

Plasmapheresis as adjunct treatment of severe sepsis in pediatric patients

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ABSTRACT

Aim: Investigation of therapeutic efficacy of plasmapheresis as an adjunct treatment of sepsis in surgical pediatric patients. **Objective:** Determination of relative risk of mortality in patients who received plasamapheresis with standard treatment of sepsis, in comparison to patients who received standard treatment alone. **Design:** prospective, randomized controlled clinical trial. **Setting:** Intensive Care Unite at Pediatric Clinic of Tbilisi State Medical University. **Patients:** 0-14 years old surgical pediatric patients with severe sepsis, septic shock and MODS. **Interventions:** 257 patients were stratified in 4 age groups and then randomized to receive either standard sepsis treatment or an add-on treatment with plasmapheresis. **Measurments:** Primary endpoint was intrahospital survival. Mortality rates were detected in plasmapheresis and control groups and relative risk of mortality associated with plasmapheresis were calculated. Differences were considered statistically significant at P values less than 0,05. **Results:** All cause mortality rate was 23,2% (29/125) in consolidated plasmapheresis group and 46,97% (62/132) in control group. This represents relative risk of fatal outcome in plasmapheresis group of 0,49 and absolute risk reduction 23,77%. Relative risk of mortality associated with plasmapheresis was the lowest in 1-12 months age group patients (Risk Ratio – 0,32). **Conclusions:** Plasmapheresis may be an important add-on to conventional treatment of severe sepsis in surgical pediatric patients.

KEYWORDS: *plasmapheresis, plasma exchange, sepsis, severe sepsis. shock, MODS, pediatrics, treatment, survival, surgery, PICU*

Sepsis is an increasingly common cause of morbidity and mortality in critically ill patients. Several studies are dedicated to plasmapheresis as an adjunctive therapy of sepsis in adults [7,9]. Significantly less works was done in pediatric population with same illness and their results are controversial [8].

There is both a non-specific and specific rationale for using plasmapheresis (plasma exchange) in septic patients. It could remove excessive cytokines and other pro- and anti- inflammatory mediators from blood and restore levels of deficient substances in case of using fresh-frozen plasma as replacement fluid. Otherwise, several recent works show efficacy of plasma exchange during thrombotic micrangopathies in pediatric patients. By modern view of the disease pathophysiology: endothelial injury, hemostasis disturbances and microcirculatory failure play key role in progression of septic process and lead to development of Multiple Organ Dysfunction Syndrome (MODS) and death. So, plasmapheresis, as adjunctive therapy, should resist progression of MODS and sepsis and improve patient survival [11].

Aim: Investigation of therapeutic efficacy of plasmapheresis as an adjunct treatment of sepsis in surgical pediatric patients.

Objective: Determination of relative risk of mortality in patients who received plasamapheresis with standard treatment of sepsis, in comparison to patients who received standard treatment alone.

Design: Prospective, randomized controlled clinical trial.

MATERIALS AND METHODS

257 pediatric patients aged 0-14 years, admitted at Tbilisi State Medical University Pediatric Hospital in 2001 – 2005, with different (infectious and non-infectious) surgical diseases, where also diagnosed severe sepsis, septic shock and/or MODS, while they received treatment at PICU.

Diagnostic criteria for sepsis, severe sepsis and septic shock were those suggested by the American College of

Chest Physicians (ACCM) and Society of Critical Care Medicine (SCCM) consensus conference [1,2] and adjusted for pediatric patients by Jafari H. et al [4]. Appropriate criteria was obtained from reference to define “suspected infection”, hypoperfusion [10], hypotension in pediatric patients [5]. A MODS was diagnosed according to Wilkinson et al [6].

As soon as the diagnosis of severe sepsis, septic shock or sepsis with MODS was established patients were randomized to receive plasmapheresis in addition to conventional treatment or standard sepsis treatment alone. Conventional treatment in general performed according to the “Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock” [3]. Patients with incurable multiple congenital malformations were excluded from study. Informed consent was obtained from the parents or supervisors of all involved patients.

Plasmapheresis was initiated within 3 hours after the diagnosis were established. This procedure performed using centrifugation technique. Catheterization of femoral vein used for venous access. Extracorporeal circuit was constructed from single use parts at the patient bedside using aseptic technique. Heparin used for regional stabilization of blood in extracorporeal circuit. 40% of plasma was exchanged during single session. Sessions were repeated in 18 hours. So, during whole operation 120 % of body plasma was exchanged in 3 days. Fresh-frozen plasma was used as replacement fluid.

Primary endpoint of study was all cause intrahospital mortality in plasmapheresis and control groups. Data were analyzed on “intention to treat” basis.

Patient baseline demographic, prognostic and treatment characteristics, making influence on survival, such as: age, sex, Pediatric Risk of Mortality (PRISM) score, primary site of infection, type of identified microorganism, invasive treatment procedures, antibiotics and inotropes were recorded and took in consideration during comparison of groups.

Data for statistical analysis were collected using patients computer database created by our team on the basis of

Microsoft Access. Statistical Analysis performed using SPSS for windows v. 11.5. Summaries of numeric data are presented as Mean \pm SD, categorical – by proportions and percents. Univariate comparisons were made by unpaired t test for continuous variables and Fisher's exact test for categorical variables. Fisher's exact test was also used to test differences in survival between plasmapheresis and control groups. Multiple logistic regression was used to assess the effect of baseline variables on survival. Differences were considered significant at p values less than 0,05. For relative risk of mortality 95% CI should not include value 1,0.

Variable	Plasmapheresis (n = 125)	Control (n= 132)	p
Gender (M/F)	71/54	72/60	0.24
Mean age (months)	19.2 \pm 37.3	21 \pm 39.5	0.84
Mean PRISM score	18.4 \pm 13.4	15.3 \pm 11.8	0.40

Tab.1 Baseline characteristics of 257 patients randomly assigned to plasmapheresis or control groups

RESULTS AND DISCUSSION

There were 125 patients randomized in plasmapheresis group and 132 patients in control group. From 257 patients 111 were female and 146 male. 138 babies

were newborn, 32 – infant, 28 aged 1-3 years and 59 over 3 years old. There were no statistically significant differences between the groups with respect to their baseline characteristics (Tab.1).

The worst condition among septic patients was: severe sepsis in 84 patients, sepsis with MODS in 103 patients and septic shock in 70 patients.

29 deaths occurred in plasmapheresis group (23,2%) and 62 in control (46,9%) (p=0,05). Relative risk of fatal outcome in plasmapheresis group was 0.49 (95% CI 0.27-0,71) and absolute risk reduction 23.8%. Comparison of outcomes in patient groups with different septic state showed up lowest relative risk of mortality in patients with severe sepsis 0,37 (95% CI 0,26 – 0,45) and absolute risk reduction 25,3 %. Also relative risk of mortality associated with plasmapheresis was the lowest in 1-12 months age group patients, Risk Ratio – 0,32 (95% CI 0,21-0,43) and absolute risk reduction 27,8%. Multiple logistic regression analysis decrease influence of plasmapheresis on patient's mortality.

According to our results plasmapheresis performed by technique described above, is important adjunctive treatment of sepsis in surgical pediatric patients, especially in infants and in case of early initiation, at the stage of severe sepsis.

CONCLUSIONS

Plasmapheresis may be an important add-on to conventional treatment of severe sepsis in surgical pediatric patients.

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Плазмаферез как вспомогательное лечение тяжелого сепсиса у детей

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РЕЗЮМЕ

Исследована терапевтическая эффективность плазмафереза как вспомогательного метода лечения тяжелого хирургического сепсиса у детей. Для определения возможного относительного риска смертности среди пациентов, дополнительно леченных, наряду со стандартными методами плазмаферезом. Изучение осуществляли путем рандомизированного, контролируемого клинического эксперимента среди 257 пациентов с тяжелым хирургическим сепсисом, септическим шоком и полиорганной недостаточностью в возрасте от 0 до 14 лет, лечившиеся в отделении реанимации и интенсивной терапии педиатрической клиники ТГМУ в 2001-2005 годах. Изучали внутрибольничную смертность в соответствующих группах и определяли относительный риск смертности. Установлено, что относительный риск смертности в группе плазмафереза составляет 0,49 в сравнении с контрольной группой. Этот показатель оказался наименьшим среди младенцев в возрасте от 1 до 12 месяцев (0,32). Полученные данные позволяют заключить, что плазмаферез уменьшает смертность пациентов с тяжелым хирургическим сепсисом, особенно среди младенцев, и может служить существенным дополнением к комплексу стандартных методов лечения.

Ключевые слова: плазмаферез, плазмообмен, сепсис, тяжелый сепсис, шок, полиорганная недостаточность, педиатрия, хирургия, лечение, выживаемость, отделение интенсивной терапии

□ International committee of medical journal editors. Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med 1997;126:36-47.

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Describe your selection of the observational or experimental subjects (patients or laboratory animals, including controls) clearly. Identify the age, sex, and other important characteristics of the subjects. The definition and relevance of race and ethnicity are ambiguous. Authors should be particularly careful about using these categories.

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