

Review

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# Cytosorb® haemoadsorption: a potential game changer for patients needing myocardial surgical revascularisation

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## Abstract

Cytosorb, an extracorporeal blood purification system, utilises the principles of haemoadsorption to remove low molecular weight substances from the blood, including multiple cytokines such as interleukin (IL)-1b, IL-6, IL-8, and tumour necrosis factor- $\alpha$ , and anti-platelet drugs aiming to improve clinical outcomes. Given the prominent role of pro-inflammatory cytokines in various inflammatory states, Cytosorb has seen growing application as a therapeutic immunomodulator including surgery. This review focuses on the effects of the use of Cytosorb in patients undergoing coronary artery bypass grafting (CABG) and the indications of removal of cytokines and anti-platelet agents such as ticagrelor. The evidence supports the feasibility and safety profile of Cytosorb, with no device-related adverse events reported in all studies. Initial studies suggest significant potential for Cytosorb in urgent or emergency CABG surgery to remove anti-platelet medication with promising benefits on clinical outcomes including fewer blood product transfusions, decreased length of intensive care unit stay, and lower re-sternotomy rates. Furthermore, a cost saving analysis indicated that intraoperative removal of ticagrelor with Cytosorb would be cost effective in the setting of emergency cardiac surgery. However, the evidence remains inconclusive when Cytosorb is used in elective CABG surgery for cytokine removal. Definite high quality clinical trials for both



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indications for Cytosorb in CABG surgery are needed to clarify if there is a clinically significant benefit in clinical outcomes. There is substantial trial activity for the application of Cytosorb in higher risk cardiac surgery to establish the place of Cytosorb in future treatment pathways in cardiac surgery.

**Keywords:** Cardiac surgery, coronary artery bypass grafting, cytokines, anti-platelets, ticagrelor

## INTRODUCTION

Cytosorb is an extracorporeal blood purification system characterised by a large surface area due to the special design of biocompatible absorbent polymer micro-beads. It utilises the principle of haemoadsorption, with confirmed efficacy for removal of a spectrum of low molecular weight substances from the blood<sup>[1]</sup>. As an approved technology for multiple cytokine removal, Cytosorb has excellent adsorption rates for multiple inflammatory cytokines such as interleukin (IL)-1b, IL-6, IL-8, and tumour necrosis factor (TNF)- $\alpha$ , which has translated to improved clinical outcomes such as resolution of shock<sup>[2]</sup> and a significant reduction in mortality<sup>[3]</sup> when used in the context of inflammatory conditions such as sepsis. Given the prominent role of inflammation and pro-inflammatory cytokines in various clinical situations, Cytosorb has seen growing application as a therapeutic immunomodulator in different contexts over the recent years, expanding to liver failure and major surgery such as organ transplantation and cardiac surgery<sup>[4]</sup>. In coronary artery bypass graft (CABG) surgery, Cytosorb therapy could be utilised to modulate the inflammatory response and to remove anti-platelet drugs.

Open-heart surgery, particularly those with long cardiopulmonary bypass (CPB) times, initiates a complex inflammatory response known as systemic inflammatory response syndrome (SIRS)<sup>[5]</sup>. In CABG patients, although mortality is estimated to be 2%-3%, major complications from surgery occur in up to 20%-30% of patients<sup>[6]</sup>. Post-CPB cardiovascular dysfunction and subsequent post-operative complications including ischemia, myocardial stunning, and other morbidities are thought to result from systemic increases in pro-inflammatory mediators such as IL-6<sup>[7]</sup>. Other pro- and anti-inflammatory mediators identified as key factors in the CPB-induced post-operative organ dysfunction include IL-1b, TNF- $\alpha$ <sup>[8]</sup>, leucocytes<sup>[9]</sup>, elastase, heparin-binding protein, myeloperoxidase, and factors involving the endothelial glycocalyx<sup>[10]</sup>. As such, modulation of SIRS through Cytosorb haemoadsorption is proposed to be able to improve the peri-operative course and positively influence clinical outcomes.

Furthermore, specific to CABG patients, the current recommendation by the European Society of Cardiology for patients presenting with acute coronary syndrome includes immediate dual anti-platelet treatment before therapeutic primary percutaneous coronary intervention<sup>[11]</sup>. However, up to 10% of patients with acute coronary syndrome require urgent or emergent CABG instead, where the use of these agents is associated with increased peri-operative bleeding risk and complications<sup>[12,13]</sup>. Common dual anti-platelet regimes include aspirin and ticagrelor. While aspirin binds irreversibly to inhibit cyclooxygenase-1 in platelets<sup>[14]</sup>, ticagrelor, a platelet P2Y<sub>12</sub>-receptor antagonist, binds reversibly to inhibit the receptor and its effect is related to plasma concentration<sup>[15]</sup>. The current standard of care for emergent CABG while on anti-platelets is simply supportive management of bleeding complications, while in urgent CABG, the recommendation is delaying surgery for 5 to 7 days for physiological clearance with bridging therapy<sup>[11]</sup>. However, to date, no bridging regime has demonstrated a reduction in major adverse events<sup>[16]</sup>. Cytosorb offers these patients the potential for prompt and safe surgery by removing anti-platelets and restoring platelet activity, improving clinical outcomes.

## REMOVAL OF PRO-INFLAMMATORY MEDIATORS AND OTHER SUBSTANCES

The current evidence is conflicting when considering the effect of Cytosorb therapy on adsorption of multiple proinflammatory cytokines during CABG surgery utilising cardiopulmonary bypass [Table 1]. Notably, most of these studies have some limitations as they were mainly pilot randomised controlled trials (RCT) of small sample size, and all studies (where reported) were conducted during elective cardiac surgery. Importantly, there were no Cytosorb-related adverse events reported in all studies demonstrating exceptional safety of the technology.

An RCT conducted by Garau *et al.*<sup>[17]</sup> with 40 patients comparing Cytosorb haemoadsorption with no haemoadsorption found that Cytosorb adsorption was associated with lower IL-8 and TNF- $\alpha$  levels, but not IL-6. However, there was no significant difference in all parameters 6 h after CPB. Similarly, a pilot RCT of 46 patients conducted by Gleason *et al.*<sup>[18]</sup> found a reduction in C3a and C5a throughout surgery and plasma-free haemoglobin, a surrogate marker for haemolysis, 3 h after CPB. There was no significant difference in serious adverse events or 30-day mortality, although the authors acknowledge the study was not adequately powered to detect a difference in clinical outcomes. An observational study by Hohn *et al.*<sup>[19]</sup> found that post-Cytosorb adsorption was associated with reduced heparan sulphate levels but not atrial-natriuretic peptide or syndecan-1 levels, while hyaluronan levels were even increased.

Interestingly, although Bernardi *et al.*<sup>[20]</sup> did not find a difference in IL-1b, IL-6, IL-18, and TNF- $\alpha$  levels in their 37-patients pilot RCT, they reported significantly higher levels of the anti-inflammatory IL-10 48 h after post-CPB. Again, there was no difference in clinical outcomes. A post-hoc analysis of the same cohort revealed significantly higher levels of haptoglobin and lower levels of lactate dehydrogenase, a secondary marker of haemolysis, on post-operative day 1 in the Cytosorb group which may be an indication of some moderate effect of Cytosorb<sup>[21]</sup>.

By contrast, Poli *et al.*<sup>[22]</sup> conducted a pilot RCT with 30 patients and reported no significant difference in IL-1 $\alpha$ , IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10, interferon- $\gamma$ , monocyte chemoattractant protein-1, TNF- $\alpha$ , or any clinical outcomes including use of post-operative inotropes, duration of mechanical ventilation, acute kidney injury, length of intensive care unit (ICU) stay and ICU and hospital mortality. Wisgrill *et al.*<sup>[23]</sup> reported no difference in circulating microvesicle count.

Taleska Stupica *et al.*<sup>[24]</sup> conducted a parallel 3-arm RCT of 60 patients comparing Cytosorb adsorption, intraoperative methylprednisolone and standard care (no haemoadsorption or additional drug therapy) and suggested that intraoperative glucocorticoids are superior to both Cytosorb and standard care. They reported that methylprednisolone administration was associated with lower pro-inflammatory cytokines TNF- $\alpha$ , IL-6, and IL-8, and higher anti-inflammatory cytokines IL-10 when compared to both in the Cytosorb and control group. Cytosorb was associated with the highest CD64 expression on monocytes but was not associated with a significant decrease in pro-inflammatory cytokines or increase in anti-inflammatory cytokines. Neither methylprednisolone nor Cytosorb was associated with a significant difference in clinical outcomes.

Although these data are conflicting, it is worth noting that as studies were mostly pilot RCTs, they were not adequately powered to detect significant clinical differences. In addition, the cytokine response and the nature and the influence of pro- and anti-inflammatory balance are influenced by the various surgical trauma, the presence and type of cardiopulmonary bypass, and the co-morbidity of patients. Since the current evidence indicates the feasibility, remarkable safety, and plausible therapeutic effects of Cytosorb in the removal of pro-inflammatory cytokines in CABG surgery, we recommend larger RCTs in higher risk

**Table 1. Studies investigating the haemadsorption of proinflammatory markers or other molecules by Cytosorb in myocardial surgical revascularisation**

Ref.	Study design	Study location	Type of cardiac surgery	Study size (n)	Interventions and control	Summary of findings
Hohn et al. <sup>[19]</sup> (2021)	Observational study	Germany	Unspecified	15	Pre- vs. post-Cytosorb adsorption	Post-Cytosorb adsorption was associated with reduced heparan sulphate ( $P < 0.001$ ) levels, but not atrial-natriuretic peptide or syndecan-1 levels, and hyaluronan levels were even increased ( $P < 0.001$ )
Taleska Stupica et al. <sup>[24]</sup> (2020)	RCT	Slovenia	Elective cardiac surgery CABG + valve/s: 38.3% Valve/s surgery: 21.7%	60	Cytosorb adsorption vs. methylprednisolone vs. standard care	Methylprednisolone was associated with lower proinflammatory cytokines TNF- $\alpha$ ( $P < 0.001$ ), IL-6 ( $P < 0.001$ ), and IL-8 ( $P < 0.0016$ ), and higher anti-inflammatory cytokine IL-10 ( $P < 0.016$ ) as compared to both the Cytosorb and control group Cytosorb was associated with the highest CD64 expression on monocytes ( $P < 0.016$ ) Methylprednisolone was associated with highest CD163 levels ( $P < 0.016$ ) There were no significant differences between treatment groups for duration of postoperative mechanical ventilation, length of ICU and in-hospital stay, or 30-day mortality
Wisgrill et al. <sup>[23]</sup> (2020)	Post hoc sub-cohort analysis of a pilot RCT	Austria	Elective cardiac surgery CABG: 27.8% CABG + valve: 22.2%	18	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was not associated with a difference in circulating microvesicle count and function
Garau et al. <sup>[17]</sup> (2019)	RCT	Germany	Elective cardiac surgery CABG: 15.0% CABG + valve/s: 70.0%	40	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was associated with lower IL-8 ( $P = 0.008$ ) and TNF- $\alpha$ ( $P = 0.034$ ), but not IL-6. There was no difference in all parameters 6 h after CPB
Poli et al. <sup>[22]</sup> (2019)	Pilot RCT	Switzerland	Elective cardiac surgery CABG + valve: 30%	30	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was not associated with a difference in any change in blood levels of key cytokines (IL-1 $\alpha$ , IL-1b, IL-2, IL-4, IL-5, IL-6, IL-10, IFN- $\gamma$ , MCP-1, and TNF- $\alpha$ ). Cytosorb adsorption was not associated with a difference in any clinical outcomes, including use of any post-operative inotropes ( $P = 0.68$ ), duration of mechanical ventilation ( $P = 0.31$ ), incidence of AKI ( $P = 1.0$ ), ICU length of stay ( $P = 1.0$ ), and ICU and hospital mortality (both $P = 1.0$ )
Gleason et al. <sup>[18]</sup> (2019)	Pilot RCT	United States	Elective cardiac surgery, with $\geq 1$ procedure Involving CABG: 30.4%	46	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was associated with a reduction in plasma-free haemoglobin $\geq 3$ h post-CPB ( $P \leq 0.05$ ) and C3a and C5a throughout surgery ( $P \leq 0.05$ ) Cytosorb adsorption was not associated with a difference in serious adverse events or 30-day mortality
Bernardi et al. <sup>[21]</sup> (2019)	Post hoc analysis of a pilot RCT	Austria	Elective cardiac surgery (type not specified)	35	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was not associated with a difference in post-operative plasma-free haemoglobin. However, Cytosorb adsorption was associated with higher levels of haptoglobin ( $P < 0.01$ ) and lower levels of LDH ( $P < 0.05$ ) on post-operative day 1
Bernardi et al. <sup>[20]</sup> (2016)	Pilot RCT	Austria	Elective cardiac surgery CABG: 21.6% CABG + valve: 18.9%	37	Cytosorb adsorption vs. no haemadsorption	Cytosorb adsorption was not associated with a difference in IL-1b, IL-6, IL-18, and TNF- $\alpha$ , but higher levels of the anti-inflammatory IL-10 24 h ( $P = 0.03$ ) and 48 h ( $P = 0.02$ ) after CPB Cytosorb adsorption was not associated with a difference in fluid administration, blood substitution, catecholamines, or 30-day mortality

AKI: Acute kidney injury; CABG: coronary artery bypass graft; CPB: cardiopulmonary bypass; ICU: intensive care unit; IFN: interferon; IL: interleukin; LDH: lactate dehydrogenase; MCP: monocyte chemoattractant protein; RCT: randomised controlled trial; TNF: tumour necrosis factor.

patient populations in the future to clarify the clinical benefits of Cytosorb haemoadsorption. An ongoing German RCT, the REMoval of Cytokines during CArdiac Surgery (RECCAS) trial (DRKS00007928) will contribute to the evidence regarding Cytosorb in IL-6 removal during elective cardiac surgery.

## REMOVAL OF ANTI-PLATELETS AND ANTI-COAGULANTS

Conversely, the current evidence for the removal of anti-platelet medications and anti-coagulants in CABG patients shows great promise [Table 2]. This series of investigations started with the important demonstration of the nearly complete removal of ticagrelor (and subsequently rivaroxaban) in simulated *in vitro* circuits spiked with ticagrelor<sup>[1]</sup>. Most subsequent clinical investigations were observational studies, of small sample sizes and were targeting the removal of the anti-platelet drug ticagrelor. All studies were in the setting of urgent or emergency cardiac surgeries. There were no Cytosorb-related adverse events reported in all studies.

A non-randomized observational study with retrospective comparison to controls by Hassan *et al.*<sup>[25]</sup> with 55 patients found that Cytosorb adsorption was associated with improved clinical outcomes, including shorter total operative time, lower drainage volumes, less transfusion of red blood cells (RBCs) and platelets, lower re-thoracotomy rate, shorter ICU stay, and shorter hospital stay. Similarly, an observational study by Bradic *et al.*<sup>[26]</sup> reported that Cytosorb adsorption patients had shorter total surgery, lower average draining volumes in the first 24 h, less transfusions of RBC, platelets, and fresh frozen plasma, lower re-sternotomy rates, and shorter length of ICU stay.

A later bootstrap analysis of a retrospective case series by Hassan *et al.*<sup>[27]</sup> reported that the 33% decrease in ICU stay in the Cytosorb group had the highest impact on the level of cost savings, with the economic benefit of Cytosorb usage at 3.656€ (€) per patient without reimbursement. Another observational study by Hassan *et al.*<sup>[28]</sup> reported 80% of their 55 patients did not require RBC transfusion, 69.1% did not require platelet transfusion, and the rate of 30-day mortality was 1.8%. However, it is unclear if these patients belonged to the same cohort.

The potential cost saving of Cytosorb therapy has been modelled for the UK conditions and the practice setting of the National Health Service. The analysis of Javanbakht *et al.*<sup>[29]</sup> aimed to evaluate the cost utility of intraoperative removal of ticagrelor using Cytosorb *vs.* usual care among patients requiring emergent or urgent cardiac surgery in the UK. They developed a *de novo* decision analytic model, based on current treatment pathways to estimate the short- and long-term costs and outcomes. They demonstrated that intraoperative removal of ticagrelor using Cytosorb was less costly (£12,933 *vs.* £16,874) and more effective (0.06201 *vs.* 0.06091 quality-adjusted life-years) than cardiac surgery without physiologic clearance of ticagrelor in emergent cardiac surgery, over a 30-day time period.

Mair *et al.*<sup>[30]</sup> reported an interesting application of Cytosorb in a patient presenting with high risk of bleeding due to combined treatment with anticoagulants including ticagrelor for treatment of coronary artery disease and rivaroxaban for treatment of atrial fibrillation scheduled to undergo an urgent off-pump CABG. Cytosorb adsorption was initiated 1 h before the operation and was continued for 1.5 h during the operation by incorporating into a haemoperfusion circuit. The patient had an uneventful intraoperative and post-operative course with adequate bleeding control, requiring only 1 unit of RBC post-operatively.

Despite the limited number and quality of studies, Cytosorb remains a potential game changer for patients on anti-platelet medications requiring urgent or emergent CABG. In spite of the small sample sizes of studies, many studies already found a significant benefit in clinical outcomes with the use of Cytosorb, with

**Table 2. Studies investigating the haemoadsorption of antiplatelets/anticoagulants by Cytosorb in myocardial surgical revascularisation**

Ref.	Study design	Study location	Type of cardiac surgery	Removal	Study size (n)	Interventions and control	Summary of findings
Hassan <i>et al.</i> <sup>[25]</sup> (2019)	Non-randomised observational study with retrospective comparison to controls	Germany	Emergency cardiac surgery CABG: 89.1% CABG + valve: 9.1%	Ticagrelor (n = 43) or rivaroxaban (n = 12)	55	Cytosorb adsorption vs. no haemoadsorption	Cytosorb adsorption was associated with shorter total operative time (P = 0.0042), lower drainage volumes (P = 0.0037), less transfusion of RBC (P = 0.0119) and platelets (P = 0.0475), lower re-thoracotomy rate (P = 0.0003), shorter ICU stay (P = 0.0141) and shorter hospital stay (P = 0.0244) when compared to controls
Mair <i>et al.</i> <sup>[30]</sup> (2020)	Case study	Germany	Urgent off-pump CABG	Ticagrelor and rivaroxaban	1	Cytosorb, absorption No control	The case study patient had uneventful intraoperative and post-operative courses with adequate bleeding control. 1 unit of RBC was given post-operatively
Hassan <i>et al.</i> <sup>[28]</sup> (2020)	Observational study	Germany	Emergency isolated CABG only	Ticagrelor	55	Cytosorb absorption No control	80% did not require RBC transfusion (n = 44) and 69.1% did not require platelet transfusion (n = 38). 1 re-thoracotomy (1.8%) for surgical bleeding had to be performed. Rate of 30-day mortality was 1.8%
Hassan <i>et al.</i> <sup>[27]</sup> (2020)	Bootstrap analysis of a retrospective case series	Germany	Emergency cardiac surgery (type not specified)	Ticagrelor	43	Cytosorb adsorption vs. no haemoadsorption	Cytosorb adsorption was associated with a lower re-thoracotomy rate than the control group Cytosorb patients had 72% less transfusions of RBC and/or platelets, 33% less days on ICU, and 18% shorter operation time Cost of ICU stay had the highest impact on the level of cost savings, with the economic benefit of Cytosorb usage at 3.656€ (€) per patient without reimbursement
Bradic <i>et al.</i> <sup>[26]</sup> (2020)	Observational study with controls	Croatia	Emergency cardiac surgery (type not specified)	Ticagrelor (n = 19) or rivaroxaban (n = 12) or dabigatran (n = 3)	34	Cytosorb absorption vs. no haemoadsorption	Cytosorb patients had shorter total surgery, lower average draining volumes in the first 24 h, less transfusions of RBC, platelets, and fresh frozen plasma, lower re-sternotomy rates, and shorter length of ICU stay

<sup>\*</sup>Conference abstract only, limited in detail. CABG: Coronary artery bypass graft; ICU: intensive care unit; IL: interleukin; RBC: red blood cells; TNF: tumour necrosis factor.

one study even reporting a cost-saving benefit. However, there is still uncertainty about the extent of clinical benefit, and these results still need to be confirmed by larger, high quality RCTs. This is aimed by an ongoing clinical trial, the Ticagrelor Cytosorb haemoadsorption (TISORB) study (NCT04131959), a prospective multi-centre single-arm study in the UK with an estimated enrolment of 30 patients, investigating the use of Cytosorb to remove ticagrelor during CPB in patients undergoing emergent or urgent cardiothoracic surgery. Inclusion criteria is cardiothoracic surgery in adults from 18 to 80 years requiring CPB within less than 48 h following the last dose of ticagrelor. Primary outcome measures include change in platelet reactivity and ticagrelor blood concentrations immediately before and after CPB. We hope that this study along with other studies would better clarify the feasibility, safety, and clinical effect of Cytosorb.

## CONCLUSION AND FUTURE DIRECTIONS

In summary, the evidence supporting the feasibility, safety profile and clinical efficacy of Cytosorb is expanding. In particular, the use of Cytosorb in urgent or emergent CABG surgery to remove anti-platelet medications and anti-coagulants shows great potential, with promising benefits on clinical outcomes including fewer transfusions of blood products, decreased length of ICU stay, and lower re-sternotomy rates for bleeding complications. However, the evidence remains inconclusive when Cytosorb is used in elective CABG surgery for the removal of pro-inflammatory cytokines. Current studies were inadequately powered to detect significant differences in clinical benefits. Larger, high quality clinical trials for both indications for Cytosorb in CABG surgery are indicated to clarify if there is a clinically significant benefit in clinical outcomes. The TISORB trial (NCT04131959) will add to the body of evidence concerning Cytosorb in ticagrelor removal during urgent or emergent cardiac surgery. The RECCAS trial (DRKS00007928) will add to the body of evidence concerning Cytosorb in the removal of IL-6 in elective cardiac surgery.

Furthermore, the results of upcoming trials on Cytosorb in other types and higher risk cardiac surgery such as the REMOVE trial (NCT03266302) in patients with infective endocarditis, CYCLONE-LVAD trial (NCT04596813) for left ventricular assist device implantation, and an ongoing study on Cytosorb in heart transplantation in Hungary<sup>[31]</sup> may lead to a deeper understanding of the role of the pertinent pro-inflammatory milieu and cytokines in postoperative complications and the efficacy of Cytosorb therapy. These might have future implications on the therapeutic value of Cytosorb in higher risk myocardial revascularisation. Future development of risk scores to identify patients who are high risk for post-CPB SIRS, vasoplegia, or bleeding complications who might benefit most from Cytosorb therapy could also further refine care pathways.

## DECLARATIONS

### Authors' contributions

The original idea of the manuscript: Umakumar K, Stock UA, Raja SG, de Waal EEC, Marczin N

The manuscript and tables: Ng Yin Ling C, Marczin N

All authors have critically reviewed the manuscript for intellectual content, and all agreed for submission of the last version.

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Not applicable.

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The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

### Conflicts of interest

Marczin N and de Waal EEC report grants, personal fees, travel, and lecture fees from Cytosorbents during the conduct of the study. Marczin N served on the Advisory Board of Cytosorbents. Marczin N, Stock UA, and Raja SG served as experts on the NICE Technology Brief regarding Cytosorb and ticagrelor removal in cardiac surgery. Marczin N is a Harefield principal investigator of the TISORB study.

### Ethical approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

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