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ARTICLE

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

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What's Known on This Subject

ICH is the most devastating complication of ECMO. There is a continuous search for risk or predicting factors. There are no previous data about volume administration and ICH during ECMO.

What This Study Adds

To our knowledge, this is the first study to find a statistically significant relationship between intravascular volume administration and the occurrence of ICH during ECMO.

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, $Paco_2$, and Pao_2 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. *Pediatrics* 2008;121:e1599–e1603

SINCE BARTLETT AND colleagues in 1976 treated the first newborn successfully with venoarterial extracorporeal membrane oxygenation (va-ECMO),[1] 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.[2,3] 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%.[4] Although ECMO has increased survival, the occurrence of hemorrhagic and ischemic cerebral lesions, resulting in future neurologic and neurodevelopmental dysfunction, are major complications.[5,6] Imaging studies revealed intracranial hemorrhage (ICH) or ischemic abnormalities in 10 up to even 52% of the patients.[7–9] 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.[10] 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 al[11,12] 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 al[13] 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 al[14] reviewed that instability of ACT and platelet count are early predictors of ICH. Finally, lactate before ECMO treatment was found to be a useful marker for the development of ICH during ECMO.[15]

Especially during the first days of ECMO, intravascular volume administration is regularly required. One reason is the occurrence of bladderbox alarms, as a sign of inadequate venous drainage from the right atrium to maintain the required flow of the ECMO system, which is aimed to realize adequate oxygenation of the patient. In a reaction, volume administration is often given when other causes of bladderbox alarms are ruled out. Next to this anemia or thrombocytopenia are reasons to add volume with blood products. From our clinical experience, we had the impression that neonates who required frequent volume administration during the first days of the va-ECMO treatment developed ICH more frequently. The objective of this study was to investigate whether there is a relationship between intravascular volume administration and the occurrence of ICH in the neonate during treatment with va-ECMO.

METHODS

From September 1989 through November 2005, 236 newborns (64% boys, 36% girls) were treated with va-ECMO at the Radboud University Nijmegen Medical Centre. Overall survival rate was 77%, and ICH occurred in 25 (11%) patients. All patients with ICH were analyzed to participate in a matched case-control study. One patient was excluded because of congenital abnormality of the heart, so 24 patients with ICH were included in the study. ICH was diagnosed by cerebral ultrasound, performed daily during the ECMO treatment (n[r] = 18), by computed tomography (CT), or by MRI in the period directly after decannulation (n = 6). The 24 newborns who developed an ICH related to va-ECMO treatment (case patients) were matched with 40 patients who did not develop ICH (control subjects). Each pair of 1 case patient and 1 or 2 control subjects was matched for diagnosis, gestational age (±1 week), and birth weight (±500 g). For statistical reasons, we aimed for 2 control subjects for each case patient. When >2 possible candidates were available, the patients whose dates of birth were closest to that of the case patient were selected as control subjects. Newborns were excluded from the study when there were congenital abnormalities other than congenital diaphragmatic hernia; a second ECMO treatment, ICH before the initiation of ECMO; or coagulation disorders as screened for by the determination of prothrombin time, activated partial thromboplastin time, and platelet count. Cerebral ultrasound, none of them showing ICH, was performed for all patients, case patients and control subjects, before the ECMO treatment. Before the initiation of ECMO, informed consent from the parents was obtained, and all case patients and control subjects met institutional criteria for ECMO treatment, which did not change during the study period. All patients were treated with va-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 (Hemochron). 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 neurologist. After decannulation, 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-

TABLE 1 Patient Characteristics of Newborns With ICH (Case Patients) and Newborns Without ICH (Control Subjects) During ECMO Treatment

Characteristic	Case Patients ($n = 24$)		Control Subjects ($n = 40$)		P
	Mean	SD	Mean	SD	
Birth weight, kg	3.3	0.5	3.3	0.5	.79
Gestational age, wk	38	3	39	2	.64
Age at start of ECMO, h	35	30	53	64	.20
Duration of ECMO, h	155	76	171	81	.43
Apgar at 1 min, median	6.0	2.6	6.1	2.5	.94
Apgar at 5 min, median	7.0	2.0	7.1	2.1	.82
pH	7.23	0.15	7.33	0.15	.01
$Paco_2$, mm Hg	45.8	13.9	42.7	16.7	.46
Pao_2, mm Hg	48.1	29.6	53.7	19.1	.36
Gender, male/female	17/7	28/12	—	—	0.93
CPR before ECMO	3/24	3/40	—	—	0.51
Survival	11/24	32/40	—	—	<0.01
No. of platelet T24	2.1	1.2	1.6	1.2	.64
Volume of platelet T24, mL	85	48	67	48	.18
Loading ACT	399	136	397	161	.96
ACT, first 8 h	276	35	266	54	.42
ACT, first 24 h	258	34	246	34	.19
CV ACT, first 8 h	0.17	0.09	0.15	0.09	.41
CV ACT, first 24 h	0.15	0.07	0.15	0.10	.75
Mean MAP, first 8 h	53	10	56	7	.24
Mean MAP, first 24 h	52	8	53	7	.63
CV MAP, first 8 h	0.13	0.06	0.14	0.06	.60
CV MAP, first 24 h	0.13	0.07	0.15	0.06	0.42
Use of steroids	3/24	5/40	—	—	0.82
Use of inotropics	21/24	38/40	—	—	0.31

Number and volume of platelet T24 = number and total volumes (mL) of platelet transfusions to keep platelet counts at >80 000/mm³ in the first 24 hours of ECMO. Inotropics used were dopamine, dobutamine, epinephrine, and norepinephrine. CV indicates coefficient of variation; MAP, mean arterial blood pressure.

TABLE 2 ORs and CIs for the Relation Between pH, $Paco_2$, Pao_2, and the Number and Total Volume of Intravascular Infusion in the First 8 and 24 Hours of ECMO Treatment and the Development of ICH

Parameter	Univariate Analysis, OR (95% CI)	Multivariate Analysis, OR (95% CI)	P
pH ≤7.3 worst arterial gas	4.5 (1.4–14.0)	—	—
$Paco_2$ ≥45 mm Hg worst arterial gas	3.3 (1.0–10.9)	—	—
Pao_2 ≤50 mm Hg worst arterial gas	5.3 (1.5–19.0)	—	—
Every 100 mL of volume, first 8 h	1.5 (1.1–2.2)	1.6 (1.0–2.6)	.06
≥300 mL, first 8 h	6.3 (1.4–29.1)	10.0 (1.9–83.5)	.03
Every single infusion, first 8 h	1.2 (1.0–1.5)	1.3 (1.0–1.6)	.04
≥8 infusions, first 8 h	13.6 (1.7–106.3)	26.0 (1.6–430.2)	.02
Every 100 mL of volume, first 24 h	1.4 (1.1–1.8)	1.6 (1.0–2.4)	.04
≥400 mL, first 24 h	5.7 (1.3–25.6)	6.4 (0.5–77.1)	NS
Every single infusion, first 24 h	1.1 (1.0–1.3)	1.2 (1.0–1.4)	.04
≥10 infusions, first 24 h	3.6 (1.1–11.2)	8.5 (1.2–59.2)	.03

Results are given for the univariate analysis and the multivariate analysis (adjustment for pH, $Paco_2$, and Pao_2 mentioned) for the first 8 and 24 hours of the treatment with va-ECMO. NS indicates not statistically significant.

alyzed by Student's *t* tests for comparison of means ($P <$ .05) and χ^2 tests ($P <$ .05) for dichotomized characteristics. Univariate and multivariate testing of variables in their relation to ICH was performed by use of conditional logistic regression. For several variables, the cutoff points for which dichotomization of the variable leads to a statistically significant odds ratio (OR) at univariate analysis were determined by stepwise changing the segregation value for dichotomization. Steps were 0.1 for pH, 5 mm Hg for $Paco_2$ and Pao_2, 100 mL for the volume of infusions, and 1 for the number of infusions. Variables that were found to have a significant relationship with the development of ICH in the univariate analysis were further used in the multivariate conditional logistic regression. ORs and 95% confidence intervals (CIs) were determined. Because CPR, gestational age, and age at the start of ECMO are generally considered to be important in their relation to ICH, we performed a univariate as well as a multivariate analysis for these terms. In the latter, the outcome for volume administration was corrected for each separate parameter, CPR, gestational age, and age at the start of ECMO.

RESULTS

All 24 newborns who developed an ICH during va-ECMO treatment could be matched with 1 or 2 control patients with the same primary diagnosis. Primary diagnoses for the case patients in this study were as follows: congenital diaphragmatic hernia in 8 (33%), sepsis in 8 (33%), meconium aspiration syndrome in 5 (21%), and primary pulmonary hypertension in 3 (13%). The other matching parameters used (gestational age and birth weight) were not significantly different between the case patients and control subjects (Table 1). Maximum time span between a case patient and his or her control subject(s) was 8 months. In this study, we found the following types of ICH: parenchymal in 10 (42%), intraventricular in 9 (38%), subependymal in 3 (13%), petechial in 1 (4%), and in the posterior fossa in 1 (4%). Of these 24 cases of ICH, 18 were diagnosed by cerebral ultrasound during va-ECMO and 6 were diagnosed by either CT or MRI after decannulation. Of the 18 cases of ICH on cerebral ultrasound, 8 (44%) were demonstrated 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 (Table 1). Next to these characteristics, we found no 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, $Paco_2$ ≥45 mm Hg, and Pao_2 ≤50 mm Hg (Table 2). 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

FIGURE 1

Total number and volume of intravascular volume infusions in the first 8 and 24 hours between patients with and without ICH during the treatment with ECMO. [a] $P = .03$; [b] $P = .005$; [c] $P = .04$.
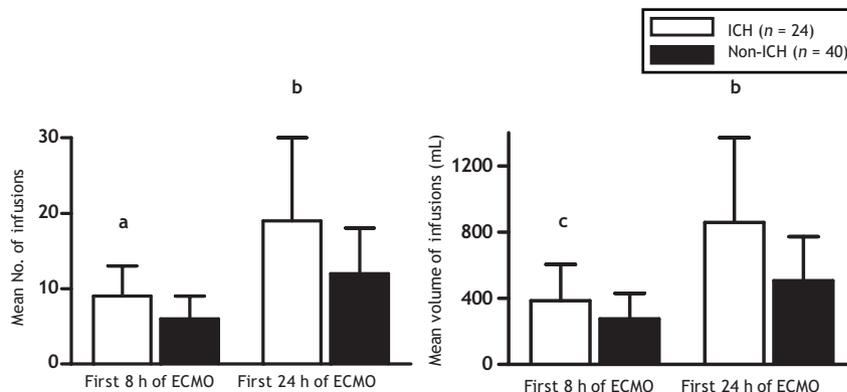
higher total volume of intravascular volume administrations during the first 8 and 24 hours of the treatment with va-ECMO, compared with the matched control patients. Statistically, there was a significant increase in the risk for ICH for every extra infusion in the first 8 and 24 hours of treatment 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, $Paco_2$, and Pao_2 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 significant 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.[16–19] Additionally studies of newborn lambs showed that prolonged hypoxia and/or the ECMO treatment itself will significantly disturb the autoregulation[20–23]; 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, $Paco_2$, and Pao_2 and ICH found in this study confirms the findings of previous studies.[12,13,15] 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,[13] 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[14] 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,[12] 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.

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