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# Use of argatroban for extracorporeal life support in patients with nonheparin-induced thrombocytopenia
## Analysis of 10 consecutive patients

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**Abstract**

Unfractionated heparin (UFH) is currently the standard anticoagulant used in extracorporeal life support (ECLS). However, severe thrombocytopenia occurs frequently during ECLS use and it may be difficult to determine whether this represents heparin-induced thrombocytopenia (HIT) or not. In this case, UFH cannot be continued. Because a confirmatory laboratory test requires time, argatroban is empirically used if HIT is suspected. However, many patients are not found to have HIT. In non-HIT patients, the effectiveness and safety of argatroban are unclear. Thus, we investigated whether argatroban was safe and useful in patients who were suspected of having HIT and were started on argatroban, but were ultimately found to have non-HIT.

We retrospectively reviewed all patients on ECLS who received the anticoagulant argatroban as an alternative to UFH between January 2014 and July 2015. The pretest clinical score (4Ts) was calculated, and a score greater than 4 was considered an indication for argatroban. The target-activated clotting time or activated partial thromboplastin time was 1.5 times the patient's upper normal value. Of 191 patients on ECLS during the study period, 10 (5.2%) were treated with argatroban infusion.

No patients were found to have antiplatelet factor 4/heparin antibodies. The average maintenance dose of argatroban was 0.1 μg/kg/min. Platelet counts increased significantly following argatroban administration ($P = .02$). There were no anticoagulation-related complications such as bleeding or thrombosis.

Our results suggest that argatroban is a safe alternative to UFH for patients with non-HIT on ECLS. Argatroban may have a more significant platelet-preserving effect than UFH, regardless of whether HIT is present.

**Abbreviations:** ACT = activated clotting time, anti-Xa = anti-factor Xa assay, APACHE = Acute Physiology and Chronic Health Evaluation, aPTT = activated partial thromboplastin time, ECLS = extracorporeal life support, HIT = heparin-induced thrombocytopenia, ICU = intensive care unit, IQR = interquartile range, SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment, UFH = unfractionated heparin, VA = venoarterial, VV= venovenous.

**Keywords:** argatroban, extracorporeal life support, nonheparin-induced thrombocytopenia

## 1. Introduction

Extracorporeal life support (ECLS) is a form of mechanical heart or lung support that incorporates extracorporeal circulation. Systemic anticoagulation is used to mitigate the thrombotic complications that might occur when blood is exposed to the artificial surfaces within the ECLS circuit.[1] Although unfractionated heparin (UFH) is currently the standard anticoagulant used for ECLS, awareness of the efficacy and safety limitations of UFH is increasing. The risk of developing heparin-induced thrombocytopenia (HIT) is of particular concern.[2] When HIT is suspected, direct thrombin inhibitors can be used instead of UFH. Argatroban is a well-known direct thrombin inhibitor that has been approved as a substitute for UFH in patients with suspected or diagnosed HIT. However, many physicians do not have the experience of using direct thrombin inhibitors as alternatives to UFH. Moreover, thrombocytopenia in patients on ECLS could have multiple etiologies. In most cases, the diagnosis is not HIT. However, the efficacy of argatroban for ECLS in non-HIT patients is not well known. Thus, we investigated whether argatroban was safe and useful in patients who were suspected of having HIT and were given argatroban but were actually identified as having non-HIT.

## 2. Methods

### 2.1. Patients

This was a retrospective study of patients on ECLS who received the anticoagulant argatroban as an alternative to UFH between

January 2014 and July 2015. The pretest clinical score (4Ts) was calculated, and a score ≥4 was considered an indication for the use of argatroban.[3] Exclusion criteria for argatroban use were as follows: age <18 years, chronic thrombocytopenia, and active bleeding or severe coagulopathy. Severe coagulopathy included patients with active bleeding, for example, gastrointestinal bleeding. The final decision to switch from UFH to argatroban was made by the ECLS team with consideration of the risks and benefits. During the study period, 191 patients required ECLS at our institution. Ten patients (5.2%) with thrombocytopenia were subsequently treated with argatroban. Five patients with cardiogenic shock were on venoarterial (VA) ECLS, and 5 patients with respiratory failure were on venovenous (VV) ECLS. Causes of cardiogenic shock included dilated cardiomyopathy (n=2), myocardial infarction (n=1), severe mitral valve stenosis (n=1), and severe pulmonary hypertension (n=1). Patients on VV ECLS had primary diagnoses of bacterial pneumonia (n=1), viral pneumonia (n=3), and acute respiratory distress syndrome after lobectomy (n=1). The study was approved by the institutional review board of our institution. Individual patient consent was waived owing to the retrospective design of the study.

### 2.2. Anticoagulation and suspicion of HIT during ECLS

Our institutional guidelines for the management of anticoagulation during ECLS include a bolus of UFH (50–100 units/kg) at the time of ECLS initiation. All patients who had no contraindications received a continuous infusion of UFH. Per our institutional nomogram, UFH was titrated to achieve an activated partial thromboplastin time (aPTT) of 55 to 75 seconds or an activated clotting time (ACT) of 150 to 180 seconds. ACT was measured with a device (HEMOCHRON Response; Accriva Diagnostics, San Diego, CA). An anti-Xa (anti-factor Xa assay) was also performed to evaluate anticoagulation. Platelet count was monitored daily. A platelet count <50,000 was an indication for transfusion.

The 4Ts score was calculated whenever significant thrombocytopenia was noted. The 4Ts score is a pretest system for HIT that was developed to improve and standardize clinical diagnostics. It considers 4 typical characteristics of HIT: the level of thrombocytopenia; the timing of thrombocytopenia after heparin exposure; the presence of thrombosis or other sequelae of HIT; and the likelihood of other cause of thrombocytopenia.[3]

When the 4Ts score was ≥4, HIT was suspected. The ECLS team then made a decision on the use of an alternative anticoagulant after considering the associated risks and benefits. Heparin infusion was stopped immediately, and testing for antiplatelet factor 4/heparin antibodies was performed.[3] When HIT was completely excluded on the basis of laboratory findings and clinical examination, UFH could be restarted. Continuous argatroban infusion was then initiated without administration of a bolus and titrated according to our hospital nomogram (Table 1). After initiating the argatroban infusion, aPTT was measured every 4 hours until it reached 55 to 75 seconds.

### 2.3. Data collection and definitions

Platelet counts were collected at baseline and every day while the patients were on ECLS support. If multiple platelet counts were performed on a given day, the lowest platelet count was considered. Baseline platelet count was defined as the most recent count before admission to our center. For patients who were

transferred from another hospital, the baseline platelet count was recorded based on documentation in the transfer note, if available, or as the first platelet count on admission to our center. Recovery from thrombocytopenia was defined as a platelet count of $100,000 \, mm^{-2}$ or higher. An argatroban responder was defined as a patient with platelet recovery following thrombocytopenia.

### 2.4. Statistical analysis

Data are presented as a median with interquartile range (IQR). The Wilcoxon signed rank test was used for comparisons between baseline values and the values obtained after argatroban infusion. $P < .05$ was used to define statistical significance. Statistical analysis was performed using Stata 13.0 software for Mac (StataCorp LLC, College Station, TX).

### 3. Results

The median age of the patients was 59.5 years (IQR, 43–64 years), and there was an equal number of males and females. The median baseline platelet count was $166.5 \times 10^3 \, mm^{-2}$ (IQR, 135–244), and the median platelet count on argatroban start day was $39 \times 10^3 \, mm^{-2}$ (IQR, 25–52). Anti-Xa was checked in 6 patients, and the values were below the normal range in all cases. D-dimer was measured in 7 patients and was found to be elevated in all patients except 1. The initial Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and Simplified Acute Physiology Score (SAPS) II were 13, 25, and 62.5, respectively. Five patients (50%) with cardiogenic shock underwent VA ECLS, and 5 (50%) with respiratory failure underwent VV ECLS. In 5 patients (50%), continuous renal replacement therapy for acute kidney injury was administered simultaneously with ECLS (Table 2).

The average time to administration of argatroban after heparin use was 11.8 days. Argatroban was administered over a median of 8.5 days (IQR, 6–14). The average initial argatroban dose was 0.175 μg/kg/min (IQR, 0.1–0.2). The average maintenance argatroban dose was 0.1 μg/kg/min (IQR, 0.05–0.28).

The intensive care unit (ICU) mortality rate was 60%. Causes of death included 2 cases of pneumonia with sepsis, 2 cases of multiorgan failure, and 1 case each of pneumonia and irreversible right heart failure. The overall hospital course of the patients in this study is described in Table 3. All patients were negative for antiplatelet factor 4/heparin antibodies. In 4 patients, the platelet count was significantly increased after heparin was discontinued and argatroban infusion was initiated (responder group). While the platelet count did not change in 6 patients (nonresponder

**Table 1**

**Argatroban nomogram at Samsung Medical Center.**

| ACT | aPTT | Rate change |
|---|---|---|
| <130 | <45 | Increase rate by 0.1 μg/kg/min |
| 130–150 | 45~55 | Increase rate by 0.05 μg/kg/min |
| 150–180 | 55~75 | No change |
| 180–200 | 75~85 | Decrease rate by 0.05 μg/kg/min |
| 200–250 | 85~105 | Decrease rate by 0.1 μg/kg/min |
| >250 | > 105 | Hold and check ACT every hour until < 200 s |
| | | If ACT < 200 s, then resume infusion at 1/2 previous rate |

ACT = activated clotting time, aPTT = activated partial thromboplastin time.
*Initial dosing: 0.2 μg/kg/min.

## Table 2

**Patient demographics.**

| | Patient (N=10) | Responder (N=4) | Nonresponder (N=6) | P |
|---|---|---|---|---|
| Patient demographics | | | | |
| Age, y | 59.5 (43–64) | 63 (59.5–67.5) | 43.5 (34–62) | .08 |
| Male, n (%) | 5 (50) | 2 (40) | 3 (60) | 1.0 |
| Weight, kg | 61.5 (52–68) | 60 (48.5–66) | 63 (52–68) | .67 |
| BMI, kg/m$^2$ | 21.5 (19.5–25) | 21.75 (18.5–26.4) | 21.5 (20.4–25) | .66 |
| Platelets, $10^3$ mm$^{-2}$ | | | | |
| Baseline platelets | 166.5 (135–224) | 207 (169–299) | 139 (125–186) | .08 |
| Lowest platelets | 29.5 (21–40) | 32 (28.5–61.5) | 24.5 (14–40) | .27 |
| Platelets on day 1 of ECLS | 103.5 (75–171) | 132.5 (63–220) | 101 (75–125) | .66 |
| Platelets on argatroban start day | 39 (28–52) | 45 (38–71) | 34 (28–43) | .28 |
| Platelet transfusion (patient no.) (%) | 8 (80) | 2 (50) | 6 (100) | .13 |
| Platelet transfusion (packs) | 23 (7–44) | 3.5 (0–17.5) | 37 (18–54) | .03 |
| Comorbid condition | | | | |
| Hypertension, n (%) | 6 (60) | 3 (75) | 3 (50) | .57 |
| Diabetes, n (%) | 2 (20) | 1 (25) | 1 (17) | 1.0 |
| Cancer, n (%) | 4 (40) | 2 (50) | 2 (33) | 1.0 |
| ECLS configuration | | | | .52 |
| VA$^*$, n (%) | 5 (50) | 1 (20) | 4 (80) | |
| VV, n (%) | 5 (50) | 3 (60) | 2 (40) | |
| ECLS duration (days) | 36 (25–58) | 38 (20–76.2) | 33.5 (25–58) | .67 |
| CRRT, n (%) | 5 (50) | 1 (20) | 4 (80) | .52 |
| ISTH score (≥ 5), n (%) | 3 (30) | 1 (33) | 2 (67) | 1.0 |
| ICU scoring system | | | | |
| SOFA | 113 (8–17) | 12.5 (8.5–17) | 13 (7–17) | .83 |
| APACHE II | 25 (19–33) | 20.5 (27.5–35) | 18 (24–30) | .33 |
| SAPS II | 62.5 (55–64) | 63 (59–63.5) | 59 (32–68) | .66 |

Values are expressed as IQR, unless otherwise specified.
APACHE = Acute Physiology and Chronic Health Evaluation, BMI = body mass index, CRRT = continuous renal replacement therapy, ECLS = extracorporeal life support, ICU = intensive care unit, ISTH = International Society on Thrombosis and Hemostasis, SAPS = Simplified Acute Physiology Score, SOFA = Sequential Organ Failure Assessment, VA = venoarterial, VV = venovenous.
* VA included VV+VA.

group), a further decrease in the platelet count was not observed (Fig. 1A). Overall, platelet counts increased significantly after argatroban administration (P = .02) (Fig. 1B).

In the nonresponder group, platelet transfusion did not improve thrombocytopenia. On the contrary, in the responder group, 2 patients did not receive transfusion and 1 patient had only 1 unit of apheresis platelet transfusion on the first day of argatroban administration. Nonetheless, platelet counts were significantly elevated (Table 2).

## 4. Discussion

ECLS therapy, as well as sepsis and disseminated intravascular coagulation, are often associated with thrombocytopenia.[4] Although thrombocytopenia occurs frequently in patients with ECLS, few cases have a definitive diagnosis of HIT, and there are many cases of non-HIT thrombocytopenia. HIT is a serious complication, particularly in patients undergoing mechanical

circulatory support therapy.[5–7] Therefore, it is important to distinguish HIT from non-HIT in patients on ECLS; however, this is challenging, and a laboratory test is required in the event of any doubt.[8]

Argatroban has been approved for anticoagulation in patients with proven or suspected HIT and has been reported to improve the outcomes in patients with HIT compared with those in historical controls.[9] However, thrombocytopenia in critically ill patients is often multifactorial. The use of mechanical circulatory support can simultaneously result in thrombocytopenia and thrombosis through platelet activation and consumption, thereby mimicking the presentation of HIT.[10] A rigorous evaluation of the safety and efficacy of argatroban in patients who become thrombocytopenic while on ECLS is critical.

To date, there are only a few reports on the use of argatroban in patients on ECLS. Cornell et al[11] reported a case series of 5 patients on ECLS in which argatroban was used in place of heparin for anticoagulation. Beiderlinden et al[5] reported 9

## Table 3

**Hospital course and outcome.**

| | Patient (N=10) | Responder (N=4) | Nonresponder (N=6) | P |
|---|---|---|---|---|
| Duration of argatroban, days | 8.5 (6–14) | 13 (5–22.5) | 8.5 (6–14) | .59 |
| Argatroban median dose, μg/kg/min | 0.1 (0.05–0.28) | 0.75 (0.04–0.31) | 0.12 (0.05–0.28) | .51 |
| Major bleeding event, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| ICU mortality, n (%) | 6 (60) | 3 (75) | 3 (50) | .57 |

Values are expressed as IQR, unless otherwise specified.
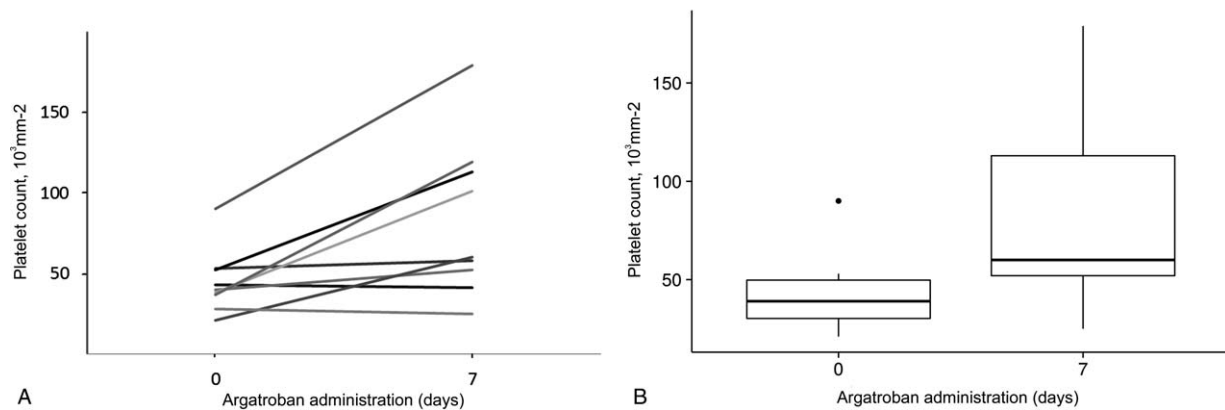ICU = intensive care unit.

**Figure 1.** Change in platelet count. Line plots (A) and box plots (B) illustrating changes in the platelet count between the start of argatroban administration and 7 days later. The y-axis represents the platelet count ($10^3$ mm$^{-2}$). Boxes represent the 25th and 75th percentiles; lines inside the boxes represent medians; whiskers represent values within the 1.5 interquartile range of the 25th and 75th percentiles; and circles represent outliers. Wilcoxon signed rank test (P = .02).

consecutive patients who were on ECLS for severe acute respiratory distress syndrome and treated with argatroban. Although both studies discuss the safety and efficacy of argatroban, they do not describe changes in the platelet count.

Our data showed that argatroban may be used safely in patients with severe thrombocytopenia while they are on ECLS. The severe thrombocytopenia was addressed without major bleeding, there was no increase in circuit thrombosis, and platelet counts increased significantly after argatroban administration. Testing for HIT was negative for all patients in this study. Although HIT is often suspected in patients on ECLS, our results suggest a very low incidence of laboratory-confirmed HIT.[12] On the contrary, platelet counts significantly increased following treatment with argatroban, which suggests its effectiveness in thrombocytopenic patients without HIT. The exact cause of severe thrombocytopenia was not clear, although sepsis or multiorgan failure was suspected. We also treated several patients with confirmed HIT using argatroban. The impact of stopping heparin and shifting to argatroban on platelet counts seemed to be quite obvious in HIT patients. This requires further study.

The initial argatroban dose used in this study ranged from 0.05 to 0.2 μg/kg/min. On average, a continuous infusion of 0.1 μg/kg/min was sufficient to maintain an aPTT of 55 to 75 seconds. A previous study reported a major bleeding event in a patient on ECLS when argatroban was administered at the manufacturer-recommended dose.[5] In the present study, we started with a lower dose (0.2 μg/kg/min) and then titrated up until a target aPTT of 55 to 75 seconds was reached. As a result, no major bleeding or circuit thrombosis occurred. Overall, we achieved a target aPTT in our patients using a lower dose than that recommended by the manufacturer, as previously reported.[5,11] In our protocol, the range of ACT (150–180 seconds) was set to be lower than the widely used range of 180 to 220 seconds. However, the acceptable range for ACT has been reported to be 160 to 250 seconds, although most guidelines narrow this range to 180 to 220 seconds. An actively bleeding patient might require this range to be lowered, which would give rise to the risk of intracircuit clot formation.

Five patients were treated concurrently with ECLS and continuous renal replacement therapy. Argatroban has a short half-life (15 minutes), and hepatic metabolism is an important consideration for patients with renal failure for whom argatroban would be suitable.[13,14]

In our study, the ICU mortality rate was 60%. Although ICU mortality was higher in the responder group (75% in the responder group and 50% in the nonresponder group), it did not significantly differ between the groups (P = .57). Furthermore, the causes of mortality were not related to thrombocytopenia or argatroban usage, and there were no major bleeding events in either group. Patients were severely ill, with an average SOFA score of 13, an APACHE II score of 25, and a SAPS of 62.5. Therefore, the anticoagulation method may not have affected the survival outcome.

Our study was limited by the small number of patients who met the criteria, which limits the applicability of our results to a general patient population. In addition, the association between increased platelet counts and the use of argatroban is not clear. Furthermore, other patient populations may require a higher or lower dose of argatroban.

Notably, in several of the 10 subjects that were studied, the platelet counts increased during the administration of treatment. Therefore, we believe that these findings support the idea that argatroban is more effective than heparin at minimizing thrombin generation.[15] In addition, the action of directly inhibiting uncontrolled thrombin generation, along with its multifactorial effects, on critically ill patients may provide further benefits apart from anticoagulation.[16]

In conclusion, argatroban can be used safely as an alternative anticoagulant in patients on ECLS with thrombocytopenia. Although no patients in this study had laboratory-confirmed HIT, their platelet counts increased significantly after argatroban administration. Large-scale prospective studies will be necessary to determine the appropriate dosing, safety profiles, and side effects of argatroban use in patients on ECLS.

## Author contributions

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## References

[1] Oliver WC. Anticoagulation and coagulation management for ECMO. Semin Cardiothorac Vasc Anesth 2009;13:154–75.

[2] Koster A, Fischer KG, Harder S, et al. The direct thrombin inhibitor argatroban: a review of its use in patients with and without HIT. Biologics 2007;1:105–12.

[3] Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759–65.

[4] Greinacher A, Selleng K. Thrombocytopenia in the intensive care unit patient. Hematology Am Soc Hematol Educ Program 2010;2010:135–43.

[5] Beiderlinden M, Treschan T, Gorlinger K, et al. Argatroban in extracorporeal membrane oxygenation. Artif Organs 2007;31:461–5.

[6] Dolch ME, Frey L, Hatz R, et al. Extracorporeal membrane oxygenation bridging to lung transplant complicated by heparin-induced thrombocytopenia. Exp Clin Transplant 2010;8:329–32.

[7] Pollak U, Yacobobich J, Tamary H, et al. Heparin-induced thrombocytopenia and extracorporeal membrane oxygenation: a case report and review of the literature. J Extra Corpor Technol 2011;43:5–12.

[8] Koster A, Sanger S, Hansen R, et al. Prevalence and persistence of heparin/platelet factor 4 antibodies in patients with heparin coated and noncoated ventricular assist devices. ASAIO J 2000;46:319–22.

[9] Lewis BE, Wallis DE, Berkowitz SD, et al. Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 2001;103:1838–43.

[10] Dewald O, Fischlein T, Vetter HO, et al. Platelet morphology in patients with mechanical circulatory support. Eur J Cardiothorac Surg 1997;12:634–41.

[11] Cornell T, Wyrick P, Fleming G, et al. A case series describing the use of argatroban in patients on extracorporeal circulation. ASAIO J 2007;53:460–3.

[12] Glick D, Dzierba AL, Abrams D, et al. Clinically suspected heparin-induced thrombocytopenia during extracorporeal membrane oxygenation. J Crit Care 2015;30:1190–4.

[13] Di Nisio M, Middeldorp S, Buller HR. Direct thrombin inhibitors. N Engl J Med 2005;353:1028–40.

[14] Murray PT, Reddy BV, Grossman EJ, et al. A prospective comparison of three argatroban treatment regimens during hemodialysis in end-stage renal disease. Kidney Int 2004;66:2446–53.

[15] Young G, Yonekawa KE, Nakagawa P, et al. Argatroban as an alternative to heparin in extracorporeal membrane oxygenation circuits. Perfusion 2004;19:283–8.

[16] Coughlin MA, Bartlett RH. Anticoagulation for extracorporeal life support: direct thrombin inhibitors and heparin. ASAIO J 2015;61:652–5.