Study Title: A Pilot Study Comparing Anti-Inflammatory Effects Of TXA Versus EACA In Pediatric Congenital Heart Surgery (TXAEACA).

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Patient Selection

This pilot study was conducted with a prospective, double blind, randomized control parallel block design. The study was conducted at a single, tertiary care center, Advocate Children's Hospital in Oak Lawn, Illinois. The United States Food and Drug Administration currently approve neither TXA nor EACA for use in children, thus investigational new drug approvals were obtained for both drugs (number 127517). The study was approved by the hospital Institutional Review Board. Informed consent/assent was obtained from all patients prior to enrollment. Patients were enrolled from February 2016 to October 2016.

Inclusion criteria included children age 3 months to 17 years undergoing heart surgery requiring CPB and redo sternotomy. Patients were excluded if they were undergoing Fontan or Glenn procedures, had coagulation profile abnormality, renal insufficiency, chronic hepatopathy, immunosuppressant drug use within last 1 month, history of seizures within last 6 months or current antiepileptic medication use, or had a known allergy to EACA or TXA. Patients were randomly assigned to TXA or EACA group in a 1:1 ratio. Patient allocation was performed by study pharmacist using a computer-generated list. Patient, family, surgical team, and cardiovascular intensive care unit (CVICU) team were blinded to treatment group. All data were managed using REDCap electronic data capture tool (16).

Parents of all patients eligible for study were informed about the research and sent a study packet including a copy of the consent and assent form (if applicable) for review. An investigator subsequently called the parents to explain the research study and answer questions. Documentation of informed consent/assent was obtained prior to surgery during the preoperative visit or on the day of surgery. Assent was obtained on all patients >7 years of age.

Perioperative Management of Patients

Medications were prepared by the pharmacy. TXA (Mylan Institutional LLC) dosing strategy used an initial 31 mg/kg load at start of surgery, followed by 14 mg/kg/hr continuous infusion, and weight-dependent bolus dose after heparinization, pre-CPB (< 16kg: 45 mg; 16-30 kg: 90mg; > 30kg: 120mg) (13). EACA (Hospira, Inc.) dosing strategy used an initial 75 mg/kg load at start of surgery, followed by 75 mg/kg/hr continuous infusion, and 75 mg/kg bolus dose after heparinization, pre-CPB (14). To ensure study blinding, loading doses for both medications were prepared in normal saline 2 ml/kg (0.9 % normal saline, Baxter). Continuous infusions were prepared in normal saline such that 1 ml/kg/hr delivered desired dosage. Second bolus was prepared in normal saline 1 ml/kg. The drugs were made similar in appearance and volume. Operating room nurse administered the study drugs. Infusion was discontinued prior to leaving operating room or immediately upon CVICU arrival.

Consented patients had research-related blood draws (0.3 ml) at three time points: pre-CPB, post-CBP following protamine administration and 24 hours post-CPB. Blood samples were centrifuged and separated plasma stored at -70°C. At mid study, 30 samples (3/patient) were sent to Eve Technology Lab (Calgary, Canada) where multiplex human cytokine assays were run in duplicate. Average of the values run in duplicate was used for calculations. For samples with values reported as out of range (due to level being below detection), the lowest detectable value was assigned for analysis. Biomarkers in the single 13 multiplex cytokine assay included granulocyte macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), TNFα, interferonγ (IFN), IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10β, IL-12, and IL-13. Same procedures were followed for remainder of the samples at the conclusion of the study.

Standard Intra-Operative Protocol

Patients received general anesthesia using sevoflurane, fentanyl and rocuronium. Once under anesthesia, arterial and central venous access was obtained. All patients received methylprednisolone (30 mg/kg; maximum dose 500 mg) after induction of anesthesia. Intra-

operative monitoring included arterial blood pressure, central venous pressure, systemic oxygen saturation, and cerebral and somatic (kidney) near-infrared spectroscopy. Surgical team and procedures remained constant during enrollment period, consisting of 3 surgeons (2 present in each surgery).

Median sternotomy incision was performed on all patients. Heparin loading dose, maintenance and reversal were guided by Medtronic HMS Plus system. Post-heparinization, kaolin activated clotting time and heparin blood concentrations were measured at routine intervals. Standard, non-pulsatile, roller pump CPB, utilizing mild to moderate hypothermia (28-32°C) with pH stat acid-base management was used. CPB circuit consisted of Terumo hard shell reservoirs, polypropylene membrane oxygenators, Medtronic tubing with Trillium coating and Medtronic Affinity arterial filters. Under full heparinization (activated clotting time >300 seconds), CPB was initiated. The CPB circuit was primed with Plasmalyte A, 3000 U/L heparin and 15 mEq/L sodium bicarbonate. Mannitol (0.5 gm/kg) was added after initiation of CPB and during rewarming. Packed red blood cells were added as needed to maintain a hematocrit >22%, in 25 ml increments, paired with additional Plasmalyte A chasers and hemofiltration. Fresh frozen plasma (FFP) was given to patients $\leq$7 kg (50 ml post-CPB initiation and 50 ml during rewarming). Myocardial protection was obtained using cold blood cardioplegia, intermittent or continuous infusion, per surgeon's request. A terminal warm reperfusion was used for all patients prior to aortic cross clamp removal. Hemoconcentration and modified ultrafiltration were used routinely. Protamine was given at conclusion of case.

Standard Postoperative Protocol

Patients were taken to a dedicated CVICU, staffed at all times by in-house pediatric cardiovascular attending physicians. Decision for transfusion was made clinically at the discretion of attending physicians.

Duration of CPB, aortic cross clamp time, Society of Thoracic Surgeons - European Association for Cardiothoracic Surgery mortality category (STAT category) and inotropic score for first 48 hours after surgery were used to compare surgical complexity between groups. Blood product utilization during and after surgery, and chest tube output for first 72 hours was documented.

Statistical Analysis

As this was a pilot study, sample size calculation was not performed. We recruited 20 patients, 10 per study group. An interim analysis was performed for safety evaluation, after which no adjustments were made to study protocol.

Between group comparisons were examined using independent groups Student's *t*-test or Mann-Whitney U tests when data were not normally distributed. Dichotomous variables were examined using Chi-square or Fisher exact test. Within group comparisons for change over time (pre-CPB, post-CPB and 24 hour post-CPB) were tested using Friedman test. A p value of <0.05 was considered statistically significant. Adjustments for multiple comparisons were not made because of the explanatory nature of this study.