115)	492 (452)	0.42

Table 2 Number of cases experiencing each bleeding type and the time from ECMO induction to bleeding

	ACT160–180 sec	ACT 180–220	Median (days)	Interquartile Range (days)
Airway bleeding, n	2	2	3.5	1–5
Trunk bleeding, n	2	2	3	1–4
Intragastric bleeding, n	5	3	1.5	1–2
Catheter insertion site bleeding, n	6	6	2	2–3
Unknown, n	0	1	1	1
Total of ACT 160–180 group	15		3	2–4
Total of ACT 180–220 group		14	2	1–2

Table 3 Statistical analysis for thrombosis of the extremities

Proportions (number of cases with thrombosis of the extremities/total number of cases)	p
4.0% (1/25) vs. 0.0% (0/49)	0.472

Table 4 Primary outcome of statistical analysis

	Hazard ratio	95% confidence interval
Main analysis		
Cox regression	1.67	0.59–4.80
Fine–Gray model	1.58	0.64–3.91
Sensitivity analysis		
Cox regression	1.53	0.66–3.57
Fine–Gray model	1.55	0.70–3.43

There was no difference in the rates of complications of hemorrhage and inappropriate coagulation.

There is no consensus on the current practices of anticoagulation during ECMO.

The ELSO guidelines recommend the target ACT of 180–220 seconds in patients with ECMO. ACT can be affected by factors such as the dose of unfractionated heparin, anemia, hypofibrinogenemia, thrombocytopenia, and other coagulation factor deficiencies because ACT can provide an accurate reflection of a patient's overall anticoagulation state [1]. However, hypothermia, hemodilution, and many factors can also affect ACT. Furthermore, in previous studies, different ACT devices have been shown to yield divergent results, and the values of ACT were highly variable [1, 15].

There was no difference in the rates of complications of inappropriate coagulation and hemorrhage in this study. The possible reason for this is the use of antiplatelet agents. There was no difference in the proportion of use of antiplatelet agents. The use of antiplatelet agents may have contributed to the incidence of hemorrhage. Subgroup analysis revealed a significant difference in the group not using antiplatelet drugs because of its small sample size.

Another possible reason is that the ACT results varied regardless of the setting of the target ACT. The difference in the target ACT between the two groups was too small to detect the effect of setting a target ACT under 180-seconds. Although the actual ACTs were not within the target range on day 1, many actual ACTs were found to be within the target range on day 2. Thus, it is possible that the small difference in target and actual ACTs between the two groups is the reason for the non-significant results. Another possible reason is the target temperature management with a perfusion temperature below 36 °C that 56 (75.7%) patients have received.

To the best of our knowledge, this is the first study to compare different ACT targets in patients with ECMO.

This study had several limitations. First, this study was single-centered. Second, there was only one case of complication of inappropriate coagulation. Third, all of the cases were VA-ECMO. It remains unknown whether the results of this study can be applied to veno-venous ECMO. Fourth, it is unknown whether the results of this study can be applied to children. Fifth, the association between the value of actual ACT and the outcomes remains unknown. Sixth, since this was an observational study, we were not able to adjust for unmeasured confounding factors. Seventh, the present study was performed only on Japanese individuals and may not be extrapolated to other races.

CONCLUSION

This study showed that the target of the ACT under 180-seconds was not associated with the reduction of bleeding (improved hemorrhage) and inappropriate coagulation compared with the target of ACT over 180-seconds. Further large studies are warranted to establish appropriate targeted ACT in ECMO.

CONFLICT OF INTEREST

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REFERENCES

1. Brogan TV, Lequier L, Lorusso R, MacLaren G, Peek G. *Extracorporeal Life Support: The ELSO Red Book 5th Edition*.
2. Bartlett RH. Esperanza: The first neonatal ECMO patient. *ASAIO J* 2017;63:832–43.
3. Lim JY, Kim JB, Choo SJ, Chung CH, Lee JW, Jung SH. Anticoagulation During Extracorporeal Membrane Oxygenation; Nafamostat Mesilate Versus Heparin. *Ann Thorac Surg* 2016;102:534–9.
4. Han W, Bok JS, Cho HJ, Yu JH, Na MH, Kang S, et al. Single-center experience of extracorporeal membrane oxygenation mainly anticoagulated with nafamostat mesilate. *J Thorac Dis* 2019;11:2861–7.
5. Murphy DA, Hockings LE, Andrews RK, Aubron C, Gardiner EE, Pellegrino VA, et al. Extracorporeal membrane oxygenation-hemostatic complications. *Transfus Med Rev* 2015;29:90–101.
6. Berkowitz I, Pronovost P. Extracorporeal Membrane Oxygenation: an International Survey. *Pediatr Crit Care Med* 2013;14:1–15.
7. Saw J, Bajzer C, Casserly IP, Exaire E, Haery G, Sachar R, et al. Evaluating the Optimal Activated Clotting Time During Carotid Artery Stenting. *Am J Cardiol* 2006;97:1657–60.
8. Doganer O, Wiersema AM, Scholtes V, Blankensteijn JD, Yeung KK, Jongkind V. No Concluding Evidence on Optimal Activated Clotting Time for Non-cardiac Arterial Procedures. *Eur J Vasc Endovasc Surg* 2020;59:137–47.
9. Lawson DS, Walczak R, Lawson AF, Shearer IR, Ing R, Schulman S, et al. North American Neonatal Extracorporeal Membrane Oxygenation (ECMO) Devices: 2002 Survey Results. *J Extra Corpor Technol* 2004;36:16–21.
10. Lawson DS, Lawson AF, Walczak R, McRobb C, McDermott P, Shearer IR, et al. North American Neonatal Extracorporeal Membrane Oxygenation (ECMO) devices and team roles: 2008 Survey results of Extracorporeal Life Support Organization (ELSO) Centers. *J Extra Corpor Technol* 2008;40:166–74.

11. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: Administrative versus clinical data. *Stat Med* 2005;24:1563–78.
12. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017;36:4391–400.
13. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* 2016;133:601–9.
14. Friedman DJ, Piccini JP, Wang T, Zheng J, Malaisrie SC, Holmes DR, et al. Association Between Left Atrial Appendage Occlusion and Readmission for Thromboembolism Among Patients With Atrial Fibrillation Undergoing Concomitant Cardiac Surgery. *JAMA* 2018;319:365–74.
15. Saifee NH, Brogan TV, McMullan DM, Yalon L, Matthews DC, Burke CR, et al. Monitoring hemostasis during extracorporeal life support. *ASAIO J* 2020;66:230–7.