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A New Series of Sorbent Devices for Multiple Clinical Purposes: Current Evidence and Future Directions

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Abstract
Adsorption is an extracorporeal technique utilized for blood purification. It complements convection and diffusion (the main modalities of solute removal). It involves the passage of blood (or plasma) through an adsorption cartridge, where solutes are removed by direct binding to the sorbent material. Over the years, new adsorption cartridges, with improved characteristics have been developed. Furthermore, the therapeutic applications of adsorption have expanded. These now involve the treatment of inflammatory conditions, chronic uremic symptoms, and autoimmune disease, in addition to intoxication, which was once considered the classical indication for adsorption therapy. HA130, HA230, and HA330 (Jafron, Zhuhai City, China) are among the widely used adsorption cartridges in China. There has been sufficient body of evidence to support their effectiveness and safety. In this review, we aim to highlight their main clinical applications.

Introduction

Extracorporeal blood purification therapy for the removal of exogenous and endogenous toxins is a rapidly evolving area. The main membrane-based mechanisms by which solutes are removed are diffusion (driven by concentration gradient across the membrane) and convection (driven by hydrostatic pressure gradient across the membrane leading to solvent drag). Adsorption, which is considered a complementary mechanism for solute removal, on the other hand, relies on direct binding of solutes to membranes or sorbent materials contained within a cartridge (adsorption unit). Adsorption can be applied both alone and in combination with other blood purification techniques (Fig. 1). An important characteristic of sorbent materials is minimizing unwanted molecules loss (such as nutrients and antibiotics), which is frequently encountered using other extracorporeal blood purification techniques (such as, high-volume hemofiltration and high cutoff membranes) [1–3].

As a technique, adsorption involves the direct contact of the sorbent material with blood or plasma, which can result in bioincompatibility mediated by complement

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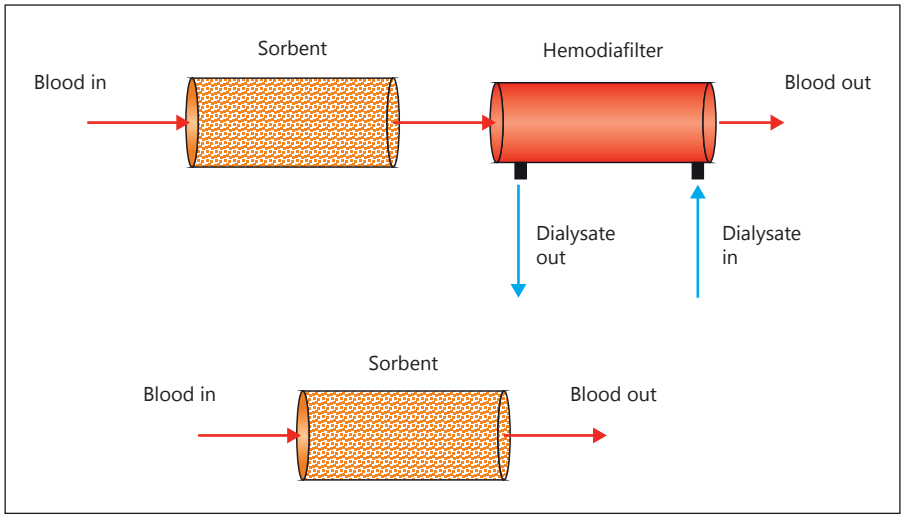

Fig. 1. Extracorporeal circuit showing the application of adsorption therapy alone or in combination with hemodialysis.

system activation. Clinically, bioincompatibility typically presents as fever, chills, skin rash, and thrombocytopenia/leukopenia. Sorbents' biocompatibility is an area that has markedly improved over the years. One approach to avoid bioincompatibility reactions is separation of plasma from cells before being circulated through the adsorption unit. Following circulation through the adsorption unit, blood is then reconstituted. In this manner, the contact of cellular components with the sorbent bed is completely avoided. Another approach is, coating of the sorbent materials [4]. In vitro cell culture assays can be used to test specific biocompatibility characteristics of a sorbent material. This technique can be really useful for the evaluation of the potential toxicity of materials and can provide an excellent screening tool prior to performing in vivo trials. In a recent in vitro study by Pomarè Montin et al. [5], the effect of hemoadsorption (HA) cartridges on cultured monocytes cell line was tested both in static and dynamic manners using a dedicated extracorporeal adsorption circuit. In comparison to control samples, both static and dynamic tests showed no difference in viability, necrosis or apoptosis of monocytes in the samples exposed to HA cartridges. The findings were suggestive that HA cartridges use is not associated with cytotoxicity [5]. With the improvement of adsorption cartridges over the recent years, their use has become adopted more widely. Poisoning was once considered the classical indication for the use of adsorption technique. Potential indications have expanded to include treatment of inflammatory conditions (such as sepsis, pancreatitis, and hepatitis), chronic uremic symptoms, and autoimmune diseases. This was made possible by the progress in the development of sorbent materials as different uses require different sorbents' characteristics.

Among the recently developed group of adsorption cartridges are the HA resin hemoperfusion (HP) cartridges, HA130, HA230, and HA330 (Jafron, Zhuhai City, China). To date, there has been a sufficient body of evidence supporting their safety and effectiveness. In this review, we aim to highlight their main clinical applications. Major characteristics of the 3 cartridges are summarized in Table 1.

Technical Aspects

The cartridges contain neutro-macroporous resin adsorbing beads made of styrene-divinylbenzene copolymer. The average diameter of the resin beads is 0.8 mm, ranging from 0.60 to 1.18 mm. The pore size distributions of the resin are 500 D–40 kD in HA130, 200 D–10 kD in HA230 and 500 D–60 kD in HA330. The different resin pore size of the sorbent material allows the removal of a wide spectrum of molecular weights. The sorbent devices have the ability to remove endogenous and exogenous materials such as middle uremic toxins, protein bound uremic toxins, hydrophobic or protein bound exogenous substances, cytokines, complements, free hemoglobin, and residual drugs by means of adsorption [5]. HA130 is mainly used in chronic conditions, HA230 in intoxication, and HA330 in acute inflammatory conditions. Similar to other sorbent devices, HA cartridges use involves direct contact of blood with the sorbent material. Equipped with advanced coating, HA cartridges use has

Table 1. The main characteristics of the HA adsorption cartridges

	HA-130	HA-230	HA-330
Indications	Chronic dialysis complications	Intoxication	Acute conditions with cytokines storm such as sepsis
Molecular weight removed	5–30 kDa	500 Da–10 kDa	10–60 kDa
Resin pore size distribution	500 Da–40 kDa	200 Da–10 kDa	500 Da–60 kDa
Toxins removed	Middle uremic toxins Protein-bound uremic toxins	Hydrophobic or protein-bound exogenous substances	Cytokines, complements, free hemoglobin, etc

kDa, kilodalton; Da, daltons.

not been associated with bioincompatibility reactions in the different studies that will be discussed in detail in the following sections. Common to all 3 reviewed cartridges is the recommended treatment duration of 2–2.5 h but not limited (treatment duration can be prolonged depending on the other hybrid therapies). The relatively short duration of each treatment session is to overcome the potential decrease in clearance efficiency related to saturation of the sorbent material with time as demonstrated in studies examining HP for the treatment of poisoning [6] (detailed in the section discussing HA-230 cartridges).

HA Cartridges in Acute Conditions (HA-330)

Adsorption using HA-330 cartridge was studied in multiple cohorts in the context of inflammatory conditions such as sepsis, acute lung injury (ALI), hepatitis, and pancreatitis. Overall, there seems to be no significant side effects associated with its use. Furthermore, in the different cohorts, remarkable reduction in the inflammatory mediators was noted. In an animal model of ALI and acute respiratory distress syndrome [7], HA reduced circulating and alveolar levels of pro-inflammatory cytokines, improved oxygenation, and attenuated lung injury. This was followed by human studies, including the study by Huang et al. [8], (summarized in Table 2) evaluating HA330 cartridge effectiveness in 44 septic patients with ALI. HP in addition to standard therapy (defined as, full intensive care management, including fluid resuscitation, vasopressors, antimicrobial therapy, and ventilatory support), compared to standard therapy alone resulted in the improvement of inflammatory cytokines level. It further resulted in improved patients' hemodynamics, shorter intensive care unit (ICU) length of stay (12.4 ± 3.1 days in the HP group vs. 19.5 ± 4 days in the control group, p = 0.03), ICU mortality (12.5% in HP group vs. 45% in the control group, p = 0.02) but not hospital or 28-day mortality. Of note, the drop in platelet count was observed in the HP group at day 3 (54.9 ± 13.2 compared to a baseline of 81.9 ± 23.1 in the HP group vs. 71.2 ± 37.6 compared to a baseline of 87.1 ± 67.1 in the control group, $p < 0.05$); however, it normalized quickly (75.6 ± 29.8 by day 7 in the HP group vs. 64.1 ± 41.6 in the control group, $p <$ 0.05). In a later study by Huang et al. [9] (summarized in Table 2), HP was compared to standard therapy in 46 patients with ALI induced by extra-pulmonary sepsis. HP resulted in a significant reduction in interleukin (IL)-1 and tumor necrosis factor-α in the broncho-alveolar lavage and plasma ($p < 0.05$). It also resulted in the improvement of patients' hemodynamics, duration of mechanical ventilation (9.2 ± 2.3 days in HP group vs. 13.6 ± 3.2 days in the control group, p = 0.01), duration of continuous renal replacement therapy (65.7 ± 14.6 h in the HP group vs. 18.6 ± 5.1 h in the control groups, p = 0.005). Furthermore, it was associated with lower ICU mortality (6/25 [24%] vs. 12/21 [57.14%], p = 0.02), 28-day mortality (7/25 [28%] vs. 14/21 [66.7%], p = 0.009), and ICU-length of stay (6.1 ± 1.2 vs. 8.9 ± 2.5 days, p = 0.047) with no reported safety concerns.

Hepatitis is another example of the inflammatory states where HA-330 was found to be effective. In a study by Hu et al. [10], a cohort of Hepatitis B patients was retrospectively reviewed. Thirty-seven patients received medical therapy, while 41 patients received medical therapy plus HP. Medical therapy consisted of bed rest, ECG monitoring, oxygenation, hydration, enteral nutrition, vitamins/amino acids supplementation, liver protection and promotion of hepatocyte growth, adjustment of intestinal flora, anti-microbials for infection, and supplementation of coagulation substances as needed. A marked

Table 2. The major studies evaluating the use of HA cartridges in sepsis

	Huang et al. [8], 2010	Huang et al. [9], 2013
Study design	RCT	RCT
Study population, *n*	44 sepsis or septic shock patients	46 ALI/extra-pulmonary sepsis patients
Prescribed dose	HP for 2 h for 3 days	HP for 2 h for 3 days
Survival	– ICU mortality 12.5% in HA vs. 45.0% in the controls ($p = 0.02$) – Hospital mortality 37.5% in HA vs. 50.0% in the controls ($p = 0.81$) – 28-Day mortality 45.8% in HA vs. 55.0% in controls ($p = 0.47$)	– ICU mortality 24% in HA vs 57.14 % in the controls ($p = 0.02$) – 28-Day mortality 28% in HA vs 66.7% in the controls ($p = 0.009$)
Length of ICU stay, days	12.4 ± 3.1 in HA vs. 19.5 ± 4.0 in controls ($p = 0.03$)	15.5 ± 4.0 in HA vs. 19.4 ± 3.1 in controls ($p = 0.04$)
Hemodynamics	Significant reduction in VP dose in the HA group vs increase in the control group ($p = 0.01$)	Significant reduction in VP dose in the HA group vs increase in the control group ($p = 0.032$)
Other results	Significant difference in IL-8 and IL-6 levels between the 2 groups at day 3 ($p = 0.03$, 0.01, respectively)	Significant difference in IL-1 and TNF-a in BAL fluid between the 2 groups ($p = 0.02$, 0.04, respectively)
Safety	– 1 patient with fever in the HA group – Transient reduction in platelets count in HP group	–

RCT, randomized controlled trial; ALI, acute lung injury; EAA, endotoxin activity assay; HA, hemoadsorption; HP, hemoperfusion; ICU, intensive care unit; TNF, tumor necrosis factor; BAL, broncho-alveolar lavage; VP, vasopressors; IL, interleukin.

decrease in IL-8 ([116.32 ± 61.25] g/L vs. [41.58 ± 25.39] g/L [$p < 0.01$]) was noted in the HP group. Ammonia reduction was more pronounced in the HP group, with rebound to some extent; however, levels remained low after multiple plasma adsorption treatments. Additionally, a mild decrease in total bilirubin was observed in the HP group. Transient chills were reported in 7 out of 123 of the treatments.

HA-330 was also studied in the context of pancreatitis [11]. In combination with high volume hemofiltration, HP led to a significant decrease in blood lipids level and serum amylase level which was associated with a dramatic alleviation of patients' symptoms and reduction of the sequential organ failure assessment score. Significant reductions of triglycerides, cholesterol, IL-1, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α were also observed in the HP group, compared to either the baseline values or the control group. Lastly, in a recent study by Bai et al. [12], HP was utilized in the treatment of patients with toxic epidermal necrolysis. A cohort of 68 patients was retrospectively studied. Conventional therapy plus continuous veno-venous hemofiltration (CVVH) + HP was compared to conventional therapy alone. CVVH + HP group had significantly higher 28-day survival compared to controls (91.2 vs. 73.5%, $p = 0.047$), shorter hospital stay (9 [4–18] vs. 13 [5–25] days, $p = 0.005$), and rash/fever/antibiotic-use durations. Importantly, CVVH + HP were not associated with a significantly higher cost.

HA Cartridges in Chronic Conditions (HA-130)

HA cartridges (HA-130 in particular) were found to be effective in reducing uremic symptoms in chronic hemodialysis (HD) patients. In a study by Li et al. [13], HP in addition to HD not only resulted in improvement of pruritus score in comparison to HD alone ($p < 0.05$) but also decreased parathyroid hormone and calcium phosphate product ($p < 0.05$). In another report by Chen et al. [14], HD plus HP was compared to HD in a 100 chronic dialysis patient for duration of 2 years. The addition of HP was found to be superior to HD alone in eliminating middle and large molecule uremic toxins, which may translate into improvement of quality of life and survival rate. Studies in the context of chronic conditions are summarized in Table 3.

Table 3. Major studies evaluating the use of HA cartridges in chronic hemodialysis patients

	Chen et al. [14], 2011	Li et al. [13], 2017
Study design	Prospective RCT	Observational
Study population, *n*	100 CHD patients followed for total of 2 years	90 CHD patients with a diagnosis of uremic pruritis
Prescribed dose	2 groups: HD alone vs HD+ HA130-HP (1 HP session weekly)	3 groups: control group (RHD alone), experiment 1 group (RHD + HA130-HP), and experiment 2 group (RHD + HA330-HP). HP in experiment 1 and 2 groups: once every 2 weeks for 2.5 h
Results	Significant improvement in the HP group compared to the control group in: – SBP, DBP, types of antihypertensive drugs, ($p < 0.05$) – HR, cardiothoracic ratio, LVMI, ($p < 0.05$), and EF ($p < 0.01$) – EPO dose, ($p < 0.05$) – HB level, ($p < 0.01$) Reduction in leptin, hsCRP, iPTH, IL-6, β2-MG, TNF-α serum levels in the HP group, compared to a rise in the control group. Significant improvement in the quality-of-life score (SF-36) in the HP group compared to the control group ($p < 0.05$). Significant reduction in 2-year mortality rate in the HP group compared to the control group (12.77 vs. 31.82%, $p < 0.01$)	Significant improvement in experiment 1 and 2 groups compared to the control group in: – Pruritus scores (VAS score, modified Duo scores; $p < 0.05$) – Parathyroid hormone and calcium phosphate product ($p < 0.05$)
Safety	– Low BP: 3 patients in the HP group. Improved with blood flow reduction. – Itching and rash: 2 patients in the HP group. Symptoms were alleviated through IV injection of dexamethasone 5 mg. – Hemorrhagic spots: 2 patients in the HP group. Resolved with no recurrence after adjusting heparin dose.	–

RCT, randomized controlled trial; CHD, chronic hemodialysis; HD, hemodialysis; RHD, regular hemodialysis; HP, hemoperfusion; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVMI, left ventricular mass index; EF, ejection fraction; EPO, erythropoietin; HB, hemoglobin; hsCRP, high sensitivity C-reactive protein; iPTH, parathyroid hormone; IL-6, interleukin-6; β2-MG, beta 2 microglobulin; TNF-α, tumor necrosis factor alpha; BP, blood pressure; IV, intravenous; VAS, visual analogue scale.

HA Cartridges in Intoxication (HA-230)

HA-230 was studied in 85 patients with paraquat poisoning and was found to be effective in decreasing its level [6]. In this cohort, all the patients were treated with gastric lavage, fluid replacement, antioxidants (Vitamin C, Vitamin B and L-Glutathione), and immunosuppressant (corticosteroids). Then HP was performed on all the patients except those who were diagnosed with multiple organ failure and had unstable vital signs on admission. A few important and clinically relevant issues about HP as a technique were highlighted in this study. First, the degree of paraquat clearance was proportionate to its initial concentration. Clearance was below 40% in patients with initial paraquat concentration below 200 ng/mL, while clearance of above 40% was observed in patients with initial level higher than 300 ng/mL ($p < 0.05$). Second, the decline in paraquat concentration was more pronounced during the first hour of therapy (about 37.066 ± 21.81% from baseline), while in the second hour, it was dramatically slower. Third, in the subgroup of patients who received repeated HP (to-

Table 4. The major studies evaluating the use of HA cartridges in intoxication

	Shi et al. [6], 2012	Bo [16], 2014	Dong et al. [15], 2017
Study design	Observational	RCT	Retrospective, observational
Study population, *n*	85 patients with acute PQ intoxication	36 patients with ASOP	68 patients with ASOP
Prescribed dose	HP for 2 h (6 patients had repeated HP)	3–4 HP ($n = 20$) vs. 1 HP ($n = 16$)	ST + HD + HP ($n = 34$) vs. ST alone ($n = 34$)
Results	– HP was more effective in lowering PQ level in patients with higher initial concentration (clearance <40% in patients with initial PQ level of <200 ng/mL vs. >40% in patients with initial level of >300 ng/mL [$p < 0.05$]) – PQ clearance is the highest within the first hour of therapy – Rebound rates are widely variable (27.56–69.80%)	Repeated HP vs single HP resulted in (all $p < 0.05$): – Less atropine use – Shorter time to coma recovery – Shorter time until normalization of cholinesterase levels – Lower rate of myasthenia syndrome – Higher survival rates	Significant improvement in the treatment group vs the control group (all $p < 0.05$) in: – Rescue success rate (97.06 vs. 82.35%) – Mortality (2.94 vs. 17.65%). – Atropinization time, recovery time of cholinesterase activity – Length of hospital stay (11.2 ± 1.4 vs. 18.3 ± 3.5 days) – Poisoning rebound rate (2.94 vs. 11.76%)
Safety	–	–	– Hypotension: higher rate in the HP group (35.3 vs. 17.65%) – Bleeding: higher rate in the HP group (11.76 vs. 2.94%)

PQ, paraquat; HP, hemoperfusion; ASOP, acute severe organophosphate poisoning; ST, standard therapy; HD, hemodialysis.

tal of 6 patients), 71.42% had plasma paraquat concentrations prior to the next session of HP higher than their concentrations after the first session of HP (rebound rates between 27.56 and 69.80%). These findings suggest that patients with higher initial levels are likely to have a better response. Furthermore, more frequent therapy seems to be more effective than a single prolonged HP session possibly due to the saturation of the sorbent beads with time. This is particularly relevant in patients with high rebound rates. Treatment frequency can be guided by checking the paraquat level, as the rebound rates varied considerably, and patients with lower rebound rates may not necessarily require repeated HP sessions.

Another example is organophosphorus poisoning. In a study by Dong et al. [15] standard therapy + HD + HP was compared to standard therapy alone in 68 patients with organophosphorus poisoning. Rescue success rate was significantly higher in the treatment group ($p < 0.05$). Additionally, poisoning rebound rate and mortality were significantly lower in the treatment group ($p < 0.05$). Furthermore, in a study examining the effect of more frequent therapy compared to single session in a cohort of 36 organophosphorus poisoning patients [16], more frequent therapy was associated with less atropine use, shorter time to coma recovery, higher cure rates, shorter time until normalization of cholinesterase levels, lower rate of myasthenia syndrome, and higher survival rates. Studies in the context of intoxication are summarized in Table 4.

Conclusions

The use of adsorption technique for extracorporeal solute removal has been utilized for years [1]. Intoxication (removal of exogenous toxins) was the typical indication for this type of therapy. The development in the technology of adsorption cartridges allowed more wide applications. This successfully expanded to involve other indications as highlighted above. HA resin HP cartridges HA130, HA230, and HA330 (Jafron, Zhuhai City, China) are among the widely studied and used cartridges in China. To date, its use has not been associated with safety concerns. Furthermore, studies suggest their effectiveness in the different clinical settings where adsorption therapy may be recommended. Large multicenter trials are needed to better evaluate the applicability of the use

of these sorbent devices more widely, as so far, most of the clinical experience with their use has been focused in China. Moreover, efforts to better define criteria to start therapy, duration of therapy and potential novel uses, are also needed.

Disclosure Statement

The authors declare no conflicts of interest to disclose.

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