ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 10, pp. 23477-23483, October, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

EFFECTS OF TRANEXAMIC ACID ON INFLAMMATORY CYTOKINES IN CARDIOPULMONARY BYPASS SURGERIES FOR CORRECTION OF CONGENITAL HEART ANOMALIES IN PAEDIATRIC PATIENTS

***[1]Gholampour, M., [1]Totonchi, M., [1]Mahdavi, M., [1]Bakhshandeh, H., [1]Korbi, M., [1]Mahyar Gholampour, [1]Pazoki, T.H.R., [1]Sheikhi, B., [1]Hosseinian, A., [1]Gorgipour, F., [2]Zeraatian, S. and [2,3]D Pazooki**

[1]Shahid Rajaei Cardiovascular Surgery Center, Tehran Iran
[2]Iran University, Hazrat Rasol Akrm Hospital, Department Cardiovascular & Thoracic surgery Tehran Iran
[3]Sahlgrenska University Hospital, Department of Surgery, Gothenburg Sweden

Article History: Received 17th July, 2018; Received in revised form 21st August, 2018; Accepted 22nd September, 2018; Published online 29th October, 2018

Key Words: Inflammatory cytokine; Cardiopulmonary bypass (CPB); SIRS; Tranexamic acid (TXA); Inflammatory response.

Citation: Gholampour, M., Totonchi, M., Mahdavi, M., Bakhshandeh, H., M Korbi, Mahyar Gholampour, Pazoki, T.H.R., Sheikhi, B., Hosseinian, A., Gorgipour, F., Zeraatian, S. and D Pazooki. 2018. "Effects of tranexamic acid on inflammatory cytokines in cardiopulmonary bypass surgeries for correction of congenital heart anomalies in paediatric patients", *International Journal of Development Research*, 8, (10), 23477-23483.

INTRODUCTION

Corrective surgeries for most of the congenital heart defects require the use of cardiopulmonary bypass (CPB) and anticoagulation therapy (Graham, 2012). Post-CPB time is usually associated with high inflammatory cytokine level. The main causes of inflammatory response include contact of blood with external surfaces and gas systems, ischemia/reperfusion, endotoxemia and surgical trauma (Hsia *et al*. 2010; Mojcik , 2001; Warltier *et al*., 2002 and Cremer , 1996). Inflammatory cascades and hemostasis problems are usually observed after CPB surgery which mandates the transfusion of blood and coagulation factors. Transfusion of blood products again elevates the inflammatory responses (Graham, 2012; Ugaki, 2010; Hickey, 2006). Elevation of inflammatory responses is demonstrated through cellular and humoral parameters of the immune activity (8-11). In the early phase after CPB, inflammatory response strike as release of cytokines such as interleukins (ILs) and tumour necrosis factor (TNF). These are able to cause some cellular and humoral events like cell death and induction of proteolytic pathways by binding to their receptors (Hsia, 2010). Generally, patients undergoing CPB experience a syndrome known by the release of pro-inflammatory cytokines like IL-6, IL-8 and TNF-α or anti-inflammatory cytokine IL-10 (Hsia, 2010).

Corresponding author: Gholampour, M.,
Shahid Rajaei Cardiovascular Surgery Center, Tehran Iran

Cytokines such as IL-1, -6, -7, 8, -10 and TNF-α are major modulators of the immune response which play a key role in the regulation of innate and adoptive immunity and induction of inflammation (Kozik, 2006). (Fig: 1,2). It is well-established that there is a direct correlation between tissue damage and circulatory inflammatory cytokines level and elevation of circulatory IL-6 and (Fig-3)IL-8 levels are associated with higher organ damage (Wan *et al*., 1999; Massoudy *et al*., 2001; Gormley *et al*., 2000 and Nandate , 1999) and death rate (Gormley, 2000). Inflammatory cytokines could have effects like myocardial dysfunction, respiratory failure, impaired renal function, neurologic problems, haemorrhagic disorders and alteration of the hepatic function and in sum, failure of multiple organs (Gormley *et al*., 2000). Tranexamic acid, like aprotinin, is a fibrinolysis inhibitor. Its effects on inflammatory response has not been proved yet (Madhok, 2006). Tranexamic acid is a synthetic derivative of lysine amino acid. It binds to plasminogen reversibly and inhibits its break down to plasmin (fibrinolysis) (Martindale, 1999). Tranexamic acid is being used in many surgical procedures such as cardiac, orthopaedic and liver transplant surgeries (De Bonis *et al*., 2000). Inflammatory response is generally activated in three times throughout the CPB: blood contact with nonendothelial surface, after reperfusion, and after protamine injection and formation of heparin/protamine complex. Two minutes after bypass start, plasma level of activated complement elevates. The next elevation happens after removal of the aorta clamp and re-warming. Plasma level

of complement factors decreases and gets back to the normal level until 18 to 48 hours post-operation.

Methods and Study design: The study is a randomized controlled trial which has been approved by the ethics committee of the Rajaie Cardiovascular and Medical Canter, Tehran, Iran. 61 patients with ventricular septal defect (VSD), TOF (Tetralogy of Fallot), double outlet right ventricle (DORV), complete atrioventricular septal defect (CAVSD) and pulmonary stenosis (PS) anomalies referring to the center were recruited. Patients were randomly (balanced block randomization) allocated in two groups tranexamic acid (TXA; n=31) and saline (n=30).

Study population: Inclusion criteria were as following: age between 6 months and 5 years, weight between 5 to 15 kg, similar pump time, aorta clamp time, extent of operation, not having current immunologic, inflammatory or infectious diseases and problems with renal or liver function, not receiving immunosuppressive drugs for minimum 2 weeks before operation, no allergy to tranexamic acid and no coagulation disorders. Exclusion criteria are using assist devices, emergency operations and lack of guardian's consent. After describing the study criteria and conditions, written informed consent was obtained from guardians of the patients. After anaesthesia induction and before incision of the skin, 100 mg.kg-1 of tranexamic acid was intravenously administered and 100 mg.kg-1 of the drug was added to the prime solution. Normal saline was added 1 mL.kg-1 was intravenously injected and equal amount was added to the prime solution.

Anesthesia technique: Anesthesia was induced in the operation room using narcotics, muscle relaxants and inhalation anaesthetics. Starch solution (15 mL.kg-1), crystalloid and pack cell were used for priming. All of the patients underwent cardiopulmonary bypass. Membrane oxygenators with hard-shell reservoirs were used for CPB. Heparin (300 U.kg-1) was used for prevention of clot for formation during CPB and extra dosing of heparin was used for maintenance of ACT over 480 seconds. Protamine (1 mg.kg-1) was used for heparin neutralization. Additional doses of protamine were used if required. Alpha-stat method was used for maintenance of acid-base balance in all patients. Bicaval cannulation was performed for all patients. Patients underwent slight hypothermia to get ready for the operation. Patients with similar aorta clamp time, pump time and the extent of surgical operation were included, and operation was performed with single surgeon with the similar approach. Ultrafiltration was performed in 27 (87.1%) patients from TXA group and 21(70%) patients from saline group (p=0.1). leukocyte filtration was not used in any patient. Surgeon put more time for establishing hemostasis in the saline group.

Clinical parameters: Demographic data including age, weight and sex were recorded. Cross-clamp time, CPB time, mechanical ventilation duration, volume of drainage from chest tube, transfusion of blood and its derivatives, inotrope requirement for 48 hours post-operation, ICU stay, and hospital stay were recorded and compared between two groups.

Cytokine measurement: Plasma cytokines IL-6, IL-8, IL-10 and TNF-α were measured in plasma samples from patients in three time points: first sample was drawn after anaesthesia induction and application of arterial line and central venous catheter, the second after aorta clamp removal and the third 24 hours after transfer to ICU. After collection of samples according to the timetable, plasma was separated by centrifuging at 4000 rpm speed for 10 minutes. Then, plasma was transferred into cryovials and stored in liquid nitrogen until the time of measurement. Then cytokines were measured using standard ELISA assay kit from commercial manufacturer (Table 1, 2, 3 & 4).

Table 1. Demographics and preoperative characteristics of patients presenting for surgical repair of congenital heart disease

Variable	TXA (n=31)	Saline (n=30)	P value
Sex,Male n (%)	17(54.8%)	8(26.7%)	0.02
Age(months)	26.9±15.58	32.7±19.26	0.20
Weight(kg)	10.2±3.17	10.8±4.36	0.50
BSA (m^2)	0.49(0.38-0.56)	0.50(0.40-0.61)	0.47
ESR	6(4.75–11.25)	6(2.75-11)	0.87
WBC	9×10^3(7500-10900)	8.9×10^3(7575-10625)	0.73
INR	1.11 ± 0.09	1.06 ± 0.09	0.07
PLT	306×10^3 ±101426	288×10^3±62760	0.40
HB	13.7 ± 1.91	13.3 ± 1.90	0.37
HCT	40.4 ± 5.69	37.9 ± 8.86	0.18

Values presented as Mean±SD. median (interquartile range) or frequencies and percentages.

Table 2. Postoperative characteristics of patients presenting for surgical repair of congenital heart disease

Variable	TXA (n=31)	Saline (n=30)	P value
Ultrafiltration	27(87.1%)	21(70%)	0.10
Cross clamp time(min)	91.03 ± 27.92	78.33 ± 25.29	0.068
CPB time (min)	133.52 ± 32.91	118.63 ± 29.67	0.069
Chest tube drainage (ml)	142 ± 100	146 ± 154	0.90
M.V (Hours)	11.50(9-19)	11.75(8-16)	0.26
Icu stay (Hours)	65(44-88)	65(42-75)	0.91
Hospital stay (Days)	9(7-10)	7(6-8.2)	0.13
FFP(ml)	OR 0(0-0)	0(0-150)	0.07
	ICU 0(0-0)	0(0-15)	0.86
PLT(ml)	OR 0(0-50)	0(0-50)	0.62
	ICU 0(0-0)	0(0-50)	0.17

Values presented as Mean±SD. median (interquartile range) or frequencies and percentages.

Data analysis design: Clinical parameters from each patient were collected in questionnaires and analysed. Data analysis was performed using proper statistical methods in SPSS software V20. One-sample Kolmogorov-Smirnov test was used for testing the normality of distribution of the numerical data. Quantitative data were represented as mean ± standard deviation (SD) for normally distributed or median (interquartile range; IQR) for non-normally distributed one.

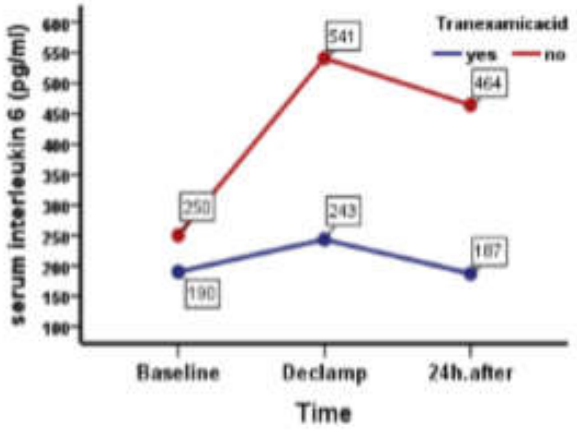
Qualitative data were presented as relative frequency or frequency percent. Independent samples t-test was used for pairwise comparison of the data with normal distribution and Mann-Whitney test was used for comparison of groups with non-normal data distribution. For testing the changes of the parameters with repeated measures over time, repeated measures analysis of variance (ANOVA) was used for normally distributed data and Friedman's test was used for non-normally distributed data.

Table 3. Comparison of changes in interleukin-6 during the time between the two groups

Variable	TXA (n=31)	Saline (n=30)	P value
IL-6 base	190.73 ± 178.91	250.45 ± 401.39	0.45
IL-6 Declamp	243.17 ± 127.87	541.68 ± 787.37	0.04
IL-6 (24h)	187.27 ± 155.47	464.22 ± 643.20	0.2

Value expressed as meant ± standard deviation

Comparison of interleukin 6 changes during the three different time intervals between the two groups; Before induction of anesthesia, one minute after the clamp, and 24 hours later



Comparison of change in interleukin-6 during the between the two groups

Data analysis: Clinical parameters from each patient were collected in questionnaires and analysed. Data analysis was performed using proper statistical methods in SPSS software V20. One-sample Kolmogorov-Smirnov test was used for testing the normality of distribution of the numerical data. Quantitative data were represented as mean ± standard deviation (SD) for normally distributed or median (interquartile range; IQR) for non-normally distributed one. Qualitative data were presented as relative frequency or frequency percent. Independent samples t-test was used for pairwise comparison of the data with normal distribution and Mann-Whitney test was used for comparison of groups with non-normal data distribution. For testing the changes of the parameters with repeated measures over time, repeated measures analysis of variance (ANOVA) was used for normally distributed data and Friedman's test was used for non-normally distributed data.

RESULTS

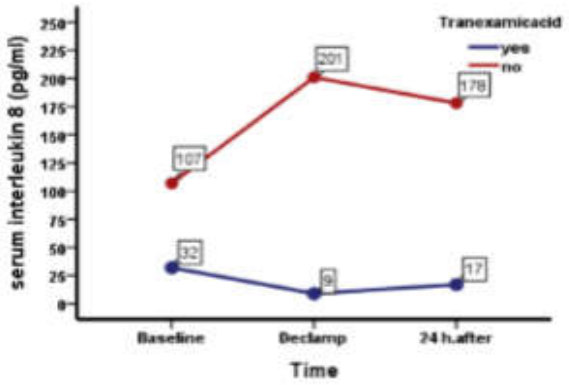
61 patients were recruited: 31 assigned to tranexamic acid group (TXA) and 30 to saline group. Demographic information, baseline clinical parameters, congenital defects and surgical procedures were similar between two groups. Perioperative parameters were similar between two groups as well. Cross clamp time and CPB time were not significantly different between two groups (respectively, 91.03±27.92 in TXA vs. 78.33±25.29 in saline group and 133.52±32.91 in TXA vs. 118.63±29.67 in saline group; p>0.05). (Tab-4,5,6,7).

Table 4. Comparison of changes in interleukin-8 during the time between the two groups

Variable	TXA (n=31)	Saline (n=30)	P value
IL-8 base	32.91± 61.36	107.60±216.30	0.07
IL-8 Declamp	9.26±25.99	201.68±437.62	0.01
IL-8 (24h)	17.50±36.13	178.23±392.34	0.02

Value expressed as meant ± standard deviation

Comparison of interleukin 8 changes during the three different time intervals between the two groups; Before induction of anesthesia, one minute after the clamp, and 24 hours later



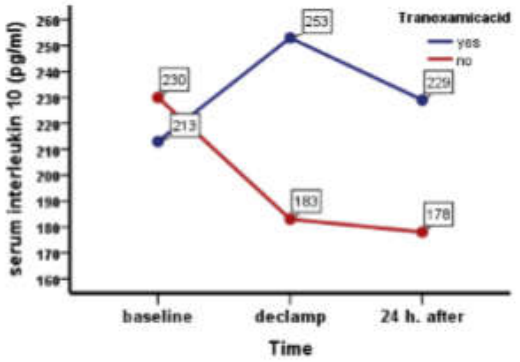
Comparison of changes in interleukin-8 during the time between the two group

Table 5. Comparison of changes in interleukin-10 during the time between the two groups

Variable	TXA (n=31)	Saline (n=30)	P value
IL-10 base	213.26±177.32	230.54±213.85	0.73
IL-10 Declamp	253.26±254.99	183.07±149.07	0.19
IL-10 (24h)	229.97±193.11	178.43±150.86	0.25

Value expressed as meant ± standard deviation

Comparison of interleukin 10 changes during the three different time intervals between the two groups; Before induction of anesthesia, one minute after the clamp, and 24 hours later.



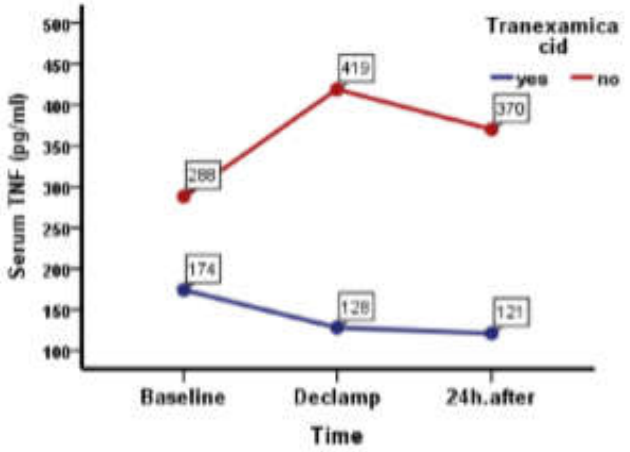
Comparison of changes in interleukin-10 during the time between the two groups

Table 6. Comparison of changes in TNF-α during the time between the two groups

Variable	TXA (n=31)	Saline (n=30)	P value
TNF-α base	174.96±199.15	288.06±646.64	0.32
TNF-α Declamp	128.03±173.99	419.85±733.07	0.03
TNF-α (24h)	121.69±146.04	370.14±624.81	0.03

Value expressed as meant ± standard deviation TNF=Tumour Necrosis Factor

Comparison of TNF-α changes during the three different time intervals between the two groups; Before induction of anesthesia, one minute after the clamp, and 24 hours later



Comparison of changed in TNF-α during the time between the two groups

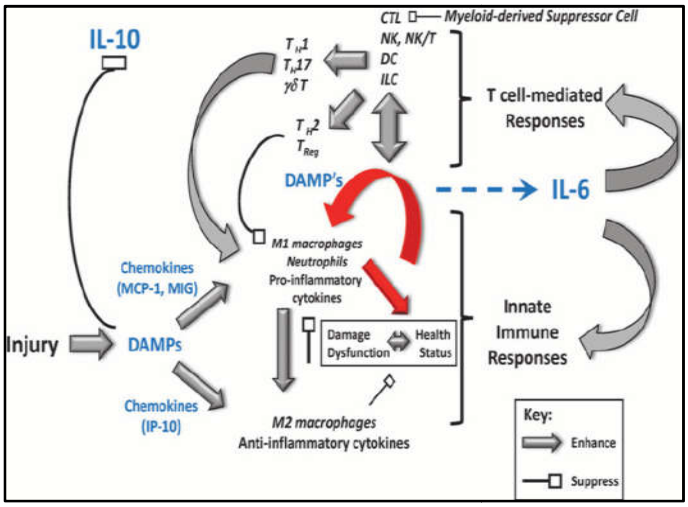


Fig. 1.

Post-surgical outcomes: Median and the IQR of the body temperature in 6 and 9 hours after transfer to ICU was significantly higher in TXA group compared to saline group. SBP, DBP and PR did not show significant differences between two groups ($p>0.05$). Adverse outcome including tamponade, hemorrhage, sepsis and return to operation room was not observed in any of the study groups. Also, elevation of the liver enzymes (as an adverse outcome of long-term use of TXA) was not observed and two groups were similar in this case. One case of pericardial effusion and one case of seizure were observed in the TXA group which showed no significant difference with the saline group ($p>0.99$). Mechanical ventilation time, ICU stay time and hospitality time was not different between groups ($p>0.05$).

Chest tube drainage and blood products consumption: Chest tube drainage was less in the TXA group compared to saline group in 48 hours post-operation, although the difference was not statistically different (142±100 in TXA vs. 146±154 in saline group ($p=0.9$). Also, differences in FFP and platelet consumption in OR and ICU were not significant ($p>0.05$).

Inflammatory markers: Plasma levels of cytokines before and after operation are summarized in Preoperative plasma level of cytokines was similar between groups ($p>0.05$).

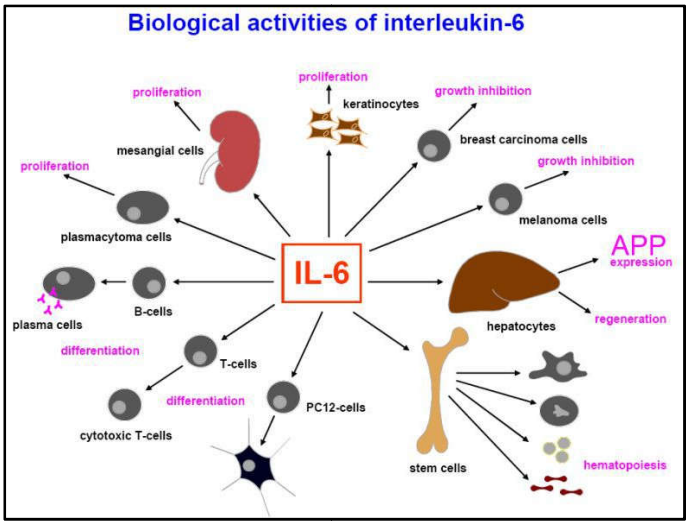
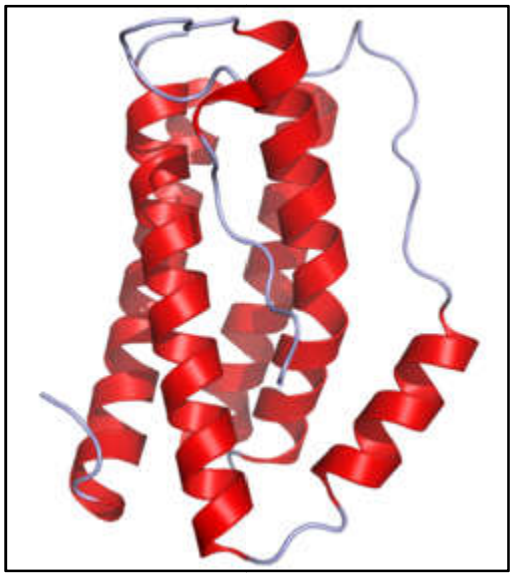


Fig. 2. The Biological activities of interleukin-6



IL-6

Fig. 3. The microscopic form of interleukin-6

Levels of IL-6, IL-8 and TNF-α elevated significantly after decamping compared to the baseline. Level of IL-6 and IL-8 reached two-times the baseline amount in this time in the saline group (Table 1,2,3,4). 24 hours after transfer to ICU plasma level of these cytokines dropped, although it was yet significantly higher in the saline group compared to the TXA group and baseline amount in the saline group. Results demonstrated that using tranexamic acid reduces the plasma IL-8 level 24 hours after transfer to ICU by 50%. Also, it is associated with lower, although not statistically significant increase in the plasma IL-10 level ($p=0.19$). Also, significant differences were observed in IL-6, IL-8 and TNF-α levels in repeated measures over time ($p<0.05$ for repeated measures ANOVA). This difference was not observed on IL-10 levels over time ($p=0.1$), (Table 1,2,3,4).

DISCUSSION

In the current study we investigated the effects of TXA on cytokine response following cardiopulmonary bypass. Many of the post-surgical adverse outcomes are related to the systemic inflammatory response such as pro-inflammatory cytokines, chemokines, complement activation, leukocyte activation,

thrombin, kallikrein and other kinins (Hsia, 2010). Moreover, risk factors like long duration of bypass and cross clamp, frequent use of cardiotomy suction and trauma to the blood cells cause high inflammatory responses (Ugaki *et al*., 2010; Hickey, 2006). Systemic inflammatory response syndrome exerts negative effects on post-operative cardiac function, hemodynamic state, pulmonary function, renal function and immunologic competence. Concerns regarding proinflammatory responses following CPB and its consequences have inspired searching for solutions to overcome it (Graham, 2012). On the other hand, the number of studies on release of cytokines following CPB surgeries in patients with congenital heart diseases are limited (Jiménez , 2011; Asehnoune, 2002 and Jimenez, 2007). In the current study 61 patients were randomly allocated in TXA and saline groups. Two groups were similar in terms of age, weight, BSA and baseline laboratory parameters such as ESR, blood cell count, INR, hemoglobin and hematocrit. Also, Perioperative parameters such as CPB time and hemofiltration were similar between two groups. Also baseline (before anesthesia induction) level of cytokines TNFα, IL-6, IL-8 and IL-10 were similar between two groups. Results from analysis of the study data revealed that levels of IL-6, IL-8 and TNF-α was significantly different between groups after removal of the aorta clamp. Levels of IL-6 and IL-8 after 24 hours was yet higher than baseline, although it was declined compared to aorta decamp time (Table 1,2,3,4). The level of these cytokines was significantly higher in saline group compared to TXA in this time.

The maximum elevation of IL-6 in this study was consistent with some of the previous studies (Graham, 2012; Madhok , 2006; Berdat , 2004; Jimenez *et al*., 2007; Casati *et al*., 2004; Roth□Isigkeit *et al*., 2001 and Meng, 2008). In contrast, in another study the elevation observed in the IL-6 levels persisted until 48 hours post-operation (Hsia, 2010). This could be described by the lower dose of tranexamic acid (100 mg.kg-1 bolus and 10 mg.kg-1.h-1 maintenance) used in that study, while we used initial dose of 100 mg.kg-1 and also added the drug to the prime solution. This may have resulted in the decline of IL-6 levels 24 hours after transfer to ICU. Our study replicated the results from other studies regarding changes in IL-8 levels following CPB (Graham**, 2012;** Hsia *et al*., 2010; Asehnoune, 2002). In the current study TNF-α level was significantly lower in TXA group compared to saline group at clamp removal time and it was near baseline level at 24 hours post-operation while remained above the baseline in the saline group. In the present study the level of IL-10 was significantly increased following CPB in the TXA group and was reduced in the saline group.

These results are similar to previous studies (Hsia *et al*., 2010; Madhok *et al*., 2006; Kozik, 2006). Intergroup comparison did not reveal statistically significant difference between TXA and saline groups in clamp removal time and 24 hours after transfer to ICU, although in TXA group enhanced plasma IL-10 was observed after surgery compared to preoperative measure. IL-6 and IL-8 are strong pro-inflammatory cytokines which are potent activators of inflammatory cells like neutrophils and lymphocytes (Kozik, 2006; Brix□Christensen, 2001). On the other hand, IL-10 as an anti-inflammatory cytokine modulates the pro-inflammatory effects of the cytokines IL-1β, IL6, IL-8 and TNF-α (8-10, 26). It appears that in the current study administration of TXA have resulted in the modulation of the immune response to CPB by regulating the circulatory level of cytokines IL-6, IL-8 and TNF-α along with the elevation of circulatory IL-10 level as a potent anti-inflammatory cytokine. Considering the half-life of TXA which is around 80 minutes (Jiménez, 2011), it appears that its plasma level is adequate to exert anti-inflammatory effects following clamp removal time (mean 91 minutes after operation start time). Where the highest pro-inflammatory cytokine response is observed in the saline group at this time, TXA group have experienced significantly lower pro-inflammatory cytokine levels along with higher mean level of anti-inflammatory Il-10 level. In the current study one case (3.2%) of seizure was observed in the TXA group and none was observed in the saline group which demonstrated no statistically significant differences between two groups. these results has been reported in similar studies (Graham, 2012; Jiménez *et al*., 2011).

This patient had history of seizures and the appearance of seizure could not be attributed to the administration of TXA. The observed rates of nonischemic seizures have been reported to be from 2.7% to 4.6% in wide operations (Sander , 2010; Martin *et al*., 2008; Murkin *et al*., 2010), around 0.4% in CABG (28) and from 6.7% (Sander *et al*., 2010) to 7.9% (Martin, 2008) in massive operations with opening of the cardiac chambers. This reaction has appeared with various doses from 61 to 259 mg.kg-1 (Jiménez, 2011). Our observed rate was less than the reported prevalence to date. Chest tube drainage was not significantly different between groups until 48 hours post-operation. This agreed with Castai *et al*. (2004). However, another study by Jiménez *et al*. reported significant differences between groups (Jiménez, 2011). This may be due to the differences in the time and dose of the TXA administration. In that study one of the groups received TXA before and the other received TXA before CPB and normal saline solution after CPB. Since single dose of TXA inhibits most of the plasmin in circulation, administration of the second dose of TXA early after CPB would decrease the volume of drainage from chest tube. In a clinical trial in adults, there was a significantly higher volume of chest tube drainage in the saline group compared to TXA group (Jimenez, 2007). This appears to happen due to lack of adequate bleeding management in the saline group. This study was stopped by the ethics committee due to excessive bleeding in the saline group. We did not observe significant differences in the drainage from chest tube between two group.

This may be described by the higher level of FFP and platelet administration in both operation room and ICU and assigning more time by surgeon for maintaining the hemostasis. Data obtained from recording the use of blood products demonstrated higher amount of use of these products in the saline group, although this difference was not statistically significant. These data are consistent with a couple of previous studies (Jiménez *et al*., 2011 and Casati, 2004). In one study comparing the aprotinin to TXA, there was a significant difference between groups which could be attributed to different mechanisms of action of these drugs. Also, internal regulations of the clinical setting could affect the amount of consumption of blood products. In the study of Jimenez *et al*. (Jimenez, 2007), use of blood products was significantly higher in the control group which could be described by the attempts to control severe bleeding in the saline group. There were no significant differences between two groups in terms of mechanical ventilation time which is consistent with two other studies by Jimenez *et al*. (Jiménez *et al*., 2011 and Jimenez *et*

al., 2007). In two other studies by Graham *et al*. (Graham, 2012), and Jimenez *et al*. (Jimenez, 2007), there was significant differences between two groups which should probably be due to extubating immediately after hemodynamic stability of the patients. We did not observe significant differences in ICU stay duration between two groups. This is consistent with the previous reports by other researchers (Graham, 2012; Jiménez, 2011; Jimenez, 2007; Casati, 2004). It appears that lack of significant differences between duration of mechanical ventilation time, ICU stay and hospitality between two groups in the present study is not only affected by the surgical procedures and factors like routine practice of surgical management and internal medicine in the clinical settings for affect these parameters. One such item in our setting is that estuations are not done in the night shifts (Tab-4,5,6,7).

Limitations

Like many other clinical trials our study is investigating the effects of a specific medication in the pathophysiological context. Although we tried to allocate the patients into two similar groups by randomization, there could be factors affecting the outcomes which are not equal between two groups. We observed significant decrease in plasma inflammatory cytokines following treatment with TXA, however for observing the differences in hemodynamic parameters more cases should be investigated.

Conclusion

The relationship between post-CPB inflammatory responses in pediatric patients with many of the adverse outcomes is well-established. Using pharmacological strategies such as glucocorticoid therapy inhibits the cytokine cascade. The present study demonstrated that beyond its antifibrinolytic properties, TXA reduces the number of circulatory cytokines post-CPB without significant adverse outcomes. Further studies are required to reveal the mechanisms involved in anti-inflammatory effects of TXA and whether it is dependent on antifibrinolytic properties of the drug, also to determine the clinical outcomes of this anti-inflammatory action of TXA in pediatric CPB patients.

Disclosure: The authors declare no conflicts of interest.

REFERENCES

Asehnoune, K., Desmonts, J.M., Durand, G., Philip, I., Dehoux, M., Leçon-Malas, V., *et al.* Differential effects of aprotinin and tranexamic acid on endotoxin desensitization of blood cells induced by circulation through an isolated extracorporeal circuit. *Journal of cardiothoracic and vascular anesthesia.*, 16(4):447-51.

Berdat, P.A., Eichenberger, E., Ebell, J., Pfammatter, J.P., Pavlovic, M., Zobrist, C., *et al.* 2004. Elimination of proinflammatory cytokines in pediatric cardiac surgery: analysis of ultrafiltration method and filter type. *The Journal of thoracic and cardiovascular surgery.*, 127(6):1688-96.

Brix□Christensen, V. 2001. The systemic inflammatory response after cardiac surgery with cardiopulmonary bypass in children. *Acta anaesthesiologica scandinavica*., 45(6):671-9.

Casati, V., Della Valle, P., Benussi, S., Franco, A., Gerli, C., Baili, P., *et al.* 2004. Effects of tranexamic acid on postoperative bleeding and related hematochemical variables in coronary surgery: comparison between on-pump and off-pump techniques. *The Journal of thoracic and Cardiovascular Surgery.,* 128(1):8391.

Cremer, J., Martin, M., Redl, H., Bahrami, S., Abraham, C., Graeter, T. *et al*. 1996. Systemic inflammatory response syndrome after cardiac operations. *The Annals of thoracic surgery.,* 61(6):1714-20.

De Bonis, M., Cavaliere, F., Alessandrini, F., Lapenna, E., Santarelli, F., Moscato, U., *et al.* 2009. Topical use of tranexamic acid in coronary artery bypass operations: a double-blind, prospective, randomized, placebocontrolled study. *The Journal of thoracic and cardiovascular surgery.,* 119(3):575-80.

Ghosh, S., Falter, F., Cook, D.J. 2009. Cardiopulmonary bypass: Cambridge University Press.

Gormley, S., McBride, W.T., Armstrong, M.A., Young, I.S., McClean, E., MacGowan, S.W., *et al.* 2000. Plasma and urinary cytokine homeostasis and renal dysfunction during cardiac surgery. *Anesthesiology.,* 93(5):1210-6; discussion 5A.

Graham, E.M., Atz, AM., Gillis, J., DeSantis, SM., Haney, AL., Deardorff, RL. *et al*. 2012. Differential effects of aprotinin and tranexamic acid on outcomes and cytokine profiles in neonates undergoing cardiac surgery. *The Journal of thoracic and cardiovascular surgery.* 143(5):1069-76.

Greilich, P.E., Brouse, C.F., Whitten, C.W., Chi, L., DiMaio, J.M., Jessen, M.E. 2003. Antifibrinolytic therapy during cardiopulmonary bypass reduces proinflammatory cytokine levels: a randomized, double-blind, placebocontrolled study of ϵ-aminocaproic acid and aprotinin. *The Journal of thoracic and cardiovascular Surgery.,* 126(5):1498-503.

Greilich, P.E., Okada, K., Latham, P., Kumar, R.R., Jessen, M.E. 2001. Aprotinin But Not ε-Aminocaproic Acid Decreases Interleukin-10 After Cardiac Surgery With Extracorporeal Circulation Randomized, DoubleBlind, Placebo-Controlled Study in Patients Receiving Aprotinin and ε-Aminocaproic *Acid. Circulation*., 104(suppl 1):I-265-I-9.

Hickey, E., Karamlou, T., You, J., Ungerleider, R.M. 2006. Effects of circuit miniaturization in reducing inflammatory response to infant cardiopulmonary bypass by elimination of allogeneic blood products. *The Annals of thoracic surgery.* 81(6):S2367-S72.

Hsia, T-Y., McQuinn, TC., Mukherjee, R., Deardorff, R.L., Squires, J.E., Stroud, R.E., *et al.* 2010. Effects of aprotinin or tranexamic acid on proteolytic/cytokine profiles in infants after cardiac surgery. *The Annals of thoracic surgery.* 89(6):1843-52.

Jiménez, J.J., Iribarren, J.L., Brouard, M., Hernández, D., Palmero, S., Jiménez, A., *et al.* 2011. Safety and Effectiveness of two treatment regimes with tranexamic acid to minimize inflammatory response in elective cardiopulmonary bypass patients: a randomized double-blind, dose-dependent, phase IV clinical trial. *Journal of Cardiothoracic Surgery.* 6(1):1-10.

Jimenez, J.J., Iribarren, J.L., Lorente, L., Rodriguez, J.M., Hernandez, D., Nassar, I., *et al.* Tranexamic acid attenuates inflammatory response in cardiopulmonary bypass surgery through blockade of fibrinolysis: a case control study followed by a randomized double-blind controlled trial. *Crit Care.*, 11(6):R117.

Kozik, D.J., Tweddell, J.S. 2006. Characterizing the inflammatory response to cardiopulmonary bypass in

children. *The Annals of thoracic surgery.,* 81(6):S2347-S54.

Madhok, A.B., Ojamaa, K., Haridas, V., Parnell, V.A., Pahwa, S. and Chowdhury, D. 2006. Cytokine response in children undergoing surgery for congenital heart disease. *Pediatric cardiology*. 27(4):408-13.

Martin, K., Wiesner, G., Breuer, T., Lange, R., Tassani, P. 2008. The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients. *Anesthesia & Analgesia.,* 107(6):1783-90.

Martindale, W., Sweetman, S.C. 1999. Martindale: the complete drug reference: Pharmaceutical press London.

Massoudy, P., Zahler, S., Becker, B.F., Braun, S.L., Barankay, A., Meisner, H. 2001. Evidence for inflammatory responses of the lungs during coronary artery bypass grafting with cardiopulmonary bypass. *CHEST Journal.*, 119(1):31-6.

Meng, Q.H., Zhu, S., Sohn, N., Mycyk, T., Shaw, S.A., Dalshaug, G., *et al.* 2008. Release of cardiac biochemical and inflammatory markers in patients on cardiopulmonary bypass undergoing coronary artery bypass grafting. *Journal of cardiac surgery.,* 23(6):681-7.

Mojcik, C.F., Levy, J.H. 2001. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. *The Annals of thoracic surgery.* 71(2):745-54.

Murkin, J.M., Falter, F., Granton, J., Young, B., Burt, C., Chu, M. 2010. High-dose tranexamic acid is associated with nonischemic clinical seizures in cardiac surgical patients

Nandate, K., Vuylsteke, A., Crosbie, A.E., Messahel, S., Oduro-Dominah, A., Menon, D.K. 1999. Cerebrovascular cytokine responses during coronary artery bypass surgery: specific production of interleukin-8 and its attenuation by hypothermic cardiopulmonary bypass. *Anesthesia & Analgesia,* 89(4):823.

Roth□Isigkeit, A., Hasselbach, L., Ocklitz, E., Brückner, S., Ros, A., Gehring, H., *et al.* 2001. Inter□individual differences in cytokine release in patients undergoing cardiac surgery with cardiopulmonary bypass. *Clinical & Experimental Immunology*. , 125(1):80-8.

Sander, M., Spies, C.D., Martiny, V., Rosenthal, C., Wernecke, K.D., von Heymann, C. 2010. Mortality associated with administration of high-dose tranexamic acid and aprotinin in primary open-heart procedures: a retrospective analysis. *Crit Care.*, 14(4):R148.

Ugaki, S., Honjo, O., Nakakura, M., Douguchi, T., Itagaki, A., Yokoyama, N., *et al.* 2010. Transfusion-free neonatal cardiopulmonary bypass using a TinyPump. *The Annals of thoracic surgery.* 90(5):1615-21.

Wan, S., Izzat, M.B., Lee, T.W., Wan, I.Y., Tang, N.L., Yim, A.P. 1999. Avoiding cardiopulmonary bypass in multivessel CABG reduces cytokine response and myocardial injury. *The Annals of thoracic surgery.,* 68(1):52-6.

Warltier, D.C., Laffey, J.G., Boylan, J.F., Cheng, D.C. 2002. The systemic inflammatory response to cardiac surgeryimplications for the anesthesiologist. *The Journal of the American Society of Anesthesiologists*. 97(1):215-52.

****