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Safety and utility of increased doses of Nadroparin during Extracorporeal Membrane Oxygenation in Respiratory Failure

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Abstract

Introduction and Objective. Continuous monitoring of coagulation is essential during venovenous Extracorporeal Membrane Oxygenation (VV ECMO) therapy because the extracorporeal circuit can activate the coagulation system and may lead to clot formation or bleeding. Various anticoagulant agents are used for this purpose, and unfractionated heparin is considered the gold standard of anticoagulant therapy. The biocompatibility of the extracorporeal circuit also allows antithrombotic treatment with low molecular weight heparins (LMWHs) administered subcutaneously (s.c.). There is increasing evidence that the use of LMWHs produces identical therapeutic effects with fewer side-effects. Our primary aim was to compare thrombotic complications and bleeding events.

Materials and Method. The study evaluated the safety and efficacy of anticoagulation with single-dose nadroparin administered s.c., compared with a twice daily regime of this LMWH during ECMO therapy in patients with severe respiratory failure treated in an intensive care unit (ICU). Changes in flow resistance in the oxygenator and the number of transfused blood products were monitored. No differences were found in bleeding events between once and twice-daily dosing of nadroparin during ECMO therapy (34% vs. 53%, p = 12).

Results. Both regimes of administration were similar in the number of life-threatening bleeding events (p =.26) and a daily number of transfused red blood cells (p =.37). The change in flow resistance in the oxygenator was comparable between the two groups (11.28% vs. 6.13%, respectively, p = .26).

Conclusions. Once daily administration of nadroparin appeared comparable to the twice daily regime in terms of the number of thrombotic complications.

Key words

anticoagulation, nadroparin, extracorporeal oxygenation

INTRODUCTION

Venovenous extracorporeal membrane oxygenation (VV-ECMO) serves as a form of rescue therapy for patients with acute respiratory distress syndrome (ARDS) whose condition has not improved after mechanical ventilation [1, 2]. ECMO therapy requires constant management of coagulation to prevent thrombotic complications associated with extracorporeal blood flow in the oxygenator and in the circuit[3, 4]. Extracorporeal Life Support Organisation (ELSO) guidelines recommend unfractionated heparin (UFH) as the first choice therapy in the management of coagulation during ECMO [5], but haemorrhagic sequelae remain one of the more frequent complications of the therapy [6, 7]. Occasionally, severe bleeding localized in the lungs or the central nervous system may lead to a fatal outcome [8].

Thus, unfractionated heparin (UFH) requires periodically assessment of the activated partial thromboplastin time (APTT) or the activated clotting time. Unfortunately, these measurements must be performed several times a day. However, the safety and utility of alternatives to UFH anticoagulation during ECMO, including argatroban and low-molecular-weight heparins (LMWHs), are being investigated [9, 10]. Several studies have elucidated the pharmacokinetics of LMWHs in the population of critically ill patients, and concluded that regular thromboprophylaxis may be suboptimal [11, 12].

A recent study on the pharmacokinetics of nadroparin in the various stages of respiratory failure found that only an increased dose of nadroparin given twice daily during ECMO therapy could ensure an adequate level of thromboprophylaxis [9]. Following that rationale, the aim of the study was to assess the safety and feasibility of an increased dose of nadroparin anticoagulation during ECMO therapy in the population of end-stage respiratory failure.

MATERIALS AND METHOD

Patients and data collection. This was an observational, single-centre study in patients supported with VV-ECMO. The data were collected from April 2023 – May 2023 from the First University Hospital in Lublin, eastern Poland. Two intensive care specialists made the decision to initiate ECMO therapy. Prior to treatment therapy, the patients had to meet specific criteria. The study targeted adult patients diagnosed with severe ARDS. The partial pressure of oxygen (PaO2) to the fraction of inspired oxygen (FiO2) ratio (PFR) is a key parameter used to assess the severity of hypoxaemia in ARDS. A PFR below 80 indicates severe

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hypoxaemia and is one of the conditions for qualifying for VV ECMO therapy. Patients eligible for VV-ECMO had demonstrated resistance to conventional treatments, including mechanical ventilation. The eligibility criteria include the consideration of a potentially reversible cause for the respiratory failure. Patients were eligible for VV-ECMO if the duration of mechanical ventilation did not exceed 10 days. The study included 31 consecutive adult patients; 20 were anti-coagulated with single-dose nadroparin (0.6 ml -5700 international units (IU)) s.c. once daily and 11 with double-dose nadroparin (0.6 ml – 5,700 IU) twice daily s.c.

Consent for the study was approved by the Ethics Committee of the Medical University of Lublin (Approval No. K.E.0254/38/2018). The study was retrospective, anonymous and descriptive, therefore consent from individual patients could be waived. It was also ensured that individual patient data remained confidential and cannot be identified in the study results.

Single-dose LMWH. Patients in this group received a single s.c. dose of nadroparin (GlaxoSmithKline Pharmaceuticals, Poznań, Poland) with the dosage specified as 5,700 International Units (IU) once daily.

Twice-daily LMWH. Patients in this group received a s.c dose of nadroparin, with the dosage specified as 5,700 International Units (IU), administered every 12 hours.

ECMO Therapy. The patients were managed using a protective ventilation, characterized by a tidal volume of 4–6 ml/kg. This approach aims to minimize ventilator-induced lung injury and is often associated with a lower tidal volume to prevent over-distension of the lungs. The aim of protective ventilation was to achieve normocapnia or mild hypercapnia. Patients were sedated, and the decision to use neuromuscular blocking agents (NMBAs) was made by the attending physician. The ECMO parameters, including blood flow in the ECMO circuit and sweep gas flow, were adjusted to achieve specific blood gas targets. The aims included maintaining a partial pressure of oxygen (PaO2) greater than 70 mm Hg, and a partial pressure of carbon dioxide (paCO2) less than 45 mm Hg. The specified blood gas targets are indicative of the desired oxygenation and ventilation levels in patients supported by ECMO. These targets are critical for ensuring adequate gas exchange and supporting the patient's respiratory needs. Normothermia refers to maintaining body temperature within a normal range, usually around 37 °C. Therefore a heat exchanger is commonly used during ECMO therapy.

Patients supported by ECMO therapy received standard ICU care, which included fluid administration, sedation, vasopressors, blood products, antibiotics, and continuous nutritional therapy provided through enteral or parenteral nutrition, depending on the patient's condition and nutritional tolerance. In patients who developed renal failure requiring continuous renal replacement therapy, UHF was not used, a regional citrate infusion was substituted in both groups.

VV ECMO weaning is a stepwise process designed to assess a patient's ability to maintain adequate oxygenation and ventilation without ECMO support. This process occurs by slowly reducing the blood flow in the circuit to a minimum value of 3.5 L/min to prevent oxygenator thrombosis. The Lublin hospital in the study has a practice of not making planned changes to the oxygenator or pump head; only circuit components are replaced when faults are detected. In the presented case, pump replacement was indicated when blood flow dropped below 2 L/min for reasons other than cannula kinking or hypovolaemia. The indication for replacing the oxygenator was a decrease in the patient's oxygenation (PaO_2 below 60 mm Hg and PFR after oxygenation below 200).

Extracorporeal system. Appropriate catheters were used to connect the patient to the ECMO circuit. Most often, these were two single-lumen HLS catheters (15–25 Fr) covered with Bioline material, which improve the biocompatibility of the catheter, reduces the risk of clot formation and increases compatibility with the patient's blood. An Avalon dual-lumen catheter (24–27 Fr) was also used to connect the patient to the ECMO circuit. (Catheters manufactured by Maquet Cardiopulmonary GmbH in Rastatt, Germany). Both types of catheters were connected to a polymethylpentene oxygenator in which extracorporeal gas exchange took place (X Lung Kit, Xenios, Heilbronn, Germany; HLS Set Advanced, Maquet Cardiopulmonary GmbH, Rastatt, Germany). A centrifugal pump was used to generate blood flow within the ECMO circuit. The ILA Novalung (Xenios AG, Heilbronn, Germany) and Maquet consoles were used to regulate ECMO therapy. Blood flow in the ECMO circuit was regulated in the range of 3.5–6.0 L/min., determined based on clinical indications and the decision of the attending physician. The blood flow rate is adjusted based on the patient's needs, clinical condition and response to treatment.

Outcomes. The primary aim of the study was to compare haemorrhagic and thrombotic complications during ECMO treatment The definition of thromboembolic complications includes two main elements: acute peripheral thrombosis and a change in flow resistance in the oxygenator. Monitoring changes in flow resistance helps clinicians assess the integrity and functionality of the ECMO circuit and detect potential thrombotic complications that may impact circuit function and patient outcomes. The intensivists in the hospital checked the oxygenator for clot formations twice a day. Flow resistance in the oxygenator is defined as the pressure drop across the oxygenator divided by the flow in the extracorporeal circuit. These measurements were recorded every six hours. It has been proven that increasing flow resistance in the oxygenator in the ECMO circuit is directly correlated with the occurrence of thrombosis[13].

Bleeding complications were recorded as the number of bleeds (including those life-threatening), the amount of blood products transfused, serum haemoglobin levels after ECMO completion, and platelet counts during the first sevendays of ECMO. The ELSO definition was used to define life-thretening bleeding [5]. The presence of bleeding was assessed twice daily. The study compared the first seven days of ECMO support, which is the median duration of therapy, in the group treated with nadroparin in a single dose, and in the group receiving nodraparin twice daily. The end of follow-up was defined as the patient's death or discharge from the ICU.

Statistical analysis. Continuous data were presented as medians and interquartile ranges. The Mann-Whitney U test and Kruskal-Wallis ANOVA were used for these variables. Proportions and categorical data with the Chi2 test were analyzed. The statistical tests were two-sided, and $p < .05$ was considered significant. Microsoft Excel (Redmond, WA) was

used for data collection and Statistica 13.1 software (StatSoft, Tulsa, OK) for statistical analysis.

RESULTS

Study population. The baseline characteristics of both study groups are presented in Table 1. There was no difference in terms of age between the group that received a single daily dose of nadroparin and the group that received extended anticoagulation (53 vs. 43, $p = .26$); BMI (34.5 vs. 35.0, $p = 0.85$), haemoglobin level (10.95 mg/dL vs. 10.2 mg/dL, $p = .19$), or sequential organ failure assessment (SOFA) score (10 vs. 8, $p = .12$), respectively.

ECMO therapy duration was non-significantly longer in the twice daily nadroparin group than in the once daily group (8.0 [6.5–18.0] vs. 6.5 [5.0–8.5], respectively ($p = .2$). The most common diagnosis at admission in the group that received the extended nadroparin dose was viral pneumonia, whereas bacterial and viral pneumonia were the most common diagnoses equally in the single nadroparin dose group.

Table 1. General demographic data Variables are reported as medians [interquartile range]. The distribution of variables was similar in both treatment groups

	Single-dose nadroparin, 5,700 IU s.c.(n = 20)	Twice daily nadroparin, 11,400 IU s.c.(n = 11)	*p*
Age (years)	53 [44–65]	43 [37–56]	.26
Female gender n(%)	5 (25)	5 (45)	.24
BMI	34.5 [25.2–41.5]	35 [28.9–41.0]	.85
SOFA score at ECMO initiation	10 [8.5–10.5]	8 [8–10]	.12
Lactate level at ECMO initiation (ng/dl)	1.45 [1.0–1.7]	1.1 [0.8–1.8]	.368
Haemoglobin level at ECMO initiation (mg/dl)	10.95 [10.0–12.4]	10.2 [10.6–14.6]	.19
ECMO duration (days)	7 [5.0–8.5]	8 [6–18]	.19

BMI:body mass index; ECMO:extracorporeal membrane oxygenation support; ICU:intensive care unit; RBC:red blood cells; s.c –subcutaneous injection

Table 2. Comparison of outcomes between patients receiving single-dose nadroparin and those receiving twice daily nadroparin during extracorporeal oxygenation. Variables are reported as medians [interquartile range] unless otherwise noted. The number of transfused units is presented per therapy without evaluation of the duration of the ECMO therapy. Haemoglobin concentration at the termination of ECMO and number of RBC and PC units transfused per therapy were similar in both groups

	Single-dose nadroparin, 5,700 IU s.c.(n = 20)	Twice daily nadroparin, 11,400 IU s.c.(n = 11)	*p*
No. of acute thrombotic events (n [%])	0	1 (9)	NA
Change in resistance to flow in the oxygenator during treatment from day 1 – 7 (%)	11.28	6.13	.42
No. of bleeding events (n) [%])	9 (45)	7 (63)	.27
No. of life-threatening bleeding events (n) [%])	0	1 (9)	NA
Haemoglobin level after ECMO (mg/dl)	11 [10.2–12.0]	10.2 [8.5–12.3]	0
Transfused RBC units (n)[IQR]	5.5 [3.0–8.5]	4.0 [2–8]	.37
Transfused PC units (n) [min–max])	0 [0–7]	0 [0–8]	.08
Transfused FFP units (n) [min–max])	0 [0–3]	0[0–4]	.54

ECMO – extracorporeal membrane oxygenation; FFP – fresh-frozen plasma; RBC – red blood cells; PC – platelets concentrate; s.c – subcutaneous injection; IQR – interquartile range

Bleeding and thrombotic complications. Both administration regimens were similar in terms of the number of life-threatening bleeding events (p = .26) and the number of red blood cells transfused per day (p = .37). Haemoglobin concentration at the end of ECMO support was similar (single dose of nadroparin 11mg/dl vs. 10.2mg/dl nadroparin twice a daily). The most common sites of bleeding were the oral cavity and the site of cannula implantation. However, the bleeding was not life-threatening. There was no difference in the number of platelet units transfused during ECMO therapy (p=.54). Comparison was made of APTT between the study groups and found no significant differences between them (Fig. 2).

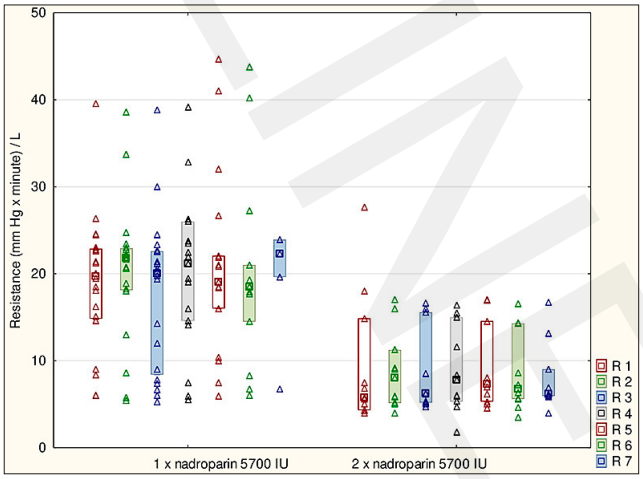

Figure 1. Daily resistance to flow across the oxygenator (R) in patients receiving nadroparin in once vs. twice daily doses during 7 days of EMCO. Resistance to flow in the oxygenator is defined as pressure difference across the oxygenator divided by flow in the ECMO circuit ([mm Hg ×minute]/L) for the two groups.
Resistance values are presented as medians (empty squares) with interquartile ranges (boxes). Empty triangles denote individual patient resistance results. Empty circles denote outliers. Distribution of variables was significantly different in both groups (p<.0001; Kruskal-Wallis ANOVA)

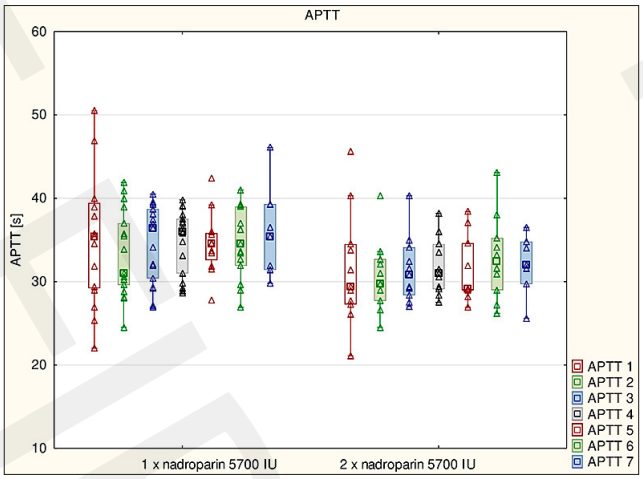

Figure 2. Comparison of daily APTT between patients receiving nadroparin in once vs.twice daily doses during 7 days of extracorporeal oxygenation. No differences were observed in median APTT values between the 2 groups during the 7 days of ECMO (p =0.24; Kruskal-Wallis ANOVA).
APTT values are presented as medians (empty squares); interquartile ranges – boxes; empty triangles – individual patient APTT results; empty circles – outliers

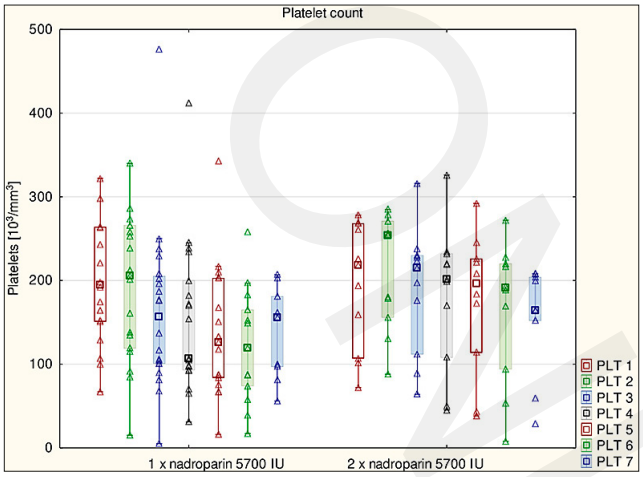

Figure 3. Comparison of daily platelet count between patients receiving nadroparin in once vs. twice daily doses during 7 days of extracorporeal oxygenation. No differences were observed in median platelet count between the two groups during the 7 days of ECMO (p= 0.4; Kruskal-Wallis ANOVA).
Platelet count values are presented as medians – empty squares; interquartile ranges – boxes. Empty triangles – individual patient platelet results; empty circles – outliers

The change in flow resistance in the oxygenator was comparable in both groups (11.28% vs. 6.13%, respectively (p = 0.26).

DISCUSSION

This study found that throughout the therapy the increased frequency of nadroparin administration did not significantly affect the number of transfused PRBC and fresh frozen plasma units The mean flow resistance in the oxygenator was significantly lowered in the twice-daily nadroparin group.

Why alternatives to unfractionated heparin? UFH remains the gold standard of anti-coagulation during ECMO [5]. The target APTT for UFH infusion is 60–80 s. However, bleeding complications, which are the most common adverse effect of ECMO therapy, are proportional to increased APTT, and in the literature are associated with an estimated prevalence of 40% [7]. The most serious bleeding is intracranial haemorrhage, present in 4.5% of cases. According to Nunez et al., the presence of any bleeding event increases the risk of death compared to experiencing any thrombotic event during ECMO therapy [7]. Additionally, the risk of bleeding and thrombosis in patients undergoing ECMO therapy is increased by age, higher weight, higher pH at initiation and lower PFR [8]. Bleeding events were observed in the twice-daily nadroprine group, and one major bleeding site in 63% of cases. There was also one case of distal thrombosis (9%) in the group with a double daily dose of nadroparin.

Single-dose nadroparin studies. Increasing attention is being paid to the use of LMWH as an antithrombotic agent during ECMO therapy, but there are few scientific studies on its use. Krueger concludes that using a single dose of LMWH does not increase the number of thrombotic complications and reduces the amount of bleeding in patients during ECMO therapy[14]. In a study comparing UHF and LMWH for anti-coagulation during ECMO therapy, no differences were found in the occurrence of clotting in the ECMO circuit (2.8% vs. 12.5%, respectively; p =.13) [9].

A single dose of nadroparin was also used in a group of patients undergoing EMCO as a bridging to lung transplantation [15]. No statistically significant differences were observed in the number of bleedings (22.7% in the UFH group vs. 12.5% in the LMWH group, p = .31), but the researchers report a lower rate of thromboembolic events in the LMWH group (0.3 [±0.6]) (p = .03). than in the UFH group (0.9 [±1.2]). The use of LMWH preparations allows for an easy route of administration, and ensures effective anti-coagulation when using extracorporeal techniques [9].

Elevated LMWH studies. A single prophylactic dose of LMWH may be insufficient however, to prevent thromboembolic complications and clotting in the extracorporeal circuit in the critically ill population [16, 17]. During the Covid-19 pandemic, the prevalence of thromboembolic complications in ICU patients was as high as 49% [16]. Moreover, the peak anti-Xa level, regarded by many as the best marker for the goal-directed dosing of LMWH, did not reach the target level after regular thromboprophylactic dosing in a population of critically ill patients [17]. The authors of a study of the population pharmacokinetics of nadroparin in critically ill Covid-19 patients indicate that, due to changes in absorption, volume of distribution and clearance, appropriate peak anti-Xa levels were achievable only by either increasing the nadroparin dose or administering it more frequently [18]. Thus, the present study compared a single s.c. dose of administered once daily with a 5,700 IU dose twice daily, and found that the change in resistance to flow throughout the therapy did not differ between the groups. No significant changes were observed in the number of clotting events or number of bleedings in the two groups.

The presented results correspond with those of Circelli et al., who introduced three times daily dosing 5,000 IU of LMWH during ECMO therapy, and found that the bleeding (including severe) and thrombosis rates were unchanged in comparison to the previous approach [19]. The peak level of anti-Xa was measured after each dose. Moreover, the authors conclude that their new approach to ECMO anti-coagulation may simplify ECMO management, reduce the staff workload during massive outbreaks of critical respiratory failure, and possibly expand ECMO capacity [19].

Limitations of the study. The limitations of the present study include its small sample size and retrospective design, which may increase the chance of selection and observational bias. No routine anti-Xa level monitoring were performed in the historical matched cohort. Due to financial limitations, no routine screenings were performed for the presence of early signs of deep vein thrombosis in the ultrasound examination and thromboelastography essays.

CONCLUSIONS

Extended s.c. nadroparin anti-coagulation administered twice daily during ECMO may be safe in terms of bleeding complications compared to regular nadroparin thromboprophylaxis. An increased nadroparin dose may decrease the median resistance to flow in the oxygenator in comparison to a single dose, but the relative change in the resistance to flow throughout the therapy may not be

influenced by the anticoagulant dose. Further prospective studies are needed to elucidate the present findings.

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