Surgical Repair of Congenital Diaphragmatic Hernia During Extracorporeal Membrane Oxygenation: Hemorrhagic Complications and the Effect of Tranexamic Acid

By F.H.J. van der Staak, A.F.J. de Haan, W.B. Geven, and C. Festen
Nijmegen, The Netherlands

Extracorporeal membrane oxygenation (ECMO) was incorporated in a strategy of delayed repair of congenital diaphragmatic hernia (CDH) and was used for preoperative stabilization in patients who were unresponsive to maximal conventional treatment. If ECMO was required for preoperative stabilization the diaphragmatic defect was repaired while the patient was on ECMO. In the early experience with this approach all patients suffered from bleeding complications. Therefore, we adopted the use of antifibrinolytic therapy with tranexamic acid (TEA) during and immediately after CDH repair on ECMO. The efficacy of TEA was studied in an unblinded study using historical controls by comparing the postoperative blood loss and the transfusion requirements of red blood cells (RBC) in patient groups treated without (n = 9) and with TEA (n = 10). Patients who received TEA had significantly less bleeding at the surgical site than patients not receiving TEA (57 vs 390 mL, P = .005) and had significantly lower RBC transfusion requirements than patients not receiving TEA (1.13 vs 2.95 mL/kg/h, P = .03). In the very first two patients of the TEA group we encountered fairly severe thrombotic complications. TEA may have contributed to those complications. Based on the authors' experience they conclude: (1) TEA is effective in reducing postoperative bleeding, hemorrhagic complications, and RBC transfusion requirements associated with CDH repair on ECMO. (2) TEA may be responsible for thrombotic complications. (3) The appropriate, empirically established, dosage and administration patterns of TEA for CDH repair during ECMO seem to be one bolus of 4 mg/kg TEA intravenously 30 minutes before the anticipated CDH repair and a continuous infusion of 1 mg/kg/h TEA during the 24 hours after CDH repair.

Copyright © 1997 by W.B. Saunders Company

INDEX WORDS: Congenital diaphragmatic hernia, extracorporeal membrane oxygenation, bleeding complications, tranexamic acid.

Since extracorporeal membrane oxygenation (ECMO) became available in our institution in January 1991, ECMO was incorporated in a protocol of preoperative stabilization and delayed repair for congenital diaphragmatic hernia (CDH). If ECMO was necessary for preoperative stabilization, surgical repair of the diaphragmatic defect was performed while the patient was on ECMO at the end of the ECMO-run. In the early experiences with this approach significant postoperative bleeding complications were encountered at the surgical site. In all first six patients—who form part of this study—bleeding complications occurred, requiring 455 to 1215 mL red blood cells (RBC; mean, 850 mL). Four of the six patients were forcefully weaned from ECMO because of the hemorrhage, and three of these four died of recurrent pulmonary hypertension.

Wilson et al were the first who described the effect of an antifibrinolytic agent on hemorrhagic complications during ECMO. They administered e-aminocaproic acid (EACA) to 42 patients who were considered to be at high risk for bleeding complications (such as anticipated surgical procedures, preexisting intracranial hemorrhage [ICH] or profound hypoxia), starting just before or after cannulation until decannulation. Compared with 68 patients not receiving EACA, the patients who received EACA had significantly less bleeding while on ECMO and required fewer blood transfusions. This difference was most significant in the congenital diaphragmatic hernia and cardiac subgroups. The incidence of ICH in the neonatal subgroup was also significantly reduced in the EACA group. These investigators advocated the use of EACA for all patients who were thought to be at risk for hemorrhagic complications on ECMO.

Therefore we adopted the use of an antifibrinolytic agent as advocated by Wilson et al. Since January 1993 we administered tranexamic acid (TEA) during and after CDH-repair on ECMO. In this report our experience with hemorrhagic and thrombotic complications in CDH repair during ECMO is presented, and the effect of TEA is evaluated.

MATERIALS AND METHODS

Since January 1991, 20 high-risk CDH patients needed ECMO support for preoperative stabilization in our institution. In all patients veno-arterial ECMO was used as described by Bartlett et al. During the ECMO run heparin was titrated to maintain the activated clotting time (ACT) at levels of 200 to 220 seconds with ECMO-flow rates higher than 250 mL/min. ACTs were monitored at the bedside using the Hemochron (International Technidyne Corp, Edison, NJ). At lower ECMO flow rates higher ACT levels were maintained (for example, ACT levels of 240 to 250 seconds at ECMO flows of 50 to 200 mL/min). ACT goals were not different in any one of the groups. Thrombocytes were administered to maintain their count above the level of 80 X 10^9/L pre-CDH repair and above 100 X 10^9/L during and after CTX repair. The ACT was monitored every hour, and the platelet...
counts were determined every 8 hours. RBCs were routinely transfused
to maintain the hematocrit greater than 40% and the hemoglobin
concentration above 8.0 mmol/L. CDH repair was performed at the end
of the ECMO run if the patient was weanable from ECMO and the
ECMO flow could be decreased to 50 mL/min.

During surgery we avoided major dissections and incidental proce-
dures, and we used running sutures to close the defect. If the defect was
too large for primary closure a prosthetic patch (Gore-tex soft tissue
patch) was used. Fibrin glue was spread on the suture line at the end of
the repair. During and directly after surgical repair we tried to preclude
major bleeding complications by running high ECMO flows, which
allow relatively low ACTs (180 to 200 seconds). This strategy was
the same during the whole study period. The surgical procedure has
been founded on a long-lasting experience, did not undergo a fundamen-
tal change, and was performed by the most experienced surgeon in the
first group and by several surgeons in the second group.

Nineteen patients underwent elective repair while on ECMO. In one
patient ECMO was stopped because of a severe intracranial hemorrhage
day 1 of ECMO, and she died. The patients were divided into 2
groups. Group 1 consisted of 9 patients who underwent repair without
the use of TEA (1991 to 1992) and group 2 contained 10 patients who
received TEA (1993 to 1995). The median intra- and postoperative blood loss
in group 1 was significantly more than in

RESULTS

Both groups were comparable with respect to birth-
weight, age at institution of ECMO, side of the defect,
patch repair, and the time of CDH repair during ECMO
(Table 1). Only for the duration of the ECMO run was there a significant
difference between both groups. Seven of the nine group 1 patients (78%) and 9 of the 10 group 2
patients (90%) had a left-sided defect. Patch repair was
accomplished in 16 patients: 8 from group 1 (89%) and 8 from group 2 (80%).

Hemorrhagic complications led to a forced discontinuation of ECMO support in five of the nine patients of
group 1—in one patient even after heparinization had
been stopped. Four of the five patients who were removed
earlier from ECMO because of bleeding died of rebound
pulmonary hypertension. One patient in each group
required an abdominal reexploration because of hemorrhage. There were four patients with thrombotic complica-
tions (two in each group). The thrombotic patient complications consisted of an upper caval vein thrombo-
sis centered around a central venous line placed immediately after ECMO, at the time of decannulation, via
the internal jugular vein. These complications seemed to be more severe in the first two patients of group 2. A
chyllothorax developed in both patients, which lasted for
several weeks despite special MCT formulas and even complete discontinuation of enteral feeding. In one
patient of group 1 the obstructed venous return may have led to a hydrocephalus. In addition, in two cases of group
2 there were clots in the circuit. The survival rate for

definitions of RBC between both groups is statistically

DISCUSSION

Hemorrhage is the major complication in neonates
during ECMO. Among all Extracorporeal Life Support
Organization (ELSO) registry patients treated by ECMO
hemorrhagic complications occurred in 21%. In CDH
patients treated by ECMO the overall incidence of
bleeding complications appears to be 43% (209 of 483)
including a 24% (117 of 483) incidence of operative site
bleeding. Repair of the hernia defect while on ECMO
may increase the risk of bleeding complications up to
58% to 60%. Our initial experience—reflected in group
1 of this study—is consistent with these reported rates:
six of the first 10 CDH patients treated by ECMO had
severe hemorrhage (intracranial, 1; surgical site, 5). Hemorrhagic complications are a hallmark of poor out-
come. A statistically significant difference in bleeding
complications has been found between surviving and nonsurviving CDH patients who needed ECMO support. The reported incidence of fatal hemorrhage is 4% to 5%. However, this rate is probably higher because any hemorrhagic complication may force the patient to be removed from ECMO earlier, and the immediate cause of death would be classified as pulmonary failure rather than hemorrhagic. We only can confirm this experience because all patients who died in this series had major hemorrhagic complications.

So far we repair CDH on ECMO late in the ECMO course when the patient had been shown to be weanable from ECMO. In this concept, a recurrence of persistent pulmonary hypertension of the newborn (PPHN), elicited by the surgical procedure and the consequently diminished thoracic compliance, can be controlled by ECMO.
Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 9)</th>
<th>Group 2 (n = 10)</th>
<th>Wilcoxon’s Rank Sum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3,200 (2,880, 3,660)</td>
<td>3,060 (2,700, 4,050)</td>
<td>.96</td>
</tr>
<tr>
<td>Age at ECMO (h)</td>
<td>25 (18, 27)</td>
<td>18 (16, 28)</td>
<td>.68</td>
</tr>
<tr>
<td>Duration of ECMO (h)</td>
<td>181 (150, 217)</td>
<td>130 (110, 167)</td>
<td>.02</td>
</tr>
<tr>
<td>Time of CDH repair (ECMO h)</td>
<td>108 (87, 143)</td>
<td>92 (67, 110)</td>
<td>.15</td>
</tr>
</tbody>
</table>

NOTE. The median values are stated with the 25% and 75% percentiles for all variables.

whereas ECMO could be withdrawn soon in case of hemorrhagic complications.

Adhering to our strategy, in which the benefits of perioperative ECMO support have to be outweighed by the risks of hemorrhagic complications, it seemed to be important to diminish the chance of those complications. Initially it was thought that bleeding complications during ECMO were caused by the anticoagulation. Undoubtedly heparinization is an important, but certainly not the only, factor in the occurrence of hemorrhage. It is known from the cardiopulmonary bypass (CPB) surgery, that fibrinolysis is a cause of postoperative bleeding and that the fibrinolytic activity increased immediately after CPB had begun and remained elevated throughout the period of extracorporeal circulation (ECC). So, the increased fibrinolytic activity seems to be caused by ECC itself. Fibrinolysis is believed to play a role in the increased hemorrhage tendency in patients who require extracorporeal life support (ECLS) as well.

The increased fibrinolysis during ECC and ECLS is possibly caused by an imbalance between tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI), two of the major components regulating fibrinolysis (Fig 3). McVeen et al. found a marked elevation of both PAI activity and TPA antigen in pre-ECMO infants experiencing respiratory distress. After institution of ECLS there is a rapid reduction of PAI activity within 24 hours, whereas TPA levels appear to remain more elevated and decline more gradually during ECMO treatment. This imbalance may cause an increased risk for hemorrhage. Therefore, antifibrinolytic therapy represents a pharmacological modality to reduce hemorrhagic complications on ECMO.

Drugs used to inhibit fibrinolysis during and after CPB surgery are epsilon-aminocaproic acid (EACA), TEA and aprotinin. TEA and TPA inhibit fibrinolysis by binding to the lysine binding sites of plasminogen and plasmin, which are the binding sites for fibrin (Fig 3). In this manner they blocked the fibrin breakdown by plasmin. The affinity of TEA for plasminogen is much stronger than EACA, so that TEA is 6 to 10 times as potent as EACA. Moreover TEA also competitively inhibits the activation of enterokinase. EACA has been adopted for use in neonatal ECLS patients by Wilson et al. Because EACA was not registered in the Netherlands, we choose TEA instead of EACA. Because the optimal dosage of TEA for neonates on ECMO is not known, we tried to determine the dosage and the means of administration on the basis of the report of Horrow et al. about TEA. The recommended dosage by the manufacturer and the dosage of EACA used by Wilson (taking into consideration the greater efficacy of TEA) gave us guidelines for the dosing scheme.

Patients who received TEA perioperatively had significantly less blood loss while on ECMO than the patients who did not receive TEA (Wilcoxon’s rank sum, P = .005). Similarly the transfusion requirements of RBC were significantly less in the TEA-treated group (Wilcoxon’s rank sum, P = .003). No patients in the TEA-treated group had to be withdrawn early from ECMO support because of major bleeding. The survival rate for group 2 was much higher (100% vs 56%). The improved survival in group 2 may be attributed to the decreased occurrence of severe hemorrhages.

Those data may reflect the possibility that antifibrinolytic therapy has played a role in the diminution of bleeding complications and the improved survival. However, these results may be attributed as well to the increased experience of the whole ECMO team. Because this is an unblinded study with historical controls, it is...
more difficult to unravel the influence of the gained experience on the one hand and the influence of TEA on the other hand on the improved results. It can be supposed that less blood loss and less RBC requirement can be explained by a better and more well-balanced anticoagulation management in the second group as a result of learning over time.

To investigate the effect of the learning curve, the RBC requirements were studied in all other ECMO patients (CDH excepted) in the same time frames as group 1 and 2 CDH patients were treated. In the first episode (1991 to 1992) the median RBC requirement during ECMO was 0.66 mL/kg/h of ECMO versus 0.75 mL/kg/h in the second episode (1993 to 1995, $P = .27$). This observation does not suggest a big alteration in ECMO handling caused by the learning curve.

With respect to the operative technique there was no fundamental change in the surgical approach with the advent of ECMO. This technique has been rooted in a more than 20-year surgical experience with CDH repair. So it is hard to believe that a learning curve or a big alteration in the operative procedure is responsible for the bleeding complications in the early part of this study (group 1 CDH patients).

Although the validity of this study may be a point of debate because of the use of historical controls, the following points can be made: (1) The preoperative RBC requirements in CDH patients on ECMO in both episodes (0.83 mL/kg/h in group 1 and 0.96 mL/kg/h in group 2) were comparable to the RBC requirements in all other indications in both episodes (0.66 mL/kg/h and 0.75 mL/kg/h, respectively). (2) The postoperative RBC requirements after CDH repair on ECMO in the second episode (group 2, 1.13 mL/kg/h) were comparable to the RBC requirements in the pre-CDH repair episodes (0.83 to 0.96 mL/kg/h) and in all other ECMO indications (0.66 to 0.75 mL/kg/h). (3) The postoperative RBC requirements after CDH repair on ECMO in the first period (group 1 without the use of TEA, 2.96 mL/kg/h) differed significantly from the requirements in the second period (group 2 with the use of TEA, 1.13 mL/kg/h) ($P = .03$). (4) The surgical procedure was well established over years and did not change with the introduction of ECMO or during the study period. Therefore it may be concluded that TEA is effective in controlling bleeding complications and in reducing RBC transfusion requirements.

Although thrombotic complications are to be expected with the use of TEA, the reports concerning antifibrinolytic therapy during and after CPB surgery did not show an increase in those complications. To study rather severe thrombotic complications were encountered in the first two patients treated with TEA. Right atrial and superior caval vein (SCV) thrombosis developed on an SCV syndrome and a long-lasting chylothorax. It was unclear whether these complications of central venous line thrombosis several days after ECMO were caused by TEA because we experienced the similar complications previously in two patients of group 1 who did not receive TEA. In addition those complications have been reported as well after ECMO without the use of antifibrinolytic therapy, and thrombosis around an indwelling central venous line is a fairly known complication in neonates. However, meeting these problems and noting fatal thrombotic complications by the use of antifibrinolytic therapy, we decided to adapt the dosage and the administration of TEA. Since that alteration, neither severe hemorrhages nor severe thrombotic complications were observed.

This study demonstrates that TEA is effective in reducing postoperative blood loss and hemorrhagic complications associated with CDH repair on ECMO. It also reflects the possibility that TEA may be responsible for severe thrombotic complications. Empirically, based on our experience, the appropriate dosage and administration pattern of TEA for CDH repair during ECMO seem to be one bolus of 4 mg/kg TEA intravenously 30 minutes before the anticipated CDH repair and a continuous infusion of 1 mg/kg/h TEA during the 24 hours after CDH repair.

REFERENCES