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Negative results - Cardiopulmonary bypass

A lipopolysaccharide adsorber in adult cardiopulmonary bypass: a single centre randomised controlled pilot trial☆

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Abstract

Objectives: The aim of this study was to describe the biochemical effects and safety of selective removal of endotoxin from whole blood using a lipopolysaccharide adsorber during complex cardiac surgery. **Methods:** We carried out a single centre prospective randomised controlled pilot trial in patients undergoing elective cardiac surgery using cardiopulmonary bypass (CPB) at a large UK cardiothoracic institution. Seventeen patients were randomly allocated to one of two groups: with or without an adsorber included in the CPB circuit. Fourteen patients were included in a complete case analysis. Blood samples were taken at the time of consent, immediately following anaesthesia, at 60, 180 and 360 min after the institution of CPB, and the morning following surgery. Primary outcomes were plasma levels of endotoxin, IL-6, IL-8 and TNF-α. Secondary outcomes were measures of patient safety including blood chemistry and coagulation parameters, length of stay, and adverse events. **Results:** No differences were seen in endotoxin or cytokine levels between adsorber and control groups at any of the measured time-points. No difference between groups was detected in measures of patient safety following the intervention. Haemoglobin and haematocrit were significantly lower in the intervention group pre-bypass, $P=0.02$ in both instances. **Conclusion:** There was no effect of the adsorber on endotoxin levels or inflammatory response in this study, we have demonstrated the device to be safe in a complex cardiac surgery setting.

Keywords: Cardiopulmonary bypass; Randomised controlled trial; Systemic inflammatory response syndrome; Endotoxin

1. Introduction

Cardiopulmonary bypass (CPB) is the established method of circulatory support for cardiac surgery, however, it can trigger a potentially harmful cascade of inflammatory responses [1]. Systemic endotoxin, the lipopolysaccharide (LPS) complex associated with the outer cell wall of Gram-negative bacteria, has been shown to increase during and after CPB [2–5], and is thought to originate from the gut following periods of inadequate perfusion and increased mucosal permeability [3, 6]. Endotoxin is thought to play a role in the activation of cytokines and complement, increasing the risk for postoperative inflammatory complications and prolonged postoperative recovery [6].

The Alteco® LPS Adsorber (Alteco Medical AB, Lund, Sweden) is an extracorporeal device for selective removal of endotoxin from whole blood. Studies in animals subjected to endotoxin insult have shown lower endotoxin levels and better cardiovascular stability when using this device [7]. A similar device has also been shown to reduce interleukin (IL) levels following CPB in pigs [8] and also improved haemodynamics and organ dysfunction in septic shock in a multi-centre randomised controlled trial [9]. A small clinical study (nine patients in the intervention group) demonstrated the Alteco® LPS adsorber to be safe for use in humans undergoing CPB, however, the number of patients experiencing an endotoxin insult was very low and as such efficacy of the device could not be tested [10]. The aim of this study was to describe the biochemical effects of LPS adsorber treatment during cardiac surgery using CPB, in patients with a more pronounced endotoxin response. Primary outcome measures were systemic detection of endotoxin, IL-6, and IL-8, and TNF-α. Secondary outcome measures were to assess the safety of the device in this patient population.

2. Materials and methods

2.1. Trial design

We carried out a single centre prospective randomised controlled pilot trial in patients undergoing elective cardiac surgery using CPB at a large UK cardiothoracic institution.

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A study population was chosen in which high endotoxin levels could be expected, i.e. longer bypass times [11].

The study protocol was approved by our regional Ethics Committee (ref: 07/Q0104/49) and informed consent was obtained prior to any trial related activities being carried out. Patients aged 18 years and over were eligible to take part if they were scheduled for cardiac surgery with an expected CPB time in excess of 60 min. Exclusion criteria included planned hypothermia (<28 °C), use of steroids in the last six months, currently undergoing immunosuppressive therapy, anaemia [preoperative haemoglobin (Hb) <10 g/dl], haematological malignancy, disease of the immune system, female patients of childbearing age, and participation in another clinical trial.

This study is reported in accordance with the CONSORT statement.

2.2. Randomisation

Patients were randomly allocated to one of two groups: with or without an adsorber included in the CPB circuit. The allocation sequence was generated by a computer-generated simple random number scheme, and was performed by our biostatistician. The allocation sequence was concealed in consecutively numbered sealed envelopes. Neither trial coordinators nor investigators had access to the allocation sequence. Once informed consent was obtained the next available envelope was opened and the allocation revealed. This study was not blinded. Nine adsorbers were available for the study and randomisation was continued until all adsorbers had been used.

2.3. The device

The Alteco® LPS adsorber (Alteco Medical AB, Lund, Sweden) is a CE-marked (CE 0088) disposable Class IIa medical device designed for extracorporeal use. It is housed in a polycarbonate exterior that contains a series of polyethylene porous plates coated with a peptide specific to LPS (see supplementary figures online). The internal surface has an effective surface area of 3.3 m^2. The LPS adsorber is a single use only product sterilised by gamma irradiation. The device was handled according to manufacturer's instructions.

2.4. Intervention

The adsorber was prepared by flushing with 500 ml of 0.9% NaCl under gravity. The unit was primed upright and air removed by gentle tapping. The adsorber was incorporated into the CPB circuit with inflow to the device coming from a side arm of the arterial line of the CPB circuit, and endotoxin-filtered blood returning to the CPB venous reservoir. The unit was secured upside down to maximise flow distribution through the system. The flow through the adsorber was maintained at 150 ml/min and monitored using a flow probe (Levitronix, Zurich, Switzerland).

Heparin (100 IU/kg) was added to the CPB prime and activated clotting time (ACT) was maintained above 450 s during the duration of CPB. Ultrafiltration was not used during CPB.

All patients received the same anaesthetic regimen (based on propofol and fentanyl), the same muscle relaxant (pancuronium), the same dose of antifibrinolytic (tranexamic acid) and the same antibiotics.

2.5. Trial objectives and outcome measures

The aims of this study were 1) to assess whether the LPS adsorber used during CPB reduced systemic levels of endotoxin during and after CPB, 2) to describe the effects on inflammatory mediators of the Alteco® LPS adsorber treatment during cardiac surgery using CPB, and 3) to assess the safety of the device in this patient population.

Primary outcome measures were the systemic detection of endotoxin, IL-6, and IL-8, and TNF-α during and after CPB.

Secondary outcome measures, with respect to safety assessments, were a difference between treatment and control groups in red and white blood cell count, Hb, haematocrit (HCT), creatinine, blood coagulation parameters, C-reactive protein (CRP), blood glucose levels, lactate, length of stay in hospital and intensive care and adverse events.

2.6. Blood sampling and clinical data collection

Blood samples were taken at the time of consent (baseline), immediately following anaesthesia (T0), at 60, 180 and 360 min (T60, T180 and T360, respectively) after the institution of CPB, and the morning following surgery (Tpost).

'On bypass' blood samples were obtained from the arterial sampling port on the CPB manifold.

For endotoxin and cytokine assays, blood was drawn into sterile pyrogen-free collecting tubes containing sodium citrate (Sarstedt Monovette, Nümbrecht, Germany) and immediately placed into a pre-cooled centrifuge at 4 °C. The samples were spun for 5 min at 1200 g, and the supernatant (plasma) frozen at −80 °C for future batch analysis. All assays were conducted in independent laboratories. Cytokine (IL-6, IL-8, and TNF-α) analyses were performed using Luminex ELISAs as per manufacturer's instructions (R&D Systems, Oxon, UK). Endotoxin was measured using the limulus amoebocyte lysate test in combination with a rocket immunoelectrophoretic assay as described previously [12] and endotoxemia was defined as a level above 5 pg/ml (0.03 EU/ml) [3, 13].

White blood cell count, red blood cell count, Hb, HCT, creatinine, CRP, blood glucose levels, lactate and arterial blood gases were measured at baseline and at all time-points up to Tpost. Thromboelastography (TEG) analyses for whole blood coagulation parameters were performed at T0, T360 and Tpost using the TEG 5000 analyser (Haemoscope, Medicell, London, UK), according to the manufacturer's instructions.

Adverse events were recorded until Tpost. All patients were followed-up for 30 days following surgery, and length of intensive care and hospital stay were recorded.

2.7. Statistical analysis

The study was designed to be descriptive; there was insufficient clinical experience to perform a statistical power analysis.

Analysis was performed using SPSS (version 15), SAS (version 9) and STATA (version 9) statistics packages and was done on a complete case analysis basis. Pre-bypass measurements of continuous outcome variables were compared using the Student's *t*-test. Continuous outcomes were compared over the time course between the adsorber and control groups using repeated measures analysis of variance (ANOVA). Where possible, adjustment for the pre-bypass measurements of the outcome variable values was made. Mean differences between the adsorber and control groups were calculated. Many of the TNF-α values were below the threshold of measurement. In this case, the variable was dichotomised into above and below threshold. TNF-α values were, therefore, summarized using the number and proportion in each group above the threshold, and was compared between the adsorber and control groups over time using generalized estimating equations (GEE) in order to account for the repeated measurements. Intensive care unit (ICU) and hospital stay were compared by calculating the Hodges–Lehmann median difference between the filter and control group and its 95% confidence interval (CI), and the outcomes were compared between the two groups using the Mann–Whitney *U*-test.

3. Results

Seventeen patients were enrolled between September 2007 and April 2008, of which nine were randomly allocated to the adsorber group. Three patients were consented but

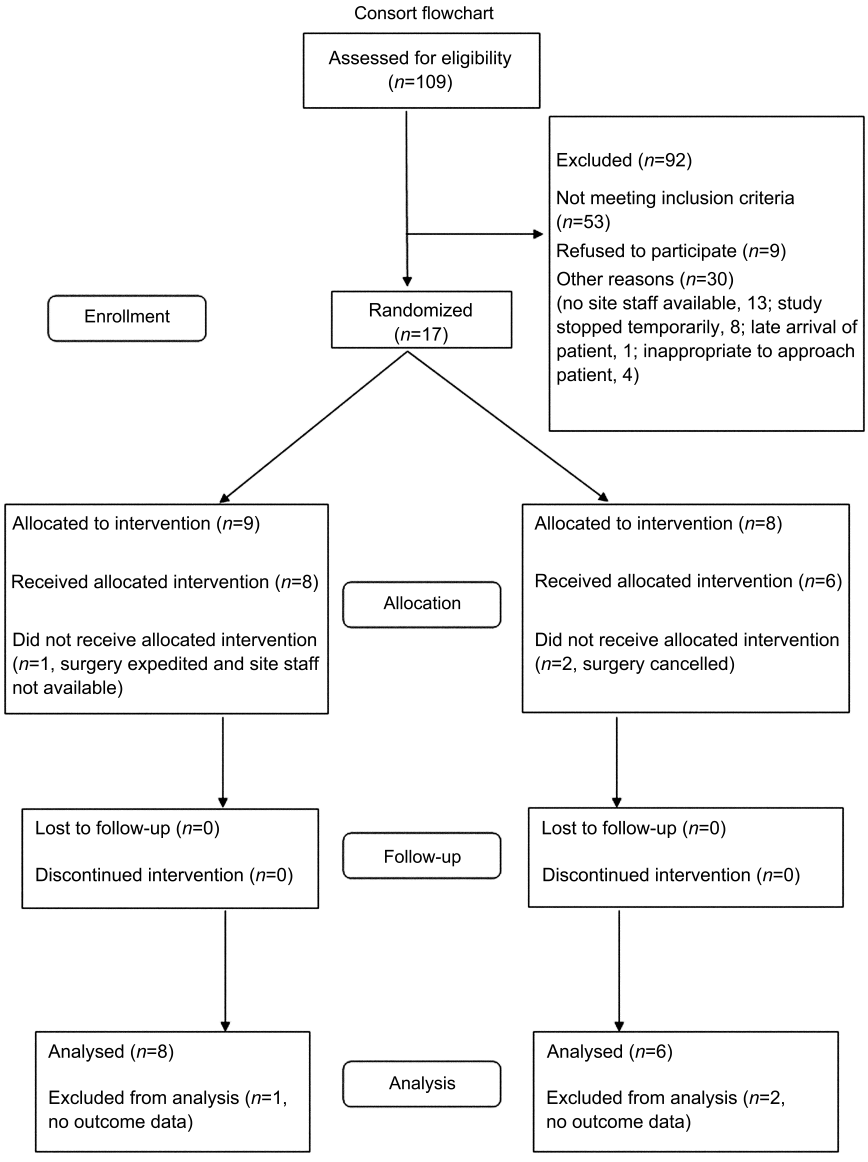

Fig. 1. Consort diagram.

Table 1
Baseline characteristics and surgical variables in the adsorber and control groups

Characteristics	Adsorber group, $n=9$	Control group, $n=8$
Mean age (years) (S.D.)	72 (9.2)	70 (10.6)
Gender: male, *n* (%)	8 (89)	7 (88)
Mean weight (kg) (S.D.)	81 (8.8)	79 (16.4)
Mean height (cm) (S.D.)	172 (8.2)	170 (8.7)
Mean BMI (S.D.)	27 (2.4)	27 (3.9)
Mean EuroSCORE (S.D.)	6.9 (4.60)	6.3 (1.98)
Median bypass time (min) (IQR)	102 (45.0)	110 (57.8)
Median ischaemic time (min) (IQR)	76 (27.5)	84 (43.0)
Mean systolic BP (S.D.)	141 (30.2)	119 (26.7)
Mean diastolic BP (S.D.)	72 (11.4)	65 (17.3)
Mean heart rate (S.D.)	73 (15.6)	73 (11.6)

S.D., standard deviation; BMI, body mass index; IQR, inter-quartile range; BP, blood pressure.

had their operations cancelled due to lack of ICU beds on the day of the operation. One of these was in the adsorber group. Therefore, for primary and secondary outcome data, there are six patients in the control group and eight patients in the adsorber group (Fig. 1).

Demographics and surgical data were comparable between groups and are shown in Table 1.

Endotoxin levels are shown in Table 2 and in box plot graphs in Fig. 2. One patient in the control group had slightly raised endotoxin levels at baseline (8 pg/ml). Endotoxaemia was detected in all patients after the induction of CPB. The highest levels of endotoxin [mean $\pm$ standard deviation (S.D.)] were measured at 3 h after commencement of CPB in both groups (363.3 ± 252.0 pg/ml and 286.0 ± 233.4 pg/ml in the adsorber and control groups, respectively). Levels were still well above baseline the morning after surgery. There was no statistically significant difference in endotoxin levels between control and adsorber groups.

The results for IL-6 and IL-8 (Table 2) show a very similar pattern, with IL-6 peaking in both groups at 6 h after commencement of CPB, and IL-8 peaking at 3 h after commencement of CPB. IL-6 and IL-8 were generally higher in the adsorber group at most time points. Overall, IL-6 was 58.9 pg/ml higher in the adsorber group on average (95% CI −179.6, 297.4, $P=0.60$). It was not possible to adjust for baseline IL-6 levels because of several below threshold measurements at that time point. Overall, IL-8 was 6.1 pg/ml lower in the adsorber group on average after adjusting for baseline (95% CI −37.1, 24.9, $P=0.67$). No significant difference for either of these assays was observed between the two groups. For TNF-α, the overall odds of having above threshold measurements between the adsorber and control groups were similar.

Data for all secondary outcome measures in shown in Table 3. Hb and HCT were significantly lower in the adsorber group pre-bypass: Hb in the intervention group was 11.1 g/dl $\pm$ 1.0 (mean $\pm$ S.D.) vs. 12.5 g/dl $\pm$ 0.8 in the control group, $P=0.02$. HCT was 0.33 ± 0.03 vs. 0.37 ± 0.01, $P=0.02$. TEG analysis demonstrated no differences between groups in either the r-value (time to form fibrin clot), k-value (speed of clot formation) or maximum amplitude (MA, strength of the final clot) at any time-points investigated (T0, T360 and Tpost). No significant difference between groups was detected in creatinine, CRP, red and white blood cell count, platelets, glucose or lactate.

There was no significant difference in length of ICU stay [1 (1.0) days vs. 1 (0.8) days, median (inter-quartile range)] and hospital stay [9 (8.0) days vs. 6 (2.8) days] between the groups.

There were a total of seven adverse events in five patients, and none of these were directly related to the device. Four of these events were in the adsorber group. Haemodynamic instability requiring intra-aortic balloon pump insertion, and haemostatic issues accounted for all the adverse events. There were no deaths during the 30 days surveillance period.

4. Discussion

This study, in patients undergoing cardiac surgery with CPB, has shown that insertion of the Alteco® LPS adsorber into the CPB circuit did not affect blood endotoxin and

Table 2
Endotoxin and cytokine concentrations

	T0	T60	T180	T360	Tpost	Overall difference between groups
TNF-α (pg/ml)						
Adsorber	0	1 (13)	4 (50)	4 (50)	3 (38)	
Control	0	1 (17)	4 (67)	4 (67)	1 (17)	
Odds Ratio (95% CI)						1.00 (0.22, 4.47), $P=1.00$
IL-6 (pg/ml)						
Adsorber	3.5 ± 0.9	7.3 ± 5.1	117.9 ± 118.5	381.6 ± 778.8	140.1 ± 145.2	
Control	1.7 ± 0.2	23.7 ± 35	114.9 ± 117.6	167.4 ± 237.7	59.5 ± 34.7	
Mean difference	1.8	−16.4	2.9	214.2	80.6	58.9
(95% CI)	(−0.3, 3.9)	(−59.7, 26.9)	(−136.0, 141.9)	(−508.6, 937.0)	(−52.6, 213.7)	(−179.6, 297.4), $P=0.60$
IL-8 (pg/ml)						
Adsorber	13.4 ± 19.2	28.4 ± 50.8	98.3 ± 142.0	71.2 ± 87.4	50.9 ± 97.8	
Control	5.8 ± 3.5	13.8 ± 11.3	62.5 ± 64.3	37.6 ± 43.6	17.5 ± 19.8	
Mean difference	7.6	15.4	35.8	33.6	33.5	−6.1
(95% CI)	(−9.9, 25.0)	(−31.0, 61.9)	(−100.9, 172.4)	(−51.7, 118.9)	(−55.7, 122.6)	(−37.1, 24.9), $P=0.67$

For adsorber group $n=8$, for control group $n=6$. Endotoxin, IL-6 and IL-8 values represent the mean $\pm$ standard deviation (S.D.). TNF-α values represent the number and (proportion) of samples with greater than threshold levels of TNF-α. CI, confidence interval; IL, interleukin.

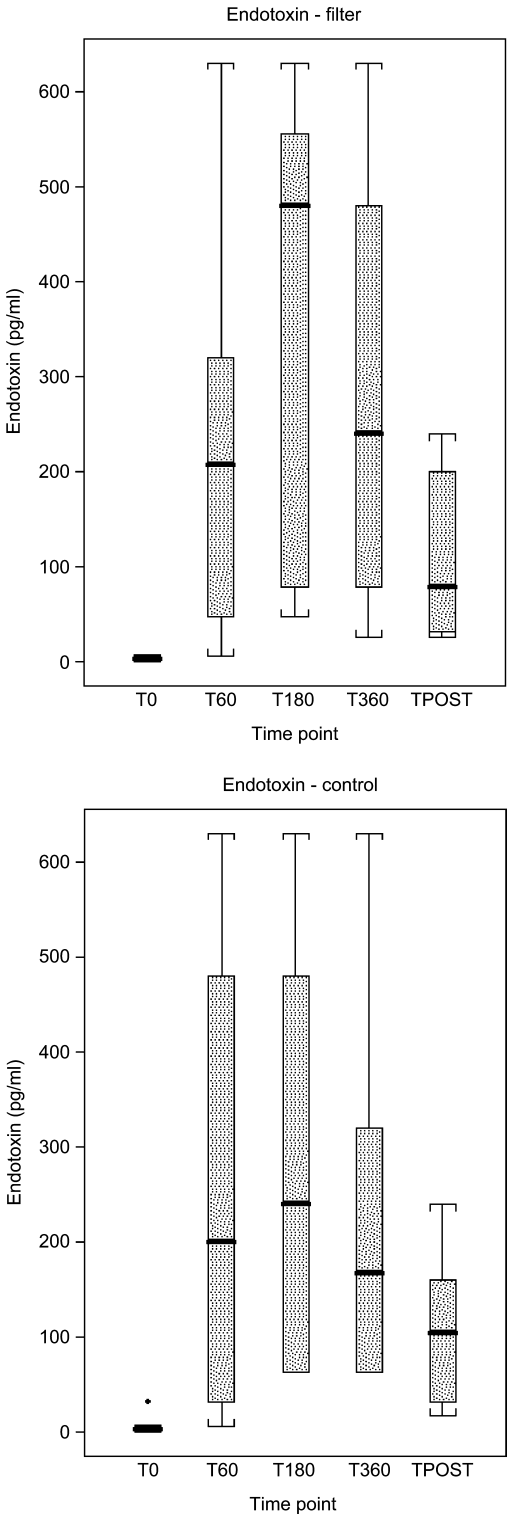

Fig. 2. Boxplots of endotoxin levels in adsorber and control groups. The midline is the median, the box spans the 25th–75th percentile, whiskers show the minimum and maximum values within the 1.5×inter-quartile range (IQR). Outliers, which are designated as data outside of 1.5×IQR, are shown as dots outside the range of the whiskers.

cytokine levels. Furthermore, there was no difference between groups in relation to the blood levels of commonly used markers of inflammation, renal function and coagulation. Intensive care or hospital duration of stay was identical in both groups. The use of the adsorber did not cause any harm to patients, although this is in a small sample size.

These findings corroborate the ones published by Blomquist et al. (2009) relating to patients with marginally shorter CPB and cross-clamp times and undergoing a single procedure only, who concluded that the device is safe but could not report an effect on endotoxin as only two patients in the study suffered endotoxaemia [10].

The absence of an effect on endotoxin level in this study is surprising in the light of results obtained in an animal model [8] but there are several factors other than an inefficient technology that may explain this. First is the sample size that may well have hidden a small but significant statistical difference in measured levels. However, the clinical significance of a small difference would then be questionable. Second is the imbalance in the number of intervention and control group subjects due to the randomization of patients whose operations were cancelled, and the ethical obligation to stop the study when the last adsorber had been used. We intended to analyse the data on an intention to treat basis, but did not anticipate problems with cancelled surgical procedures; a complete case analysis was performed instead. Future studies should endeavour to randomise closer to the time of surgery to avoid this problem. Third, the adsorber flow rate was $<5\%$ (150 ml/min) of the total CPB blood flow and the magnitude of its impact could have been negligible. In this case, it is unknown if modifying the flow capacity of the device would allow it to effectively clear endotoxins from the blood stream, and impact on the inflammatory response. Fourth, the large internal surface area of the device may in itself have caused activation of the inflammatory cascade. Finally, selective endotoxin removal from the blood by the adsorber may promote a dynamic equilibrium between the tissue and blood compartments, thus enabling a continuous withdrawal of mediators from the tissues [14]. As such the observed blood levels may not represent the levels found in the tissues, but instead a fairly stable concentration after peaks of endotoxin have been removed. Consequently, a suitable method for detecting tissue-level endotoxin may be required.

The degree of endotoxin release following CPB appears to vary considerably from patient to patient and this has been documented previously in the literature [15]. Endotoxin release has been shown to correlate with CPB time and aortic cross-clamp time [11], and the differential responses seen may be due to the ability of the reticuloendothelial system to remove endotoxin [11] or to varying levels of endotoxin antibodies present in the blood prior to surgery [16]. Endotoxin levels during and after CPB vary considerably in the literature ranging from just above 5 pg/ml [3] to up to 30 ng/ml [15], and the mean peak endotoxin levels in our study are consistent with this data, albeit at the higher end of the range. Peak levels of endotoxin appear to occur after CPB, during the period of reperfusion [2, 11, 17]. Cytokine levels and profile of expression in this study are consistent with historical data.

In conclusion, although we have shown no effect of the adsorber on blood endotoxin levels or inflammatory

Table 3
Secondary outcome measures

	Baseline	T0	T60	T180	T360	Tpost
White blood cell count (10^9/l)						
Adsorber	6.2±1.0	4.7±1.0	4.0±1.7	7.2±3.2	11.9±7.9	13.6±5.8
Control	7.3±2.3	5.9±2.0	5.1±5.5	8.4±3.3	12.1±5.3	11.8±2.9
Mean difference	−1.2	−1.2	−1.1	−1.2	−0.2	1.7
(95% CI)	(−3.6, 1.3)	(−3.0, 0.7)	(−3.8, 1.6)	(−5.0, 2.6)	(−8.6, 8.2)	(−4.5, 8.0)
Red blood cell count (10^{12}/l)						
Adsorber	4.4±0.4	3.6±0.4	2.6±0.5	2.7±0.5	2.6±0.8	3.1±0.4
Control	4.6±0.3	4.0±0.3	3.0±0.4	3.1±0.9	2.9±0.7	3.3±0.4
Mean difference	−0.2	−0.4	−0.4	−0.4	−0.3	−0.2
(95% CI)	(−0.6, 0.2)	(−0.8, 0.1)	(−1.0, 0.2)	(−1.3, 0.5)	(−1.2, 0.6)	(−0.6, 0.3)
Haemoglobin (g/dl)						
Adsorber	13.4±1.0	11.1±1.0	8.0±1.4	8.3±1.5	8.2±2.4	9.6±1.0
Control	14.4±0.6	12.5±0.8	9.2±1.1	9.6±2.4	9.1±1.9	9.8±1.1
Mean difference	−1.0	−1.3	−1.2	−1.3	−0.9	−0.2
(95% CI)	(−2.0, −0.0003)	(−2.5, −0.2)	(−2.9, 0.6)	(−3.6, 1.0)	(−3.5, 1.7)	(−1.5, 1.0)
Haematocrit (l/l)						
Adsorber	0.40±0.03	0.33±0.03	0.23±0.04	0.24±0.04	0.24±0.07	0.28±0.03
Control	0.41±0.02	0.37±0.01	0.27±0.03	0.28±0.07	0.26±0.06	0.29±0.03
Mean difference	−0.02	−0.04	−0.03	−0.03	−0.03	−0.01
(95% CI)	(−0.05, 0.01)	(−0.07, −0.01)	(−0.08, 0.02)	(−0.10, 0.03)	(−0.11, 0.05)	(−0.05, 0.03)
Platelets (10^9/l)						
Adsorber	200±40	162±46	118±45	111±36	150±38	143±36
Control	227±41	187±46	124±32	135±51	132±80	148±63
Mean difference	−27	−26	−6	−24	18	−5
(95% CI)	(−75, 20)	(−82, 31)	(−62, 51)	(−75, 26)	(−67, 102)	(−65, 55)
Creatinine (μmol/l)						
Adsorber	123±38	117±40	–	–	119±41	154±53
Control	100±21	91±23	–	–	94±13	125±63
Mean difference	24	26			24	28
(95% CI)	(−14, 61)	(−15, 67)			(−34, 83)	(−39, 96)
Mean blood glucose (mmol/l)						
Adsorber	5.5±0.7	5.9±1.1	6.7±1.6	6.6±1.8	6.9±1.1	7.8±1.8
Control	6.2±2.6	5.5±1.0	6.3±1.2	7.3±1.0	8.3±1.0	8.6±1.3
Mean difference	−0.7	0.4	0.5	−0.7	−1.4	−0.8
(95% CI)	(−3.5, 2.0)	(−0.9, 1.7)	(−1.3, 2.2)	(−2.5, 1.1)	(−2.6, −0.1)	(−2.7, 1.2)
Lactate (mmol/l)						
Adsorber	–	1.2±0.4	1.9±0.4	1.6±0.8	1.6±1.3	2.2±0.7
Control	–	1.3±0.5	1.8±0.7	1.4±0.4	1.8±0.9	2.3±1.6
Mean difference	−0.1	0.1	0.3	−0.1	−0.1	−0.1
(95% CI)	(−0.7, 0.5)	(−0.7, 0.8)	(−0.6, 1.1)	(−1.6, 1.3)	(−1.5, 1.3)	(−1.5, 1.3)
C-reactive protein (mg/l)						
Adsorber	–	3.6±3.3	–	–	3.4±1.9	118.3±37.4
Control	–	3.8±3.7	–	–	4.2±3.9	109.4±32.2
Mean difference		1.9			−0.3	8.9
(95% CI)		(−4.5, 4.0)			(−4.4, 3.8)	(−37.3, 55.0)
TEG parameters						
R (min)						
Adsorber	–	9.4±4.4	–	–	11.9±7.8	6.5±1.1
Control	–	8.5±0.6	–	–	8.8±3.9	6.8±2.0
Mean difference		0.9			3.0	−0.4
(95% CI)		(−4.1, 5.9)			(−5.3, 11.4)	(−2.4, 1.7)
K (min)						
Adsorber	–	2.8±2.1	–	–	6.1±8.9	2.1±0.4
Control	–	2.1±0.4	–	–	2.8±1.2	2.2±0.4
Mean difference		0.8			3.3	−0.1
(95% CI)		(−1.7, 3.2)			(−5.7, 12.2)	(−0.7, 0.6)
MA (mm)						
Adsorber	–	63.3±7.7	–	–	59.4±7.5	64.2±7.6
Control	–	65.9±4.4	–	–	56.0±5.3	58.3±0.1
Mean difference		−2.6			3.4	5.9
(95% CI)		(−12, 6.8)			(−5.2, 11.9)	(−0.4, 12.3)

For adsorber group $n=8$, for control group $n=6$. Values represent mean±standard deviation (S.D.). CI, confidence interval; TEG, thromboelastography.

response, we have demonstrated the device to be safe in a cardiac surgery setting. The incentive to develop an effective device that reduces endotoxin load in extracorporeal circuits is strong with an excess of one million patients undergoing surgery with CPB each year and a substantial proportion suffering the consequence of an activated inflammatory response. Further work is necessary before an endotoxin adsorber can be ruled out as a means

of solving this problem, and it is likely that these studies will have to enrol hundreds, if not thousands of subjects to reach a statistically significant conclusion.

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