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Safety of Intravenous Heparin for Cardiac Surgery in Patients with Alpha-Gal Syndrome

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Abstract

Background: Alpha-gal syndrome is a tick-acquired disease caused by IgE to the oligosaccharide galactose-alpha-1,3-galactose (alpha-gal), causing allergic reactions to meat and products sourced from non-primate mammals. As heparin is porcine-derived, we hypothesized that patients with alpha-gal syndrome who received high-dose heparin for cardiac surgery would have increased risk of anaphylaxis.

Methods: All cardiac surgery patients at an academic medical center from 2007–2019 were cross-referenced with research and clinical databases for the alpha-gal IgE blood test. Clinical data was obtained through the institutional Society of Thoracic Surgeons Adult Cardiac Database and chart review. Patients were stratified by development of an allergic reaction for univariate statistical analysis.

Results: Of the 8,819 patients, 17 (0.19%) had a positive alpha-gal test prior to cardiac surgery. Of these 17 patients, 4 (24%) had a severe allergic reaction. The median alpha-gal titer was significantly higher in patients with a reaction (75 [61–96] vs 8 [3–18] IU/mL, $p=0.006$). There were no differences in median heparin loading dose, total dose, or maximum activated clotting time (all $p>0.05$). In a subgroup of 8 patients with recent alpha-gal IgE level, 4 (50%) developed an allergic reaction.

Conclusions: Although alpha-gal is rare in patients undergoing cardiac surgery, there is up to a 50% risk of serious allergic reaction to heparin for cardiopulmonary bypass. Higher preoperative alpha-gal titers may confer a higher risk of severe allergic reaction. For patients with a clinical suspicion of alpha-gal syndrome, we recommend pre-screening with IgE levels and pre-medicating prior to receiving high doses of intravenous heparin.

Keywords

Cardiac Surgery; Allergy; Alpha-Gal

The allergy caused by IgE to galactose-alpha-1,3-galactose (alpha-gal), commonly referred to as the alpha-gal syndrome, was originally discovered due to hypersensitivity reactions to

cetuximab, which contains alpha-gal.[1] This oligosaccharide is an evolutionarily conserved blood group-like antigen present on glycoproteins and glycolipids in most non-primate mammals. In contrast, humans and higher primates do not express alpha-gal but do produce naturally circulating IgG against alpha-gal and these antibodies are important contributors to hyperacute rejection seen with xenotransplantation.[2] The inciting event which leads to IgE sensitization against alpha-gal typically relates to tick bites, with the lone star tick (*Amblyomma americanum*) being the dominant cause in the United States.[3] Other species of tick have been associated with alpha-gal sensitization worldwide, as have Chiggers and other ectoparasites.[4] As a consequence of this IgE sensitization, subjects who consume meat or organs of non-primate mammals can experience anaphylaxis, approximately 3–6 hours following ingestion. Importantly, however, reactions can occur more rapidly when alpha-gal-containing products are introduced parenterally, as exemplified by reactions to cetuximab.[5] The syndrome is most common in the southeastern United States, but owing to climate change and other factors which have resulted in expansion of the range of the lone star tick into the northeastern United States the syndrome may be increasingly recognized in these areas.[6, 7]

There are two areas where alpha-gal becomes relevant for cardiac surgery. First, all current bioprosthetic valves are porcine or bovine derived and contain galactose-alpha-1,3-galactose.[8] Our group has previously reported patients with alpha-gal may have accelerated degeneration of their bioprosthetic valves.[9] Secondly, unfractionated heparin is a heterogenous polysaccharide derived from bovine lung and porcine intestinal mucosa and could contain galactose-alpha-1,3-galactose, as suggested by two recent reports.[10, 11] Cardiopulmonary bypass for cardiac surgery requires large doses of unfractionated heparin, carrying potential risk of allergic reaction. While there are reports of allergic reactions after cardiac surgery and intravenous heparin administration, there is no available data quantifying the risk of heparin administration.[12–14] In addition, there are currently no standards or guidelines for the administration of heparin in alpha-gal patients as the degree of risk is largely unknown. We hypothesized that patients with who had pre-existing IgE sensitization to alpha-gal would have increased risk of anaphylaxis, driven by both the amount of heparin administered and level of preoperative alpha-gal titers.

Patients and Methods

Patient Data and Variable Definitions

This study was approved by the University of Virginia Institutional Review Board (Protocol numbers 20803 and 13298). As the assay to measure IgE to alpha-gal was developed in 2007, we included all cardiac surgery patients at the University of Virginia between 2007 and 2019 who received high-dose heparin for cardiopulmonary bypass or transcatheter aortic valve replacement. Perioperative data was obtained from the institution's Society of Thoracic Surgeons Adult Cardiac Surgery Database. These patients were then cross-referenced with an alpha-gal research database, a clinical data repository and medical records to identify subjects who had been tested for IgE to alpha-gal.

The alpha-gal IgE testing was performed using the commercially available ImmunoCAP platform (Thermo Fisher Scientific Inc., Waltham, MA). The assay is comparable to a

sandwich ELISA, but uses a high-capacity cellulose sponge as the solid-phase.[15] Cetuximab and bovine thyroglobulin can both be used as the alpha-gal bearing glycoprotein with similar testing characteristics. The reported sensitivity of the two options are 91% and 88% respectively.[16] The specificity of the assay in population based studies is also high. [15]

Patients were stratified by preoperative alpha-gal status for univariate analysis. The primary outcome was defined as peri-operative anaphylaxis or allergic reaction. All clinical variables utilized standard Society of Thoracic Surgery definitions.

Statistical Analysis

Categorical variables are presented as count (%) and continuous variables as median [25th, 75th percentile] or mean $\pm$ standard deviation based on normality. Patients were stratified by alpha-gal status and peri-operative allergic reaction status for analysis using the Mann-Whitney U test for continuous variables and Chi-square test or Fischer's Exact for categorical variables. All statistical analyses were carried out using SAS Version 9.4 (SAS Institute, Cary, NC) with a p-value less than 0.05 determining significance.

Results

Baseline and Operative Characteristics

Of 12,706 patients in the STS database, 9,396 had their operations between 2007 and 2019 (Figure 1). Of these, 8,819 utilized cardiopulmonary bypass or underwent TAVR. A total of 49 patients were tested for alpha-gal, either before or after surgery, of which 13 patients (27%) tested negative. Of the 36 (73%) subjects who tested positive, the majority (58%) of cases were diagnosed after surgery. Only 17 patients had alpha-gal pre or peri-operatively, of whom 8 had alpha-gal specific IgE titers obtained within 90 days before or after surgery.

Supplemental Table 1 contains details of patient-specific information. Patients with situations resulting in missing data include patient C, who received intravenous heparin (unknown dose) with central line placement at an outside hospital resulting in anaphylaxis. After transfer to UVA this subject underwent their operation using Bivalirudin, with severe postoperative bleeding. Patient E had a known history of allergic reactions to red meat, received steroids and H2 blockers premedication, but was the alpha-gal diagnosis was confirmed after surgery. Patients I and L underwent transcatheter aortic valve replacement with slightly lower heparin bolus dosing and no cardiopulmonary bypass. Patient O tolerates eating red meat, although the system status of most patients at the exact time of surgery was unknown.

Of the 17 patients with known preoperative alpha-gal, 8 (47%) received planned prophylactic premedication prior to heparin administration with steroids, H1 and H2 blockers. One patient was tested with small doses of heparin preoperatively and the same lot number was then used during surgery.

Allergy and Clinical outcomes

Of the 17 alpha-gal positive patients, 4 (24%) developed a severe allergic reaction during cardiac surgery. By contrast, of the 13 alpha-gal negative subjects only 1 (8%) had an allergic reaction peri-operatively. Table 1 includes baseline and intraoperative characteristics by allergic reaction status of the alpha-gal positive patients. Premedication with steroids and anti-histamine agents was similar between patients with an allergic reaction compared to without (50% vs 46%, $p=0.733$). The median alpha-gal IgE levels were significantly higher in patients who developed an allergic reaction compared to those who did not (75 [61–96] vs 8 [3–18] kU/L, $p=0.006$) although there was no significant difference in total IgE titers (Table 1 and Figure 2). There was no difference in the median heparin doses or maximum activated clotting time (Table 1 and Figure 3). There were no mortalities and few complications in the cohort, with no significant differences between those with and those without allergic reactions (Table 3).

Because alpha-gal IgE titers can wane over time in some subjects, we conducted a subanalysis for patients with a recent alpha-gal titer (within 90 days of surgery).[17] A total of 8 patients met this criterion, four (50%) of whom had an allergic reaction (Table 2). Again, the alpha-gal specific IgE titer was significantly higher in patients who developed a reaction (75 kU/L vs 1 kU/L, $p=0.029$, Figure 2). There was no difference in heparin loading or total doses, nor maximum activated clotting time (Table 2).

Comment

This is the largest series to date of alpha-gal patients who received heparin, all of whom underwent cardiac procedures requiring large boluses of intravenous heparin. Of the 17 patients with preoperative alpha-gal, four (24%) developed an allergic reaction, a rate that increases to 50% in patients with recent IgE levels. As IgE levels can wane quickly over time, the best conclusions can likely be reached from this cohort of patients.[17] Median alpha-gal titers were significantly higher in patients who developed reactions (75 kU/L vs 8 kU/L, $p=0.006$). Possibly due to the extremely high doses of heparin given, there were no differences in loading dose or total dose of heparin, nor maximum activated clotting time between groups.

The risk of allergic reaction after cardiac surgery with systemic heparinization was 24% for patients with preoperative alpha-gal syndrome. Although high, this rate is roughly in line with the summation of previously published case reports. While cardiac surgery has a higher rate of anaphylactic reactions than non-cardiac surgery, estimates still range far lower than in our alpha-gal cohort, typically between 0.1% and 0.4%.[18–20] The University of Virginia has previously published accounts where two patients developed allergic reactions, and who are included in this study.[12] Alternatively, there are reports of cardiac surgery with heparin and no allergic reactions.[14, 21] Finally, a recent report of four cardiac surgery cases noted two allergic reactions.[22] These prior reports lack critical information on alpha-gal levels and heparin dosing. Although considerations have been given to the impact of bioprosthetic valve implantation and immediate allergic reactions, these patients have been noted to be tolerating their valves without ongoing allergic complications.[9, 12] In this study there was no association with type of surgery and risk of allergic reaction, and one reaction occurred

prior to initiation of surgery when heparin was administered for central line placement. Taken together, the likely culprit appears to be the large heparin doses required for surgery.

The difference in median alpha-gal titer between groups was even more pronounced in the subgroup of patients with recent titers. As Figure 2 demonstrates, there are clear groupings of patients with titers <10 kU/L, none of whom had a reaction and those >50 kU/L, all of whom did. This dichotomy suggests alpha-gal titer is likely the most important factor in predicting who develops an allergic reaction. As alpha-gal titers can change over time a common practice is to follow them with a yearly titer.[23] As such, we recommend obtaining a new alpha-gal IgE specific titer immediately prior to surgery.

There were no clear differences in heparin doses or maximum activated clotting time between groups in this study. However, there are a number of unresolved questions regarding heparin use in alpha-gal patients. First, the heparin doses for cardiopulmonary bypass are some of the highest given in medicine. It is therefore difficult to extrapolate the findings to lower doses of heparin. The heparin is given in boluses over the period of a few hours, unlike typical infusions with low doses given over hours to days. In addition, it is unclear if the route matters and thus whether chemoprophylaxis with subcutaneous heparin has similar risk. Finally, unfractionated heparin is obtained from porcine intestines with variability between lots and manufacturers. Thus, it is possible or even likely that heparin could be present in only some preparations. It is important to note that to date alpha-gal has been successfully detected in heparin samples. A further question is whether low molecular weight heparin has a different risk profile. A final consideration is to the use of heparin alternatives in patients deemed high risk. The patient who was transferred after their allergic reaction had their operation performed with Bivalirudin, and subsequently had major postoperative bleeding. The cost, unfamiliarity, lack of reversal agent and bleeding risk limit the utility of Bivalirudin, but can be used when heparin is deemed unsafe.[24] In patients with renal insufficiency Argatroban represents a viable alternative to heparin as well. We are not aware of any groups attempting strategies such as plasmapheresis or desensitization prior to cardiac surgery or for any other reason.

A total of eight patients (47%) were premedicated prior to receiving heparin. There is no standard prophylactic regime, but typically included steroids, H1 +/- H2 blockers.[13] While it is not clear that premedication reduces risk of IgE-mediated reactions, the medications are deemed low risk. Despite this, it has become the standard practice at our institution to pre-medicate patients with high alpha-gal IgE titers with steroids (Hydrocortisone 100mg or Methylprednisolone 500mg), H1 blocker (Diphenhydramine 50mg) and an H2 blocker (Famotidine 20–40 mg). While the reactions that did occur were typically severe with dermatologic, pulmonary and cardiac consequences, they were all successfully treated with the some combination of vasopressor, steroids, and H1/H2 blockers. In these patients the medications were typically continued for a short perioperative period (~24 hours). The mode of chemoprophylaxis for deep vein thrombosis was variable in these patients, ranging from successful use of subcutaneous heparin to early anticoagulation with warfarin.

This cardiac surgery population had an usually high rate of positive alpha-gal tests at 73%. This is a much higher rate than the ~20% that has been reported in adults in this region. This raises the possibility that IgE to alpha-gal could predispose some to cardiovascular conditions requiring cardiac surgery. Two recent findings suggest this may be the case. First, a recent study found sensitization to alpha-gal was a risk factor for coronary artery disease, and in particular was associated with increased atheroma burden and unstable plaques.[25] Second, we have also shown that alpha-gal results in early degeneration of bioprosthetic valves.[8, 9] Another interesting aspect of alpha-gal sensitization is that only a minority of patients develop overt red meat allergy, with the syndrome most recognized in subjects with relatively high titers.[25, 26] This suggests that a large number of cardiac surgery patients may be sensitized to alpha-gal but are unaware. Because we suspect many of these would be low-level sensitization, this further supports our finding that low alpha-gal IgE titers have low risk for allergic reactions to heparin. The high positive test rate suggests under-testing, thus we recommend evaluating for alpha-gal prior to cardiac surgery in any patient with a suspicion for a meat allergy, allergic reaction to heparin, or early bioprosthetic valve degeneration.

This study is limited by its retrospective nature precluding determinations of causation. While the sample size with alpha-gal testing is modest, this is the first cohort analysis of a cardiac surgical population allowing for prevalence and risk determination. As many patients have excluded red meat from their diet since diagnosis, it is largely unknown which patients were symptomatic at the time of surgery and thus this information cannot be correlated with titers or reaction status.

Conclusion

In this cohort analysis of a single institution cardiac surgery population only a small percentage of cardiac surgery patients had IgE to alpha-gal (0.19%). However, in this population there is an up to 50% risk of a serious allergic reaction to high doses of intravenous heparin used for cardiac surgery. Higher preoperative alpha-gal titers may confer a higher risk of severe allergic reaction. For cardiac surgical patients with a clinical suspicion of alpha-gal syndrome, we recommend pre-screening with IgE levels and pre-medicating prior to receiving high doses of intravenous heparin. The high rate of positive alpha-gal tests in this cohort suggests elevated risk of requiring cardiac surgery and further research is warranted on cardiovascular risk in patients sensitized to alpha-gal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

BSA	body surface area
CLD	chronic lung disease
CPB	cardiopulmonary bypass

ICU	intensive care unit
IQR	interquartile range
PROM	predicted risk of mortality
LOS	length of stay
PRBC	packed red blood cells
STS	Society of Thoracic Surgeons

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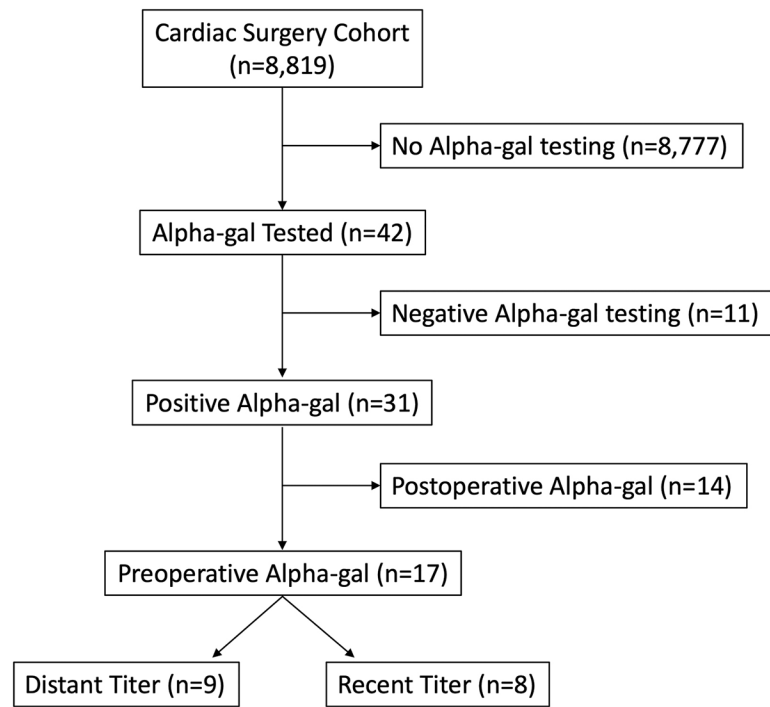


Figure 1:
Consort diagram of patient population.

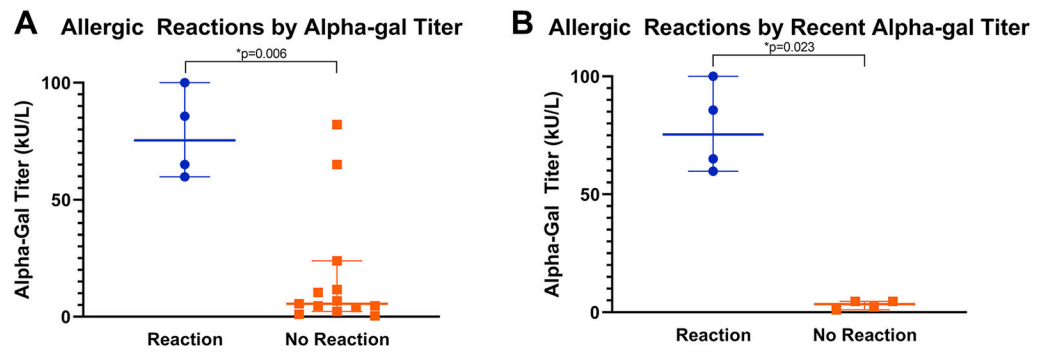


Figure 2:
Alpha-gal specific IgE levels by allergic reaction status for (A) all patients and (B) those with recent levels

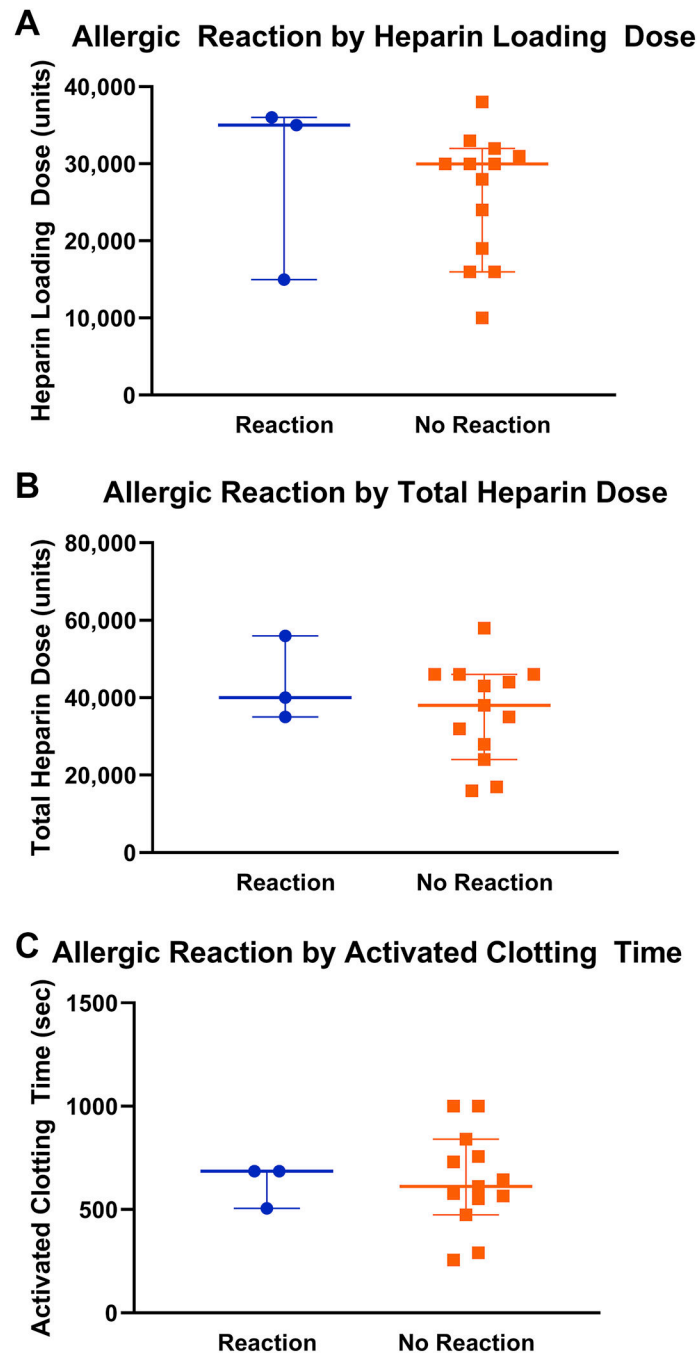


Figure 3:
All patients stratified by allergic reaction status with heparinization results including A. Loading dose of heparin. B. Total dose of heparin. C. Maximum activated clotting time.

Table 1:

Baseline and operative characteristics by allergic reaction status among subjects with preoperative diagnosis of alpha-gal syndrome

<i>Baseline Characteristics</i>	Reaction (n=4)	No Reaction (n=13)	p-value
Age (years)	63 [46–74]	67 [59–71]	
Body mass index (kg/m ²)			
Female	0 (0%)	1 (8%)	1.00
Smoker	1 (25%)	6 (55%)	0.569
Prior stroke	2 (50%)	1 (8%)	0.121
Hypertension	3 (75%)	10 (77%)	1.00
Coronary artery disease	1 (25%)	8 (62%)	0.294
Prior myocardial infarction	0 (0%)	3 (23%)	0.541
Heart failure	1 (25%)	5 (38%)	1.00
Diabetes	2 (50%)	5 (38%)	1.00
Dialysis dependent renal failure	0 (0%)	1 (8%)	1.00
Elective status	2 (50%)	11 (85%)	0.219
Alpha-Gal IgE, (kU/L)	75 [61–96]	6 [3–18]	0.006
Total IgE (kU/L)	360 [182–465]	343 [28–528]	0.774
<i>Operative Characteristics</i>			
Premedication [‡]	2 (50%)	6 (46%)	0.733
Heparin loading dose	35,000 [15,000–36,000] [†]	30,000 [17,500–31,500]	0.507
Heparin total dose	40,000 [35,000–56,000] [†]	37,500 [26,000–46,000]	0.539
Maximum activated clotting time (sec)	685 [506–686] [†]	612 [513–799]	0.986
Prior cardiac surgery	1 (25%)	3 (23%)	1.00
Surgery Type			0.444
AV replacement	2 (50%)	3 (23%)	
AV replacement + CABG	0 (0%)	3 (23%)	
Isolated CABG	0 (0%)	4 (31%)	
MV repair	0 (0%)	1 (8%)	
MV Replacement	1 (25%)	1 (8%)	
Other	1 (25%)	1 (8%)	
Cross Clamp Time (min)	72 [58–108]	72 [57–97]	
Cardiopulmonary bypass Time (min)	98 [86–153]	107 [75–119]	

[†]N=3 for patients completing cardiac surgery with heparin for anticoagulation

[‡]Premedication with H1/H2 blockers and steroids

Table 2:

Baseline and operative characteristics for patients with IgE testing within 90 days of surgery

<i>Baseline Characteristics</i>	Reaction (n=4)	No Reaction (n=4)	p-value
Alpha-Gal IgE (kU/L)	75 [61–96]	1 [3–5]	0.029
Total IgE (kU/L)	360 [182–465]	25 [7–40]	0.057
Alpha-Gal % of IgE (%)	20 [17–52]	15 [6–19]	0.143
<i>Operative Characteristics</i>			
Premedication [‡]	2 (50%)	4 (100%)	0.733
Heparin loading dose	35,000 [15,000–36,000] [†]	30,000 [17,500–31,500]	0.507
Heparin total dose	40,000 [35,000–56,000] [†]	37,500 [26,000–46,000]	0.539
Maximum activated clotting time (sec)	685 [506–686] [†]	612 [513–799]	0.986

[†]N=3 for patients completing cardiac surgery with heparin for anticoagulation

[‡]Premedication with H1/H2 blockers and steroids

Table 3:

Operative outcomes for patients by allergic reaction status

<i>Short-Term Outcomes</i>	Reaction (n=4)	No Reaction (n=13)	p-value
Operative mortality	0 (0%)	0 (0%)	1.00
Stroke	0 (0%)	0 (0%)	1.00
Renal failure	0 (0%)	1 (8%)	1.00
Atrial fibrillation	1 (25%)	3 (23%)	1.00
Reoperation for bleeding	1 (25%)	0 (0%)	0.235
Transfusion	2 (50%)	2 (15%)	0.219
Postoperative length of stay (days)	7 [6–11]	5 [4–6]	