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WHAT'S NEW IN INTENSIVE CARE

Hemoadsorption with CytoSorb®

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Background

Several extracorporeal blood purification techniques have been proposed in critically ill patients with sepsis and sepsis-like syndromes. Despite theoretical benefits, recent Surviving Sepsis Campaign guidelines have not formulated a recommendation in favour of or against such techniques and urged for further research [1]. In this context, CytoSorb® (CytoSorbents Corporation, NJ, USA) was recently licensed for extracorporeal cytokine removal within the European Union (EU).

Cytosorb® cartridges contain biocompatible polystyrene divinylbenzene copolymer beads capable of adsorbing molecules of medium molecular weight using a combination of size exclusion and hydrophobic interactions [2]. They can be used in stand-alone mode (hemoperfusion) or inserted within a continuous renal replacement therapy (CRRT) circuit (associated with a conventional hemofilter), a cardiopulmonary bypass (CPB) or an extracorporeal membrane oxygenation circuit. CytoSorb® (Fig. 1) removes a wide range of molecules from the blood: pro- and anti-inflammatory cytokines, bilirubin, myoglobin, exotoxins, but also drugs [2–4].

Cytosorb® is currently marketed in 53 countries worldwide. Its utilization has considerably expanded over recent years, with 211 centres currently participating in an international CytoSorb® registry. However, if unselective blood purification could be beneficial through removal of "bad humours", it could equally be deleterious through the removal of other important molecules. In addition, CytoSorb® cartridges are costly and require therapeutic anticoagulation. Therefore, high-quality evidence must be obtained before widespread utilization of the device can be recommended.

This article reviews the existing evidence related to Cytosorb® utilization in various clinical situations.

Available evidence

Sepsis

Septic animal models have demonstrated the ability of CytoSorb® to clear key cytokines from the blood and improve survival [5, 6]. However, only one multicentre randomized controlled trial (RCT) has evaluated its efficacy in human sepsis [7]. In this trial, 97 patients with septic shock and either acute lung injury or acute respiratory distress syndrome were randomized to either standard of care or CytoSorb® hemoadsorption (HA) 6 h per day during a maximum of seven consecutive days. The authors found no difference between the two groups in IL-6 (primary endpoint) or other key cytokine plasma levels; in addition, only a modest (5–18% per blood pass) cross-adsorber IL-6 clearance was measured. There was no sign of improved multiple organ dysfunction score in the CytoSorb® group. Finally, unadjusted mortality was higher in the Cytosorb® group, although this difference disappeared after adjustment for baseline imbalances.

Besides its small sample size, this study has several limitations worth mentioning. First, by study design, the therapy was delivered in the form of short (6 h) daily therapies. This strategy might not be adequate as full saturation of the sorbent is believed to require 24 h of running time and therapy-free intervals might enable rebound in cytokine levels [5]. Second, baseline median IL-6 levels were 552 [162–874] pg/ml (CytoSorb® group) and 590 [125–2147] pg/ml (control group), values considered low in sepsis. As cytokine removal by CytoSorb® is concentration dependent, it is possible that a combination of short therapy time and low IL-6 levels may have impeded any potential beneficial effects.

All other studies are observational. The largest cohort is based on an international registry including 198 patients

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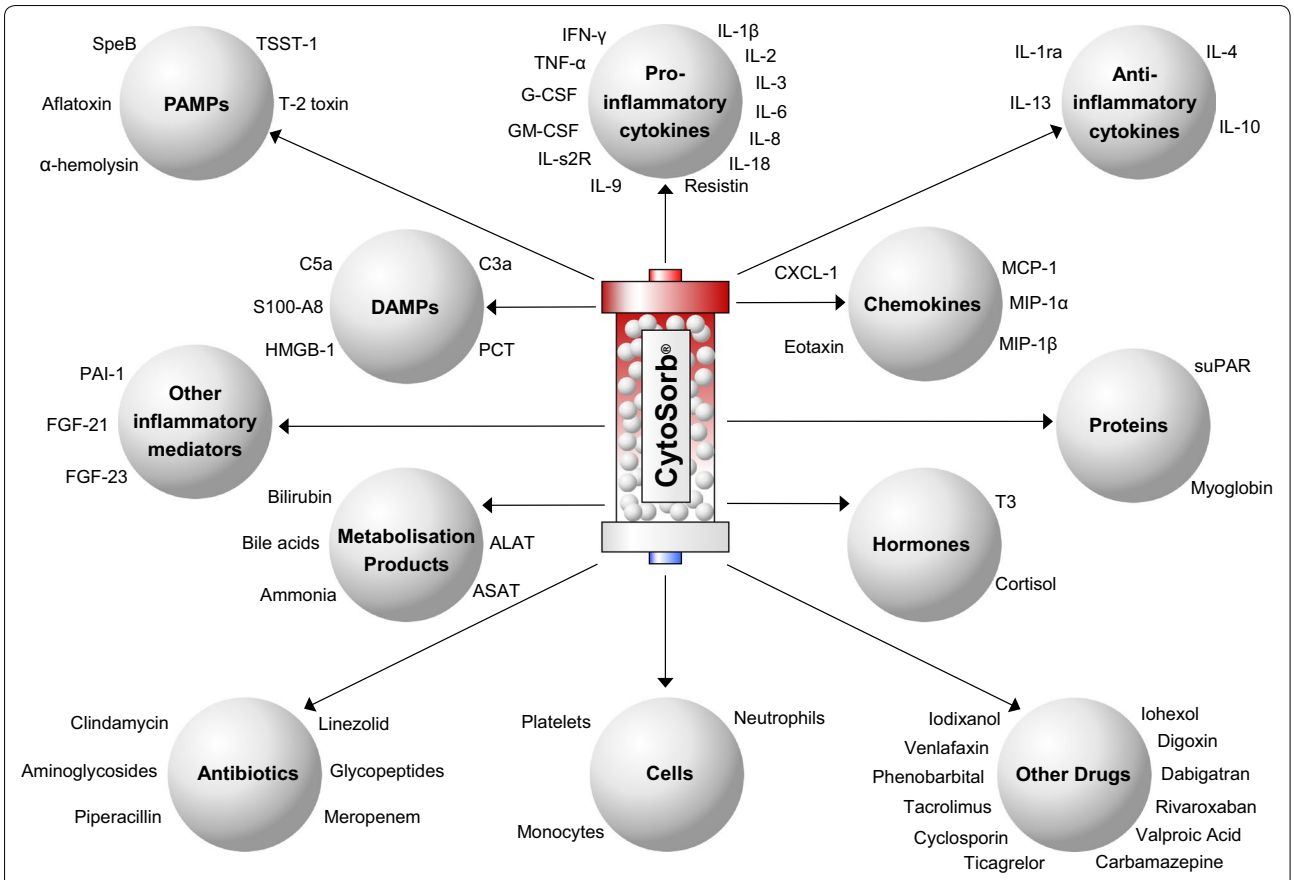

Fig. 1 Scope of adsorption by CytoSorb®. Figure mostly based on in vitro data. The clinical relevance of CytoSorb® hemoadsorption for the majority of those molecules remains to be evaluated. DAMPs damage-associated molecular patterns, FGF fibroblast growth factor, HMGB-1 high-mobility group box 1, MCP-1 monocyte chemoattractant protein 1, MIP macrophage inflammatory protein, PAI-1 plasminogen activator-inhibitor 1, PAMPs pathogen-associated molecular patterns, PCT procalcitonin, SpeB streptococcal pyrogenic exotoxin B, S100-A8 S100 calcium-binding protein A8, suPAR soluble urokinase-type plasminogen activator receptor, T3 triiodothyronine, TSST-1 toxic shock syndrome toxin 1

(68% with sepsis) [8]. In these patients, CytoSorb® HA was associated with a decrease in IL-6 levels and a lower than predicted hospital mortality. Two case series reported decreased noradrenaline need and lactate levels in respectively 20 and 26 septic patients with CytoSorb® HA combined with CRRT [9, 10]. The validity of these observational studies is largely limited by the absence of a control group.

Cardiac surgery

Cardiac surgery has been shown to produce a complex inflammatory response possibly associated with negative postoperative outcomes. Hence, by analogy with sepsis, it has been suggested that cytokine removal in the perioperative period might improve outcomes.

A single RCT has compared intraoperative CytoSorb® HA with standard operative management in 32 patients undergoing elective cardiac surgery. It failed to demonstrate a benefit in terms of perioperative cytokine levels or clinical outcomes. The therapy was associated with higher levels of IL-10 after CPB, suggesting a long-lasting anti-inflammatory effect [11]. Of note, similar to the aforementioned study in sepsis, observed cytokine levels were low (median peak IL-6 levels (2h post-CPB) 120.8 [49.0–160.8] pg/ml in the HA group and 118.7 [68.4–255.9] pg/ml in the control group, $p=0.68$), perhaps explaining the lack of demonstrated cytokine removal.

Small case-control series have suggested improved clinical outcomes with CytoSorb® during heart transplantation [12], surgical management of acute infective endocarditis [13] or in patients with post-CPB severe systemic inflammation response syndrome [14].

Drug removal

The effect of CytoSorb® HA on drugs requires particular attention. Indeed, unselective removal might translate into decreased blood levels of potentially life-saving medications such as antibiotics in sepsis. In vitro data have

suggested marginal removal of aminoglycosides, and nearly complete removal of vancomycin and teicoplanin [15] but reliable clinical data on the topic is still crucially missing. Given the importance of adequate antibiotic levels in sepsis, therapeutic drug monitoring is strongly advised during CytoSorb® HA.

On the other hand, the potential of CytoSorb® to remove medications might be beneficial in situations of intoxication (Fig. 1) with venlafaxine, dabigatran, ticagrelor, rivaroxaban or others. The relevance of this invasive therapy in these indications remains to be confirmed.

Other

According to in vitro and experimental data, CytoSorb® HA is able to remove myoglobin, bilirubin and bile acids from the blood and was recently approved within the EU for these indications. Nevertheless, besides observational reports, no data is available to confirm clinical benefit in these indications.

Safety

Post-marketing surveillance has not suggested major adverse events after more than 20,000 patients treated around the world. No adverse effect was reported in the Bernardi trial [11], while Schädler et al. [7] reported one case of severe thrombopenia potentially linked to the device. As already mentioned, the potential removal of certain drugs and antibiotics might be problematic in certain situations and requires particular attention.

Conclusions and considerations for future studies

Numerous publications have assessed the efficacy of CytoSorb® HA in various clinical situations. Experimental models and observational series have suggested dramatic clinical improvement, while RCTs have not demonstrated any clinical benefit so far. However, their limited number and size as well as the relatively low severity of included patients preclude any final conclusion being drawn. Hence, further studies should focus on populations with very high inflammatory response ideally enriched with a pre-intervention test. Adequate target population determination is essential for future assessment of the device in order to prevent either abuse of its use or its fallacious abandonment. While we wait more evidence from these RCTs, the use of Cytosorb in clinical practice should take into account the absence of clear evidence for benefit, the potential for adverse effects and the cost.

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Compliance with ethical standards

Conflicts of interest

EP has not disclosed any potential conflict of interest. TR has received speaker and consulting honoraria from Fresenius Medical Care, Baxter Healthcare Corp, Biomérieux, Medtronic and B. Braun. AS has received a grant from the Leenaards Foundation, speaker honoraria from Fresenius Medical Care, Baxter Healthcare Corp and consulting honoraria from B. Braun Melsungen AG. He is the principal investigator of the CCCC trial, a pilot trial evaluating the impact of Cytosorb during cardiac surgery (ClinicalTrials.gov (NCT02775123).

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References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche J-D, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent J-L, Wiersinga WJ, Zimmerman JL, Dellinger RP (2017) Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
2. Malard B, Lambert C, Kellum JA (2018) In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp 6:12
3. Gruda MC, Ruggeberg KG, O'Sullivan P, Guliashvili T, Scheirer AR, Golobish TD et al (2018) Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. PLoS One 13:e0191676
4. Gemelli C, Cuoghi A, Magnani S, Atti M, Ricci D, Siniscalchi A, Mancini E, Faenza S (2018) Removal of bilirubin with a new adsorbent system: in vitro kinetics. Blood Purif. https://doi.org/10.1159/000492378
5. Peng Z-Y, Carter MJ, Kellum JA (2008) Effects of hemoadsorption on cytokine removal and short-term survival in septic rats. Crit Care Med 36:1573–1577
6. Kellum JA, Song M, Venkataraman R (2004) Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. Crit Care Med 32:801–805
7. Schädler D, Pausch C, Heise D, Meier-Hellmann A, Brederlau J, Weiler N, Marx G, Putensen C, Spies C, Jörres A, Quintel M, Engel C, Kellum JA, Kuhlmann MK (2017) The effect of a novel extracorporeal cytokine hemoadsorption device on IL-6 elimination in septic patients: a randomized controlled trial. PLoS One 12:e0187015
8. Friesecke S, Träger K, Schittek GA, Molnar Z, Bach F, Kogelmann K, Bogdanski R, Weyland A, Nierhaus A, Nestler F, Olboeter D, Tomescu D, Jacob D, Haake H, Grigoryev E, Nitsch M, Baumann A, Quintel M, Schott M, Kielstein JT, Meier-Hellmann A, Born F, Schumacher U, Singer M, Kellum J, Brunkhorst FM (2017) International registry on the use of the CytoSorb® adsorber in ICU patients. Med Klin Intensivmed Notfmed. https://doi.org/10.1007/s00063-017-0342-5
9. Friesecke S, Stecher S-S, Gross S, Felix SB, Nierhaus A (2017) Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. J Artif Organs 20:252–259
10. Kogelmann K, Jarczak D, Scheller M, Drüner M (2017) Hemoadsorption by CytoSorb in septic patients: a case series. Crit Care 21:74
11. Bernardi MH, Rinoesl H, Dragosits K, Ristl R, Hoffelner F, Opfermann P, Lamm C, Preißing F, Wiedemann D, Hiesmayr MJ, Spittler A (2016) Effect of hemoadsorption during cardiopulmonary bypass surgery—a blinded,

randomized, controlled pilot study using a novel adsorbent. Crit Care 20:96
12. Nemeth E, Kovacs E, Racz K, Soltesz A, Szigeti S, Kiss N, Csikos G, Koritsanszky KB, Berzsenyi V, Trembickij G, Fabry S, Prohaszka Z, Merkely B, Gal J (2018) Impact of intraoperative cytokine adsorption on outcome of patients undergoing orthotopic heart transplantation—an observational study. Clin Transplant 32:e13211
13. Träger K, Skrabal C, Fischer G, Datzmann T, Schroeder J, Fritzler D, Hartmann J, Liebold A, Reinelt H (2017) Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass—a case series. Int J Artif Organs 40:240–249
14. Träger K, Fritzler D, Fischer G, Schröder J, Skrabal C, Liebold A, Reinelt H (2016) Treatment of post-cardiopulmonary bypass SIRS by hemoadsorption: a case series. Int J Artif Organs 39:141–146
15. Reiter K, Bordoni V, Dall'Olio G, Grazia Ricatti M, Soli M, Ruperti S, Soffiati G, Galloni E, D'Intini V, Bellomo R, Ronco C (2002) In vitro removal of therapeutic drugs with a novel adsorbent system. Blood Purif 20(4):380–388