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Investigation of the effects of leukocyte filtration in congenital heart surgery

Doğuştan kalp cerrahisinde lökosit filtrasyonunun etkilerinin araştırılması

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Background: This study aims to investigate the effect of leukocyte filtration during cardiopulmonary bypass (CPB) on inflammatory reactions in congenital heart surgery.

Methods: In the study, group 1 (n=15) administered a leukocyte filter connected to arterial line after the oxygenator during CPB, while group 2 (n=15) was the control group. The patients were thoroughly assessed with respect to age, sex, congenital heart disease, total CPB duration, aortic cross-clamp duration, duration of mechanical ventilation, duration of intensive care unit (ICU) and hospital stay, total amount of chest drainage in 24 hour, inotropic drug use, total amount of transfused blood, and postoperative complications. Blood samples for elastase and complement (C5a) were obtained after induction and before sternotomy incision, prior to CPB, after protamine injection, at postoperative first hour in ICU, and at postoperative 24th hour. Blood samples for complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase MB (CKMB), blood urea nitrogen (BUN) and creatinine level were taken preoperatively and at one and 24 hours postoperatively.

Results: The duration of hospital stay was longer in group 2 than group 1 (6.5±1.8 vs. 2: 9.7±5.1 days, respectively, p=0.015). C5a values increased in both groups during the third, fourth, and fifth period indicating no statistically significant differences (0.5±0.2 vs. 0.6±0.2; p=0.361 and 0.4±0.1 vs. 0.4±0.0; p=0.144 and 2.1±6.6 vs. 0.4±0.1; p=0.298, respectively). Subgroup analyses for ALT, AST, CKMB and leucocyte count revealed significant difference between the groups (p<0.05).

Conclusion: Although effects of systemic inflammation associated with CPB were statistically significantly different in both groups, no statistically significant difference was found between the group in which leucocyte filter was used to reduce these effects and the controls.

Keywords: Cardiac; cardiopulmonary bypass; inflammation; leukocyte.

Amaç: Bu çalışmada doğuştan kalp cerrahisinde kardiyopulmoner baypas (KPB) sırasında lökosit filtrasyonunun enflamatuvar reaksiyonlar üzerine olan etkisi araştırıldı.

Çalışma planı: Çalışmada KPB sırasında oksijenatör sonrasında lökosit filtresinin arteriyel hatta bağlandığı hastalar grup 1'i (n=15), kontroller ise grup 2'yi (n=15) oluşturdu. Hastalar yaş, cinsiyet, doğuştan kalp hastalığı, toplam KPB süresi, aortik kros klemp süresi, mekanik ventilasyon süresi, yoğun bakım ünitesi (YBÜ) ve hastane kalış süresi, 24 saatlik göğüs drenaj miktarı takibi, inotropik ilaç kullanımı, toplam kan transfüzyon miktarı ve ameliyat sonrası komplikasyonlar açısından ayrıntılı olarak değerlendirildi. Elastaz ve kompleman (C5a) için alınan kan örnekleri ameliyat sırasında indüksiyondan sonra sternotomi öncesi, KPB'ye geçmeden önce, protamin sonrası, ameliyat sonrası birinci saatte YBÜ'de ve ameliyat sonrası 24. saatte alındı. Tam kan sayımı, aspartat aminotransferaz (AST), alanın aminotransferaz (ALT), kreatinfosfokinaz MB (CKMB), kan üre azotu (BUN) ve kreatinin düzeyi için ameliyat öncesi ve ameliyat sonrası birinci ve 24. saatlerde kan örnekleri alındı.

Bulgular: Hastanede yatış süresi grup 2'de grup 1'e göre daha uzun bulundu (sırasıyla 6.5±1.8'e karşın 9.7±5.1 gün, p=0.015). C5a değerleri her iki grupta da üç, dört ve beşinci periyotlarda istatistiksel anlamlı olmayan artışlar gösterdi (sırasıyla 0.5±0.2'ye karşın 0.6±0.2; p=0.361 ve 0.4±0.1'e karşın 0.4±0.0; p=0.144 ve 2.1±6.6'ya karşın 0.4±0.1; p=0.298). Gruplar arasında ALT, AST, CKMB ve lökosit sayısı için yapılan alt grup analizinde istatistiksel anlamlı farklılık (p<0.05) bulundu.

Sonuç: Kardiyopulmoner baypasa bağlı sistemik enflamasyonun etkileri her iki grupta da istatistiksel anlamlı farklılıklar göstermekle birlikte, bu etkilerin azaltılması amacıyla kullandığımız lökosit filtresi ile kontroller arasında istatistiksel anlamlı bir farka rastlanmadı.

Anahtar sözcükler: Kardiyak; kardiyopulmoner baypas; enflamasyon; lökosit.

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Cardiopulmonary bypass (CPB) is used to support circulation during the temporary inactivation of the heart and lungs in the surgical treatment of congenital and acquired heart diseases. Its applications lead to reactions at the cellular and molecular levels, mainly in patients with congenital heart disease.[1,2] These reactions cause systemic inflammatory response syndrome (SIRS) by triggering inflammation, which results in capillary leak syndrome and multiorgan failure. In addition, SIRS can lead to pulmonary, renal, gastrointestinal, myocardial, and central nervous system dysfunction as well as coagulopathy, vasoconstriction, increased interstitial fluid, fever, leukocytosis, hemolysis, and an increased susceptibility to infections.[1-4] Furthermore, while SIRS has been thoroughly investigated in adults, it is not yet fully understood in pediatric patients. Part of the research on the improvement of CPB-associated morbidity and mortality has been directed at minimizing neutrophil activation with leukocyte filtration.[5,6] In this study, we aimed to evaluate the effects of leukocyte filtration by the Pall Leukoguard-6® arterial filter (Pall Biomedical, Portsmouth, UK) during CPB in congenital heart surgery by comparing the parameters of multiorgan functions as well as specific neutrophil elastase and complement component 5a (C5a) enzyme levels between the leucocyte filter and control groups.

PATIENTS AND METHODS

After obtaining the approval of the local ethics committee at Dr. Sami Ulus Maternity and Children's Health and Diseases Training and Research Hospital in Ankara, Turkey, 30 patients who were scheduled for open heart surgery for a congenital heart disease between November 2008 and January 2009 at the Department of Cardiovascular Surgery were divided into two groups containing 15 subjects each. In the control group (group 2) either the Dideco D901 Lilliput 1 (for infants and newborns) or the Dideco D902 Lilliput 2 (for children) oxygenator (SORIN GROUP Italia S.r.l - Cardiopulmonary Business Unit., Mirandola, Italy) was connected to the arterial line after the oxygenator. In the study group (group 1) the Dideco D733 pediatric arterial filter (SORIN GROUP Italia S.r.l - Cardiopulmonary Business Unit., Mirandola, Italy) and the Pall Leukoguard-6 arterial filter (Pall Biomedical, Portsmouth, UK) were connected to the arterial line in a parallel manner after the oxygenator with Bıçakçılar pediatric tubing sets (Bıçakçılar Tıbbi Cihazlar San. ve Tic. A.Ş, İstanbul, Türkiye). The patients were evaluated in terms of age, gender, congenital heart disease, total CPB duration, aortic cross-clamp duration, intensive care unit (ICU) and hospital stay duration, and inotropic support (Table 1). Blood samples for the neutrophil elastase and C5a were obtained after the induction of anesthesia and before the sternotomy incision (phase 1), prior to CPB (phase 2), after the protamine injection (phase 3), at the postoperative 0 hour (phase 4), and at the postoperative 24th hour (phase 5). We also took blood samples for aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine phosphokinase-MB (CPK-MB), blood urea nitrogen (BUN), and creatinine levels as well as a complete blood count (CBC) at phases 0, 1, and 2. The blood samples for the C5a and neutrophil elastase were centrifuged at 3000 rpm for 10 minutes and stored at -70 °C. The elastase levels were evaluated with an enzyme immunoassay test, whereas the C5a levels were evaluated with an enzyme-linked immunosorbent assay (ELISA) test. Normal C5a levels were accepted as being between 0.15 and 0.5 μg/ml while normal, borderline, and high neutrophil elastase levels were accepted as <12, 12-18, and 18 U/ml, respectively. The CBC along with the AST, ALT, CPK-MB, BUN, and creatinine levels were measured with a Beckman-Coulter Synchron LX20 pro autoanalyzer (Beckman-Coulter, Inc., Brea, CA, USA), and the Horiba ABX Pentra 80 chemical analyzer (Horiba Ltd., Kyoto, Japan) was used to measure the leukocyte count. Both groups were considered equal with respect to anesthesia, heparin administration, prime solution, agents added to the solution, myocardial protection, and protamine administration. The prime solution was prepared using an isolyte to obtain a hematocrit (Htc) of 30%, and methylprednisolone (30 mg/kg) and cephazoline (50 mg/kg) were added to the solution. For anesthesia, fentanyl (100 μg/kg), vecuronium (0.1 mg/kg), heparin (400 U/kg), and protamine (1.5-2 mg) were used for each 100 U of heparin. Myocardial protection was achieved by crystalloid cardioplegia with a potassium content of 25 mEq/L being administered during induction and 10 mE/L given during maintenance with an aortic root pressure of 50 mmHg at 20-minute intervals. The administered dose was calculated as 20 ml/kg for the initial dose and 10 ml/kg afterwards. Inotropic support was composed of dopamine (5-15 μg/kg/min) or any amount of dobutamine.

Statistical analysis

The data was obtained using the SPSS version 15.0 for Windows software package (SPSS Inc., Chicago, Illinois, USA) with a 95% confidence level. Categorical data was presented using numbers and percentages, and continuous data was expressed as mean ± standard deviation (SD). The groups were compared using the

Table 1. Distribution of patient data before, during, and after the operation

Variable	Group 1 (n=15)			Group 2 (n=15)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (months)			77.9±49.6			83.7±67.2	
Gender							
Males	6	40		9	60		
Females	9	60		6	40		
Diagnosis							
Atrial septal defect	3	20		2	13.3		
Discrete subaortic membrane	-	-		1	6.7		
Double-chambered right ventricle	1	6.7		-	-		
Double outlet right ventricle	-	-		1	6.7		
Complete atrioventricular septal defect	1	6.7		-	-		
Mitral valvular prolapsed	1	6.7		-	-		
Mitral regurgitation	-	-		1	6.7		
Partial anomalous pulmonary venous connection	2	13.3		-	-		
Primum atrial septal defect	-	-		1	6.7		
Tetralogy of fallot	3	20		3	20		
Ventricular septal defect	4	26.7		6	40		
Inotropic agent used							
None	5	33.3		5	33.3		
24th hour	10	66.7		5	66.7		
48th hour	-	-		1	6.7		
Intraoperative and postoperative clinical parameters							
Hospital stay (days)			6.5±1.8			9.7±5.1	0.015
Total bypass time (minutes)			51.3±28.4			46.6±21.1	NS
Cross-clamp time (minutes)			32.3±22.7			28.2±15.9	NS
Intensive care unit stay (hours)			28±13.7			29.4±12.9	NS
Drain (ml)			192.3±120.7			227.4±120.0	NS
Amount of red blood cell (ml)			118.6±112.8			250±303.1	NS
Amount of fresh frozen plasma (ml)			246.5±156.0			239.6±141.6	NS
Duration of inotropic support (hours)			13.1±11.5			8.8±11.5	NS
Extubation time (hours)			5.1±4.3			8.3±8.4	NS

SD: Standard deviation; NS: Not significant.

Mann-Whitney U test, and differences in the phases were compared utilizing the Friedman test. In addition, paired comparisons by phases were made via the Wilcoxon signed-rank test. A *p* value of less than 0.05 was considered to be statistically significant.

RESULTS

There were no significant differences between the two groups with respect to age, weight, gender, diagnosis, and inotropic support (p>0.05) preoperatively. In addition, no patient in the study developed a major complication, and no in-hospital deaths occurred (Table 1). However, the patients in group 2 had significantly longer hospital stays than the patients in group 1 (9.7±5.1 days vs. 6.5±1.8 days, respectively) (p=0.015) (Table 1). Futhermore, when the C5a values were evaluated separately in the two groups, a significant increase was detected during phases 3, 4, and 5. In phase 3, the C5a value for group 2 was 0.55±0.21 while it was 0.49±0.22 for group 1 (p=0.361). In phase 4, the C5a value was 0.39±0.04 for group 2 and 0.36±0.08 for group 1 (p=0.144), and in phase 5, group 2 had a C5a value of 0.37±0.14, whereas it was 2.06 ±6.62 for group 1 (p=0.298). However, in phases 1 and 2, the differences were not significant. Group 2 had a C5a value of 0.31±0.09 while group 1 had a value of 0.24±0.03 in phase 1 (p=0.001), whereas in phase 2, the C5a values were 0.31±0.09 and 0.23±0.01, respectively (p=0.000) (Figure 1). The low levels in group 1 in these two phases can be attributed to the differences in the pre-procedural diagnosis and other demographic features of the groups while the significant elevation in the C5a levels in phases 3, 4, and 5 were associated with CPB, suggesting that the leucocyte filtration did not produce any significant difference between the groups. These

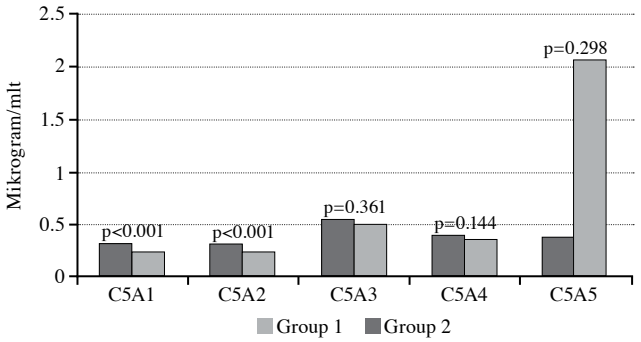

Figure 1. The mean distribution of C5A levels according to measurement times. C5A1: After induction and before the sternotomy incision; C5A2: Prior to cardiopulmonary bypass; C5A3: After the protamin injection; C5A4: At the postoperative first hour in the intensive care unit; C5A5: At the postoperative 24th hour.

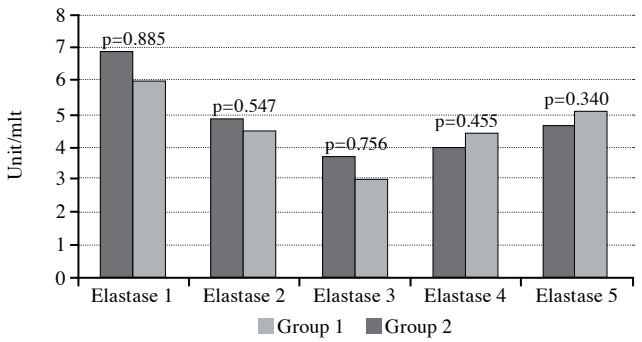

Figure 2. The mean distribution of elastase levels according to measurement times. The elastase was obtained after induction and before sternotomy incision (elastase 1), prior to cardiopulmonary bypass (elastase 2), after protamin injection (elastase 3), at postoperative first hour in intensive care unit (elastase 4), and postoperative 24th hour (elastase 5).

results are also relevant with regard to the effects of SIRS and leucocyte filtration on CPB.

When the neutrophil elastase values were evaluated in both groups, a decrease was detected in phases 1 and 2 (prior to CPB) but the values rose during phases 3, 4 and 5. Furthermore, an examination of these levels according to elapsed time revealed no significant differences between the two groups (p>0.05) (Figure 2), and there were no marked differences in terms of inotrope time and dosage or intubation duration (Table 1). Moreover, no significant differences were seen with respect to the laboratory results (p>0.05) (Table 2).

Additionally, we conducted subgroup analyses of the C5a (p=0.001) and neutrophil elastase (p=0.007) levels of group 2 and group 1 (p=0.001 and p=0.004,

Table 2. Results of the Friedman test related to the laboratory data

	Group 1		Group 2	
	Mean±SD	*p*	Mean±SD	*p*
Urea*	21.7±5.9		20.4±7.8	
Urea§	17.8±5.4	0.009	23.1±13.4	0.291
Urea¶	20.8±12.1		24.2±6.9	
Creatinine*	0.5±0.2		0.5±0.2	
Creatinine§	0.5±0.1	0.051	0.6±0.2	0.001
Creatinine¶	0.5±0.1		0.5±0.1	
Blood urea nitrogen*	9.6±2.8		9.1±3.7	
Blood urea nitrogen§	8.5±2.5	0.153	9.3±2.9	0.447
Blood urea nitrogen¶	10.2±5.7		10.7±3.6	
Alanine aminotransferase*	17.4±4.3		18.1±5.2	
Alanine aminotransferase§	25±10.9	0.020	21±4.9	0.006
Alanine aminotransferase¶	29.5±12.3		34.8±33.1	
Aspartate aminotransferase*	30.5±5.4		30±9.2	
Aspartate aminotransferase§	97.2±85.5	0.001	78.1±39.6	0.001
Aspartate aminotransferase¶	121.4±108.3		119±104.5	
Creatinine phosphokinase*	9.4±3.9		9.2±3.9	
Creatinine phosphokinase§	45.7±36.3	0.001	33.9±20.1	0.001
Creatinine phosphokinase¶	23.4±18.5		25.1±11.5	
White blood cell*	9.8±4.5		9.0±2.1	
White blood cell§	12.5±5.1	0.001	12.5±5.6	0.051
White blood cell¶	15.1±3.9		15.1±5.3	

SD: Standard deviation; *: Preoperative; §: Postoperative first hour; ¶: Postoperative 24th hour.

Table 3. Results of the Wilcoxon signed-rank test regarding the C5a and elastase levels according to the Paired phases (Subgroup analysis)

	Measurement time									
	1-2	1-3	1-4	1-5	2-3	2-4	2-5	3-4	3-5	4-5
Group 1										
C5a	0.320	0.001	0.001	0.002	0.001	0.001	0.001	0.041	0.132	0.798
Neutrophil elastase	0.065	0.001	0.041	0.201	0.078	0.826	0.496	0.005	0.009	0.410
Group 2										
C5a	0.724	0.002	0.007	0.147	0.001	0.011	0.107	0.020	0.001	0.470
Neutrophil elastase	0.053	0.009	0.056	0.133	0.256	0.776	0.047	0.233	0.035	0.118

C5a: Complement component 5a; 1: After induction and before the sternotomy incision; 2: Prior to cardiopulmonary bypass; 3: After protamine injection; 4: Postoperative first hour in intensive care unit; 5: Postoperative 24th hour.

respectively) (Table 2) and found no statistically significant differences ($p<0.05$) within the subgroups or the time of positivity of significantly different markers (e.g., between the first and third time measurements of C5a in the two groups. The results of paired sample test according to Wilcoxon paired phases are given in Table 3.

Moreover, the results of the Friedman test for the laboratory values of groups 1 and 2 revealed a significant increase in the postoperative ALT ($p=0.020$ and $p=0.006$, respectively), AST ($p=0.001$ and $p=0.001$, respectively), CPK-MB ($p=0.001$ and $p=0.001$, respectively), leucocyte count ($p=0.001$ and $p=0.051$, respectively) levels compared with the pre-procedural levels in the subgroup analysis of both groups. These results are relevant because they show the effects of CPB-associated SIRS (Table 2). Furthermore, when the ALT, AST, white blood cell (WBC) and creatinine values were evaluated, increases were detected during phases 2 and 3. In addition, there were significant differences between the subgroups with respect to significantly different parameters (e.g. between the first, second, and third ALT measurements and the first and third leucocyte count measurements in group 2 and between the first, second, and third ALT, AST, CPK-MB, and leukocyte count measurements in group 1). The results of the Wilcoxon paired sample test are presented in Table 2.

DISCUSSION

Since the early 1990s, studies have been conducted on leukocyte filters to prevent ischemia-reperfusion as well as SIRS due to CPB.[6] Age-related differences in the inflammatory response along with immature organ systems can lead to increased CPB-related injuries in the pediatric age group. In addition, the larger extracorporeal circulatory volume in this patient group compared with the body surface area causes further CBP-related hazards. Cardiopulmonary bypass induces the activation of the complement and contact systems, leading to neutrophil activation, which is triggered by contact with foreign surfaces, endotoxins, cytokines, complements, thrombocyte-activated factor, and ischemia-reperfusion.[7] Boldt et al.[8] found that in a population that underwent open heart surgery, the plasma adhesion molecule levels were higher in children than adults. Furthermore, Chen et al.[9] showed that leucocyte filtration during CPB decreases the neutrophil adhesion molecule (CD11b and L-selectin) levels. Activation of anaphylatoxins (C3a and C5a) also causes neutrophil adhesion and degranulation, basophil and mast cell activation, the release of histamine, and thrombocyte aggregation.[10] Additionally, activated neutrophils produce many lysosomal enzymes that are detrimental to cells, such as hydrogen peroxide, hypochloric acid, hydroxil radicals, elastase, myeloperoxidase, and lactoferrin. Thus, activated neutrophils cause increased morbidity and mortality.[11] Burrows et al.[12] also showed that neutrophils start to increase at the first hour and peak at 24 hours. They also do not return to normal levels at 48 hours, even though they decrease in number. Although the leucocyte count in the peripheral blood gradually increased for 24 hours after the operation in our study, there were no significant differences between the two groups.

Our subgroup analysis of both groups revealed a statistically significant increase in the peripheral leucocyte count at the postoperative 24th hour compared with the preoperative period, though the groups had similar levels. We considered this to be a systemic inflammatory response associated with the CPB.

Moreover, our results were similar to those that have been obtained in other studies.[13-15] Some have reported an association between increased complement levels and postoperative complications, whereas others did not demonstrate this association.[15] We also identified a gradual increase in C5a and neutrophil elastase

levels. The low levels of C5a in phases 1 and 2 were attributed to differences in the preoperative diagnoses and other demographic features while the insignificant increases in in phases 3, 4, and 5 across the two groups, despite the CPB-associated increase, suggested that leucocyte filtration did not have a significant effect. Additionally, when the neutrophil elastase values were evaluated in the two groups, they first decreased (prior to CPB) and then increased during phases 3, 4 and 5. These results are important with respect to the effects of CPB-associated SIRS and leucocyte filtration.

In a study by Mair et al.[16] which focused on an adult population that underwent elective coronary bypass surgery, leucocyte filtration did not alter cardiac or lung functions nor did it change the the need for inotropic support. They also determined that the perioperative CPK-MB and troponin levels did not vary. Yalçınbaş et al.[17] examined the role of leucocyte filters in congenital heart surgery and found no significant differences between the filter and control groups in terms of leucocyte count, neutrophil ratio, AST, ALT, or CPK-MB levels, even though all of these had marked increases. In a study involving patients who underwent open heart surgery, Kutsal et al.[18] reported that the serum levels of CPK-MB, AST, and lactate dehydrogenase (LDH) reached their peak 12-24 hours postoperatively and became normalized at 96 hours.

Orhan et al.[19] examined the myocardial and systemic inflammatory response in on-pump and off-pump CABG and reported that the off-pump surgery did not decrease the myocardial oxidative stress and inflammatory response, but it did cause the systemic inflammatory response to diminish. On the other hand, Leal-Noval et al.[5] reported similar cardiac index, cardiac enzyme, and cardiac dysfunction rates in the group without a leukocyte filter and a lower number of perioperative infections and fevers along with a weaker hyperdynamic picture in the group with this filter. However, the differences were statistically insignificant. We found no such findings in our study.

Emiroğlu et al.[20] investigated leucocyte filters in coronary bypass surgery and detected no significant differences with respect to CBC, biochemical markers, hemodynamic measurements, the need for inotropic support, mechanical ventilation duration, or length of ICU and hospital stays. They recommended the use of a leukocyte filter in the patients at risk for postoperative complications.

Conclusion

In our study, the short hospital stay in group 1, different patient diagnoses and demographic features, and small sample size were factors that affected the results. In addition, the two groups were mostly made up of low-risk patients. Apart from the C5a levels in phases 1 and 2, we found significant differences in the subgroup analyses performed to determine the levels of neutrophil elastase, AST, ALT, leukocytes, and CPK-MB. Hence, our study identified meaningful results concerning the effects of CPB-associated SIRS in pediatric cases, but we failed to show a significant difference between the patients with a leukocyte filter and the controls. We believe that more studies with a larger sample size should be conducted to further evaluate the useful effects of leukocyte filters.

Declaration of conflicting interests

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