Experimental Medicine

The Role of Ultrafiltration with Whole Blood Replacement in Reducing the Adverse Cardiopulmonary Effects of Sepsis in Swine Model

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ABSTRACT

Objectives: The purpose of this study was to evaluate the effect of ultrafiltration in reducing the negative impact of sepsis on cardiovascular function, and to determine whether the replacement of the ultrafiltrate with whole blood provides beneficial mediators that may have been removed during the ultrafiltration process.

Design: Despite recent advances in medicine, patients who develop serious infections frequently die. This is a result of the infections, the products they produce and the alterations the infection causes in other organs. One postulate to help treat these infections is by "cleaning" the blood through the use of a filter. While this has been utilized in other diseases, it has not been used for patients with infections. In addition, replacing the fluid with whole blood may even be better in reversing the infection process.

Setting: This study was conducted at the Duke University Medical Center, Durham, North Carolina, USA.

Methods: Twenty-three swine (10-20 kg) models were randomized to one of three groups. The first group consisted of inducing sepsis without ultrafiltration to determine the spontaneous time course of the model. The second group consisted of inducing sepsis, followed by ultrafiltration and volume replacement with normal saline. The third group consisted of inducing sepsis, followed by ultrafiltration and volume replacement with whole blood.

Results: There were no noticeable improvements in any of the cardiorespiratory variables studied after ultrafiltration with either normal saline or whole blood replacement.

Conclusion: The data obtained from this project will allow us to develop new techniques that will help patients with these serious infections.

KEY WORDS: immunomodulator, sepsis, ultrafiltration, whole blood

INTRODUCTION

Sepsis is a multi-faceted disease process, which results in multi-organ injury and dysfunction. These injuries are mediated through different mechanisms; the most important being harmful immunomodulators, including cytokines and interleukins, which are released during the infectious disease process[1]. Despite recent advances in the understanding of the pathophysiology of sepsis and its management, the mortality and morbidity still remain high. Recently, the management of sepsis has been directed towards the modulation of the host inflammatory response by inhibiting the release of the harmful mediators or antagonizing their effects[2,3]. Very preliminary data has shown that the removal of these mediators by ultrafiltration may reduce the deleterious effects of sepsis on cardiopulmonary function[4,5]. However, these beneficial effects may be significantly limited as ultrafiltration also removes immune mediators with beneficial protective effects. If ultrafiltration would preferentially remove the harmful mediators from the circulation, improved cardiac and pulmonary function should result.

METHODS

This study consisted of 23 swine (10-20 kg) randomized to one of three groups. The first group (control group, n = 9) consisted of those with induced sepsis, but without ultrafiltration to determine the spontaneous time course of the model.

The second group (n = 6) consisted of those with induced sepsis, followed by ultrafiltration and volume replacement with normal saline. The third group (n = 8) consisted of those with induced sepsis, followed by ultrafiltration and volume replacement with whole blood.

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The surgical procedures and animal care were in compliance with the guidelines established by the National Institutes of Health and the Institutional Animal Care and Use Committee of Duke University Medical Center.

Animal preparation included premedication with ketamine 22 mg/kg IM and acepromazine 1.1 mg/kg IM. After the above premedication had been given, an intravenous catheter was placed into an ear vein for additional anesthesia (fentanyl 100 μg/kg) prior to beginning the procedure. The trachea was then intubated, and the animal placed on a Siemens SV300 ventilator (Siemens-Elema, Solno, Sweden). The FiO_2 was maintained at 1.0. Throughout the procedure, the animal was maintained on a fentanyl citrate continuous infusion (50 mg/250ml D_5W, 1 ml/kg/hr) and given IV boluses of pentothal (5 mg/kg) to maintain an appropriate degree of anesthesia and analgesia.

A femoral arterial catheter was placed under direct visualization for systemic pressure monitoring and blood withdrawal for blood gas analysis. A large bore intravenous catheter was placed in the femoral vein for administration of fluids and medications. A median sternotomy was performed and the heart placed in a pericardial cradle. An ultrasonic flow probe was placed around the pulmonary artery. Millar pressure catheters were inserted in the right ventricle, pulmonary artery outflow tract, and left atrium. Ultrasonic dimension transducers were sutured on the heart in standard fashion to obtain cardiac dimensions in order to calculate ventricular contractility.

After baseline data were obtained, each animal had sepsis induced. *E. Coli* endotoxin (0.111:B4 Difiolab, Detroit, MI) was administered as a continuous infusion in a central venous line at an initial dose of 2 mcg/kg/hr. This dose was increased in 10-minute intervals by 2 mcg/kg/hr until a doubling in pulmonary artery pressure was obtained. The dose was then reduced to one-half of the maximum dose achieved and maintained until the end of the data collection.

Data were collected pre-sepsis, post-sepsis induction, and at 30, 60, 120 and 180 minutes after sepsis induction. The data from the three groups were compared using two-way analysis of variance with repeated measures.

RESULTS

Data is displayed as mean ± standard deviation (Table 1).

Table 1: Results of the study

	CO[d](mL/min)	PVR[e](d-s/cm5)	EFF[f](L/W-min)	PAP[g] (mmHg)
Control[a]:				
Pre-sepsis	1858 ± 358	363 ± 189	26.6 ± 3.8	13.7 ± 2.6
Post-sepsis	1491 ± 155*	1313 ± 358*	14.4 ± 2.5*	28.8 ± 4.7*
30 min.	1356 ± 245	1599 ± 799	14.3 ± 3.5	30.1 ± 6.5
60 min.	1312 ± 256	1858 ± 1231	12.8 ± 2.2	33.4 ± 6.0
120 min.	1067 ± 212	2331 ± 1471	12.5 ± 1.6	33.7 ± 4.7
180 min.	1011 ± 377	2247 ± 1106	14.3 ± 2.5	29.3 ± 5.2
UF+ NS[b]:				
Pre-sepsis	2133 ± 470	357 ± 127	25.6 ± 3.5	15.8 ± 2.1
Post-sepsis	1750 ± 403	1236 ± 588*	12.0 ± 1.8*	35.1 ± 5.3*
30 min	1531 ± 458	1221 ± 624	14.3 ± 2.5	29.8 ± 5.6
60 min	1396 ± 367	1402 ± 685	13.2 ± 2.3	32.3 ± 5.2
120 min	1192 ± 290	1813 ± 755	12.5 ± 2.3	34.0 ± 5.5
180 min	1237 ± 252	1800 ± 921	11.6 ± 1.4	35.9 ± 3.9
UF+bloodc:				
Pre-sepsis	1919 ± 468	309 ± 194	25.3 ± 2.0	13.9 ± 1.4
Post-sepsis	1674 ± 344	1031 ± 442*	14.1 ± 3.3*	29.0 ± 6.5*
30 min	1494 ± 181	1182 ± 559	13.8 ± 2.5	29.1 ± 6.6
60 min	1409 ± 222	1610 ± 1024	11.6 ± 1.1	34.7 ± 5.4
120 min	1272 ± 219	2037 ± 1364	10.6 ± 1.5	38.1 ± 6.4
180 min	1146 ± 267	2276 ± 1558	10.8 ± 1.9	37.8 ± 8.0

[a]Control: septic animals without ultrafiltration
[b]UF + NS: septic animals receiving ultrafiltration with normal saline replacement
[c]UF+blood: septic animals receiving ultrafiltration with whole blood replacement.
[d]C: cardiac output
[e]EFF: transpulmonary vascular efficiency
[f]PVR: pulmonary vascular resistance
[g]PAP: pulmonary artery pressure.
* p 0.05 vs. pre-sepsis.

CONCLUSION AND RECOMMENDATIONS

The results from this study demonstrate that the administration of *E. coli* endotoxin (0.111:4 Difiolab, Detroit, MI), as described above, resulted in a predictable model of sepsis. This was evidenced by the decrease of cardiac output and transpulmonary vascular efficiency in all the groups studied, and by an increase of pulmonary vascular resistance and pulmonary artery pressure. There were no improvements in any of the cardiorespiratory variables studied after ultrafiltration and replacement with either normal saline or whole blood. We speculate that the amount of deleterious immunomodulators that we removed by ultrafiltration was balanced by the amount of beneficial immunomodulators removed. Further studies to characterize the contents and the quantities of the ultrafiltrate may be beneficial in evaluating and understanding the role of ultrafiltration in sepsis.

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