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Intravascular Volume Administration: A Contributing Risk Factor for Intracranial Hemorrhage During Extracorporeal Membrane Oxygenation?

Amerik C. de Mol, MD, Luella C. Gerrits, MD, Arno F. J. van Heijst, MD, PhD, Huub Straatman, MSc, Frans H. J. M. van der Staak, MD, PhD, Kian D. Liem, MD, PhD

ABSTRACT

OBJECTIVE. The objective of this study was to determine the relationship between the frequency and total volume of intravascular volume administration and the development of intracranial hemorrhage during venoarterial extracorporeal membrane oxygenation.

METHODS. In a retrospective, matched, case-control study, 24 newborns who developed an intracranial hemorrhage during venoarterial extracorporeal membrane oxygenation treatment were compared with 40 control subjects. Both groups were analyzed for gestational age, gender, race, Apgar scores at 1 and 5 minutes, birth weight, cardiopulmonary resuscitation before venoarterial extracorporeal membrane oxygenation, age at the start of treatment, duration of treatment, worst arterial blood gas sample preceding treatment, activated clotting time values, need for platelet transfusions, mean blood pressure, and the use of inotropics and steroids before the treatment. For both groups, total number and volume of intravascular infusions of normal saline, pasteurized plasma protein solution, erythrocytes, and platelets during the first 24 hours of treatment were determined. Variables were analyzed in their relationship to intracranial hemorrhage by using univariate and multivariate conditional logistic regression.

RESULTS. The only statistically significant difference in patient characteristics between the case patients and control subjects was arterial blood gas values. Newborns who developed intracranial hemorrhage during the treatment received both a statistically significantly higher number and a statistically significantly higher total volume of intravascular volume administrations compared with control patients. After adjustment for pH, PaCO₂, and Pao₂ in the multivariate analysis, we found a significant relation between the development of intracranial hemorrhage and >8 infusions or >300 mL of volume infusion in the first 8 hours and >10 infusions in the first 24 hours of treatment.

CONCLUSIONS. The number and total volume of intravascular volume administration in the first 8 and 24 hours of venoarterial extracorporeal membrane oxygenation treatment are statistically significantly related to the development of intracranial hemorrhage.

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Key Words: extracorporeal membrane oxygenation, intracranial hemorrhage, volume administration

Abbreviations: va-ECMO—venoarterial extracorporeal membrane oxygenation
ICH—intracranial hemorrhage
ACT—activated clotting time
CT—computed tomography
CPR—cardiopulmonary resuscitation
OR—odds ratio
CI—confidence interval

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Since Bartlett and colleagues in 1976 treated the first newborn successfully with venoarterial extracorporeal membrane oxygenation (va-ECMO), ECMO has become a rescue therapy for neonates with severe but potentially reversible respiratory failure when maximal conventional therapy has failed. Without ECMO, the mortality rate is high. More than 22 000 neonates have been treated with ECMO, 15 000 of whom were treated with va-ECMO, with an overall survival rate of 80%. Although ECMO has increased survival, the occurrence of hemorrhagic and ischemic cerebral lesions, resulting in future neurologic and neurodevelopmental dysfunction, are major complications. Imaging studies revealed intracranial hemorrhage (ICH) or ischemic abnormalities in 10 up to even 52% of the patients. The cause of ICH during va-ECMO treatment is probably multifactorial and might be
determined by pre-ECMO– as well as ECMO-related events or conditions. Optimizing neurologic outcome remains 1 of the priorities in ECMO research. The population at greatest risk for ICH, however, is not clearly defined. Hardart et al11,12 determined gestational age, postconceptional age, acidosis, sepsis, coagulopathy, and treatment with epinephrine as independent factors associated with ICH in neonates who were treated with ECMO. A study by Dela Cruz et al13 demonstrated that an elevated activated clotting time (ACT) and low platelet counts that required transfusion were statistically associated with an increase in the development of ICH. Hirthler et al14 reviewed that instability of ACT and platelet counts that required transfusion were statistically associated with ICH in neonates who were treated with ECMO. The ECMO circuit itself consisted of a custom-packed ¼-in flexible polyvinylchloride tubing (Baxter, Uden, Netherlands) with a silicone reservoir, the bladderbox (Seabrook Medical System, Værløse, Denmark), a 0.6-m² membrane oxygenator (Scimed Life Systems, Minneapolis, MN), a heat exchanger (Cincinnati Sub Zero, Cincinnati, OH), and a roller pump (Polystan A/S, Copenhagen, Denmark).

A loading dose of heparin was given before cannulation to achieve an ACT of >300 seconds. After this, heparinization was checked every hour by measurement of the ACT aiming for values between 200 and 220 seconds (Hemo-chron). During the course of ECMO, platelet transfusions were given to maintain a platelet count >80,000/mm³. Erythrocyte transfusions were given to maintain a hemoglobin level >8.0 mmol/L and a hematocrit value >0.40 L/L. Hemoglobin level and platelet count were determined every 4 hours. Normal saline (NaCl 0.9%) and pasteurized plasma protein solution (albumin 3.8%) were used to restore the ECMO flow after bladderbox alarms caused by insufficient blood drainage from the right atrium.

Cerebral ultrasound imaging through the anterior fontanel (Philips HDI-3000, Ultrasound, Inc, Bothell, WA) was performed daily to check for ICH. Images were interpreted by the neonatologist and the pediatric neuroradiologist. After cannulation, CT or MRI was performed on all patients and analyzed by the neuroradiologists.

To check the matching procedure and possible differences between the case patients and the control subjects, both groups were analyzed for gestational age, gender, race, Apgar scores at 1 and 5 minutes, birth weight, cardiopulmonary resuscitation (CPR) before ECMO, age at the start of ECMO, duration of ECMO treatment, survival, worst arterial blood gas sample in the 6 hours preceding ECMO, number and volume of required thrombocyte transfusions, ACT value after the loading dose at the start of ECMO, mean of ACT and mean blood pressure values as well as the coefficient of variation for ACT and mean blood pressure during the first 8 and 24 hours of ECMO, and the use of inotropics (dopamine, dobutamine, epinephrine, norepinephrine) and steroids before the start of ECMO.

To investigate the relationship between intravascular volume administration and the occurrence of ICH, we analyzed the number and volume of intravascular infusions of normal saline, pasteurized plasma protein solution, erythrocytes, and platelets during the first 8 and 24 hours of ECMO treatment. Data were collected from the international Extracorporeal Life Support Organization forms, patient files, and patient medical checklists in which physiologic parameters, laboratory results, and ACT values were written down every hour and all volume administrations are registered.

Statistical analysis was performed by using SPSS 13.0 (SPSS Inc, Chicago, IL). Patient characteristics were an-
ECMO treatment could be matched with 1 or 2 control subjects, and age at the start of ECMO.

In the first 24 hours of ECMO treatment, the mean SD for PaCO2 was 45.8 ± 13.9 mm Hg, and for PaO2, it was 108.3 ± 54.4 mm Hg. The mean SD for pH was 7.33 ± 0.13.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate Analysis, OR (95% CI)</th>
<th>Multivariate Analysis, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH ≤ 7.3 worst arterial gas</td>
<td>OR = 4.5, 95% CI 1.4–14.0</td>
<td>---</td>
</tr>
<tr>
<td>PaCO2 ≥ 45 mm Hg worst arterial gas</td>
<td>OR = 3.3, 95% CI 1.0–10.9</td>
<td>---</td>
</tr>
<tr>
<td>PaO2 ≥ 50 mm Hg worst arterial gas</td>
<td>OR = 5.3, 95% CI 1.5–19.0</td>
<td>---</td>
</tr>
<tr>
<td>Every 100 mL of volume, first 8 h</td>
<td>OR = 1.1 (1.0–1.2)</td>
<td>1.0 (1.0–1.6)</td>
</tr>
<tr>
<td>Every single infusion, first 8 h</td>
<td>OR = 1.2 (1.0–1.5)</td>
<td>1.3 (1.0–1.6)</td>
</tr>
<tr>
<td>Every 8 infusions, first 8 h</td>
<td>OR = 1.3 (1.0–1.6)</td>
<td>1.6 (1.0–2.4)</td>
</tr>
<tr>
<td>Every 100 mL of volume, first 24 h</td>
<td>OR = 1.1 (1.0–1.3)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Every single infusion, first 24 h</td>
<td>OR = 1.0 (1.0–1.3)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
<tr>
<td>Every 10 infusions, first 24 h</td>
<td>OR = 1.1 (1.0–1.3)</td>
<td>1.2 (1.0–1.4)</td>
</tr>
</tbody>
</table>

Results are given for the univariate analysis (adjustment for pH, PaCO2, and PaO2) and for the first 24 and 24 hours of the treatment with va-ECMO. NS indicates not statistically significant.

RESULTS

All 24 newborns who developed an ICH during va-ECMO treatment could be matched with 1 or 2 control subjects, and age at the start of ECMO.

In the univariate analysis, we performed a univariate logistic regression. ORs and 95% confidence intervals (CIs) were further used in the multivariate conditional logistic regression. The predictors of ICH were selected by forward stepwise adding the variables with a p value <.05.

The results of the univariate and multivariate analysis are presented in Table 2. In the multivariate analysis, the following variables were included: pH, PaCO2, PaO2, gender, and the number of infusions and total volume of intravascular infusion in the first 8 and 24 hours of ECMO treatment. The results are given as ORs and 95% CIs.

Table 1 shows the characteristics of the newborns who developed ICH during the treatment and the newborns without ICH. The newborns with ICH were matched with newborns without ICH based on gestational age, birth weight, and survival at 24 hours. The differences in the characteristics were not significant.

At dichotomization, we found the following statistically significant ORs: for pH ≤ 7.3, PaCO2 ≥ 45 mm Hg, and PaO2 ≥ 50 mm Hg. These parameters were further used in the multivariate conditional logistic regression.

The first 24 cases of ICH were diagnosed by cerebral ultrasound during va-ECMO, and 6 were diagnosed by CT or MRI. Of these 24 cases of ICH, 18 were diagnosed by cerebral ultrasound. Of these 24 cases of ICH, 18 were diagnosed by cerebral ultrasound during va-ECMO, and 6 were diagnosed by CT or MRI. Of the 18 cases of ICH diagnosed by cerebral ultrasound, 8 (44%) were diagnosed within 24 hours after the start of va-ECMO and 14 (78%) within 72 hours. Also, for other than the matching variables, we found no statistically significant differences in patient characteristics, except for pH and survival.

The next to these characteristics, we found no statistically significant differences in ACT values, platelet requirement, blood pressures, the use of inotropics and steroids, or race of the patients.

At dichotomization, we found the following statistically significant values in the univariate conditional logistic regression for the worst arterial blood gas samples in the 6 hours preceding the ECMO treatment in relation to the development of ICH: pH ≤ 7.3, PaCO2 ≥ 45 mm Hg, and PaO2 ≤ 50 mm Hg. These parameters were further used in the multivariate conditional logistic regression.

Single infusions of intravascular volume administration ranged from 20 to 50 mL. In Fig 1, it is shown that the newborns who developed ICH during the treatment with va-ECMO had received both a statistically significantly higher number and a statistically significantly higher number and a statistically significantly
higher total volume of intravascular volume administrations during the first 8 and 24 hours of the treatment with va-ECMO, compared with the matched control patients. Statistically, there was a significant increase in the risk for ICH for every extra infusion in the first 8 and 24 hours of treatment with va-ECMO. This was also true for every 100 mL of extra volume administration in the first 8 and 24 hours (Table 2). After dichotomization and adjustment for pH, PaCO2, and PaO2 in the multivariate conditional regression, we found the following conditions to be significantly related to the development of ICH during the va-ECMO treatment: >8 infusions or >300 mL of intravascular infusion in the first 8 hours of va-ECMO and >10 infusions in the first 24 hours of va-ECMO. An overview of ORs and 95% CIs for the univariate and multivariate analysis is shown in Table 2.

In the univariate analysis, CPR, gestational age, and age at the start of ECMO did not seem to be significant risk factors for the development of ICH. ORs and CIs were 2.0 (0.4–9.0), 0.4 (0.1–1.4), and 1.0 (0.9–1.0), respectively. When these terms were used in a straight multivariate conditional regression, data found for volume administration, as shown in Table 2, were still statistically significant.

**DISCUSSION**

Because ICH is one of the most devastating complications of ECMO, it is of ongoing importance to identify patients who are most at risk and eliminate risk factors as much as possible. This matched case-control study is the first to describe a statistically significant relationship between the total number and volume of intravascular volume infusions and the development of ICH during the treatment with va-ECMO. We found that neonates who received >8 infusions or >300 mL of volume infusion during the first 8 hours or >10 infusions during the first 24 hours of va-ECMO were statistically significantly more at risk to develop an ICH. We stress that this relationship does not have to be necessarily causal. A hypothetical explanation, however, might be found in disturbances of cerebral hemodynamics caused by the infusions of intravascular volume administration and/or the often preceding bladderbox alarms with consecutive acute interruption of the roller pump resulting in interruption of blood flow to the patient. In normal, healthy situations, cerebral autoregulation maintains the cerebral blood flow over a wide range of cerebral perfusion pressures with a contraregulation response occurring with a delay of 2 seconds after sudden changes in blood pressure. It has been shown, however, that autoregulation is disturbed in severely ill term infants. Additionally studies of newborn lambs showed that prolonged hypoxia and/or the ECMO treatment itself will significantly disturb the autoregulation; therefore, frequent interruption of the roller pump, followed by infusion of intravascular volume administration, may result in frequent fluctuations in cerebral blood flow, a known risk factor for ICH. Besides this, possible disturbances in cerebral blood flow at bladderbox alarms might be too acute to be compensated for by the autoregulation system, even if not disturbed. The combination of most bladderbox alarms and intravascular volume infusion in the first 24 hours and disturbed autoregulation may be a part of the explanation of why most ICHs occur in the first few days of the ECMO treatment; however, another explanation of the relationship found in this study might be that the pathologic process that leads to ICH also causes the inadequate venous drainage to the ECMO circuit, which in turn leads to the need for volume administration.

Birth weight and gestational age were not significantly different between the ICH group and the group without ICH, which suggests that the matching procedure was successfully performed. The significant relationship between pH, PaCO2, and PaO2 and ICH found in this study confirms the findings of previous studies. Confirmation of acidosis by using lactate as other variable was not possible, because this was not always routinely determined.

In contradiction to the study of Dela Cruz et al, ACT levels, analyzed for the first 8 and 24 hours between case patients and control subjects, were not significantly different. Instability of ACT during the ECMO treatment was described by Hirthler et al but not further confirmed in this study, neither by the mean ACT nor by the coefficient of variation of the ACT. Because the exact time of ICH occurrence is not known, instability of ACT could be a risk factor as well as a consequence of the ICH. This could also be the question for possible differences in platelet counts. In all our patients, case patients and
control subjects, platelet counts were kept strictly above 80,000/mm³. Platelet requirement was slightly higher in the group of patients who developed an ICH, which seems to fit with the previous studies described. In our study, however, this was not statistically significant. We did not find a statistically significant difference in the use of epinephrine, as was found in the study by Hardart et al., or in the use of other inotropic medication or steroids before the ECMO treatment used to treat hypotension.

Although any confounding factor is not completely excluded, we think that this matched case-control study shows an important relationship between intravascular volume administration and the development of ICH. The results of this study can be translated to clinical practice. Any newborn who is treated with va-ECMO and requires high amounts or number of intravascular volume administration should alert the ECMO team. Because of the increased chance of ICH, more frequent neurologic assessment and cerebral ultrasounds are recommended to detect any ICH in an early stage and if possible avoid extension of the hemorrhage.

Additional prospective studies, as currently initiated in our ECMO center, are required to analyze the mechanisms by which volume administration and/or the often preceding bladderbox alarms are related to the development of ICH. Knowledge of these mechanisms may be useful for the development of strategies to reduce the risk for ICH during the va-ECMO treatment, such as how to react on bladderbox alarms and whether it might be indicated to be cautious with intravascular volume administration.

CONCLUSIONS
To our knowledge, this is the first study to show a statistically significant relationship between the total amount and number of intravascular volume administration and the development of ICH during va-ECMO treatment. Additional studies are needed to investigate the pathophysiologic mechanisms of this relationship.

REFERENCES
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