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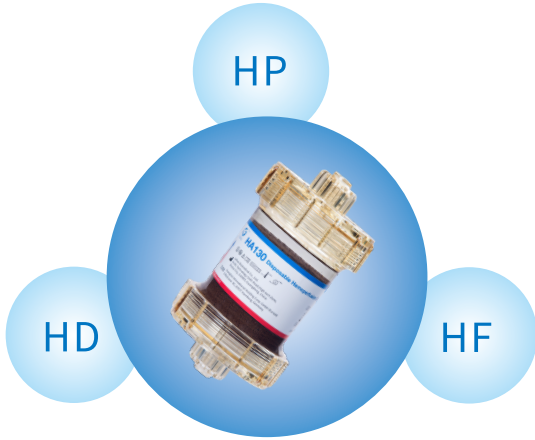
Hemoperfusion for End Stage Renal Disease

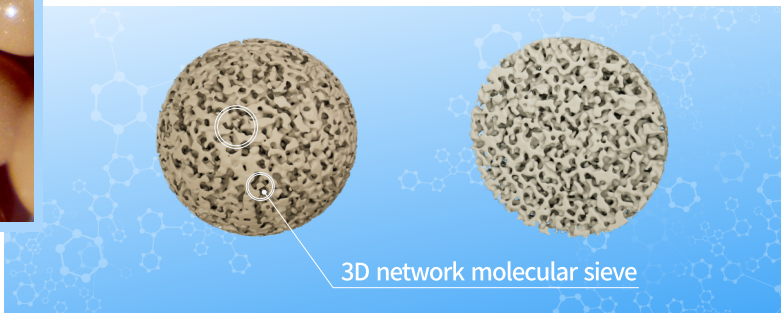


KIDNEY CARE

HAND BOOK

HA130 DISPOSABLE HEMOPERFUSION CARTRIDGE

Adsorption therapy



The neutro-macroporous resin made of double crosslinked styrene-divinylbenzene copolymers could adsorb middle and protein-bound uremic toxins

Content

Hemoperfusion in ESRD

Introduction

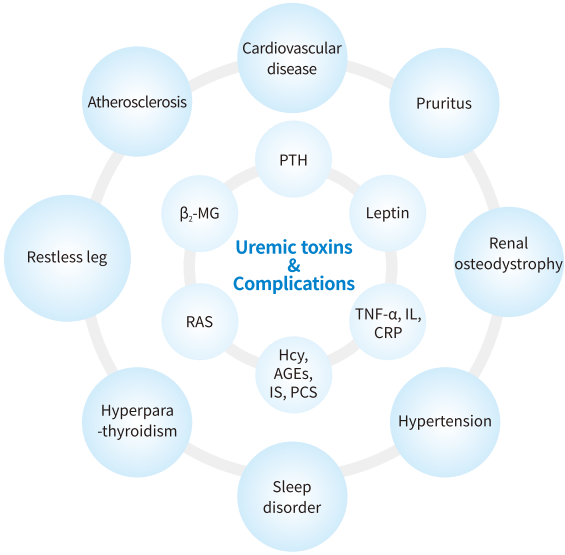
Chronic Kidney Disease (CKD) is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health. End Stage Renal Disease (ESRD) is defined as a Glomerular Filtration Rate (GFR) less than 15 mL/min[1]. Over 2 million people worldwide currently receive treatment with dialysis or kidney transplant, this number may only represent 10% of people who actually need the treatment[2,3] .

The uremic toxins play key roles in the incidence of ESRD complications such as uremic pruritis, amyloidosis, cardiovascular events etc.[4-7] Hemodialysis (HD) showed a good result in removing small water-soluble toxins, but with poor removal of middle molecule toxins and protein-bound toxins, which may remove by hemoperfusion based on adsorption principles[8].

HA130 disposable hemoperfusion cartridge manufactured by Jafron Biomedical contains neutro-macroporous resin made of double crosslinked styrene-divinylbenzene copolymers coated with collodion to mitigate the possible adverse effect of direct contact of blood to the sorbents. The biocompatibility and efficacy of the cartridge have been evaluated both in vitro and vivo[9-19].

In vitro, CT imaging showed an excellent distribution of the flow inside the cartridge without channeling phenomena. The cytotoxicity test of monocytes exposed to the HA cartridges showed insignificant necrosis or apoptosis of the exposed cells compared to controls; the results revealed that the HA cartridges carried out an optimal level of biocompatibility and its use was not associated with adverse reactions[10].

Clinically, previous publications illustrated that the combination of HA130 and HD, known as artificial kidney, could significantly remove the middle uremic toxins, protein-bound toxins, and inflammatory mediators resulting in the relief of ESRD complications such as uremic pruritis, DRA as well as improving quality of life and survival rate when compared to conventional dialysis alone[11-19].



Therapy Applications△

Hemoperfusion using HA130 cartridge can be used for ESRD patients with one or more of the following criteria:

- PTH > 300 pg/mL and/or β_2-MG ≥ 30 mg/L.
- Presence of one of the ESRD complications.
  - Uremic pruritis.
  - Secondary hyperparathyroidism.
  - Dialysis-related amyloidosis.
  - Resistance hypertension.
  - Sleep disturbances.
- It can be used as a prophylaxis therapy to prevent the complications of hemodialysis, especially for patients with long-term hemodialysis.

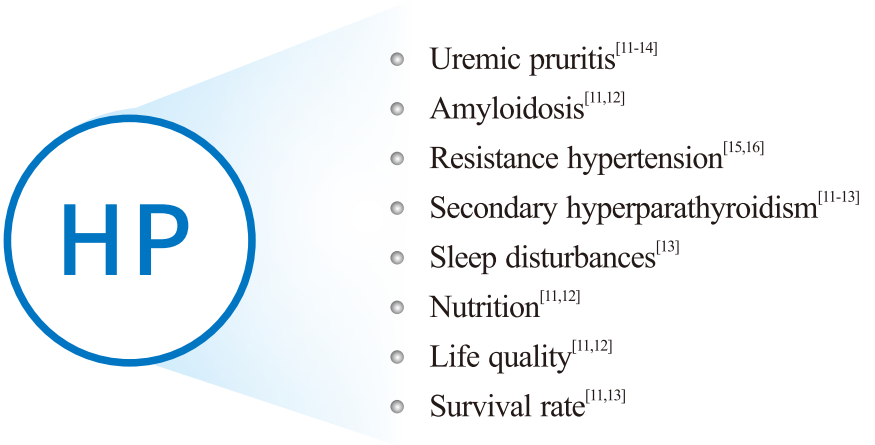
Contraindications

- Platelet count < 60×10^9/L.
- Severe hemorrhage tendency or active bleeding.
- Hypotension: BP < 90/60 mmHg.
- Allergic to hemoperfusion materials.
- Pregnancy or breastfeeding.
- History or development of heparin-induced thrombocytopenia.

△According to clinical experience, the cartridge has been used in the listed conditions. Detailed information please visit www.jafron.com.

Clinical Benefits of HA130

The HA130 disposable hemoperfusion cartridge contains neutral macroporous resins, functioning as 3D molecular sieve with large adsorption surface area (~20,000 m^2) to be able to remove high levels of uremic toxins. The coating technology of the resin ensures the protection of the blood components, such as the red blood cells (RBC). The design of adsorbents enables the HA130 cartridge to be capable of adsorbing the middle molecular and protein-bound uremic toxins with molecular weight ranged between 5-30 KDa. HA130 is applied for the prevention and treatment of uremia complications to improve the quality of patients' lives[11,12].



Remove Middle Uremic Toxins

Middle uremic toxins have been found to be associated with the complications of ESRD, such as uremic pruritis, amyloidosis, and cardiac events. Previous studies showed a significant decrease in serum PTH, β_2-MG and leptin concentrations as well as significant reduction in the inflammatory mediators and inflammatory markers such as IL-6, TNF-α and CRP in the HA130+HD group compared with HD group (Fig. 1-4)[11-13].

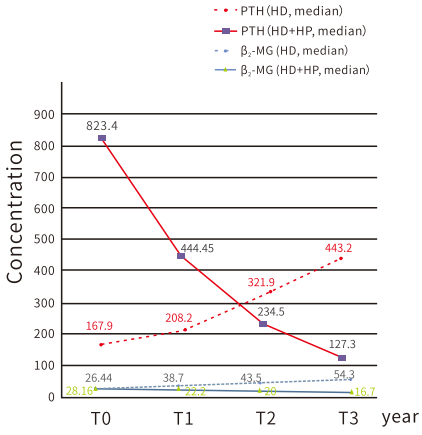


Fig.1 Changes of serum PTH and β_2-MG[10]

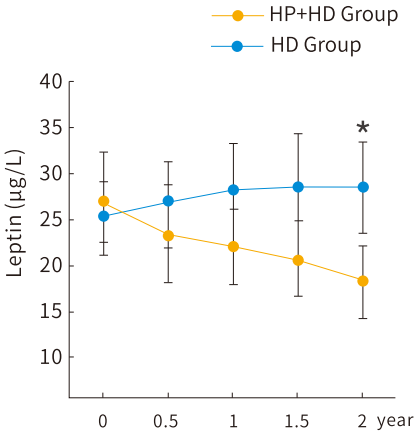


Fig.2 Changes of leptin, *p < 0.05[11]

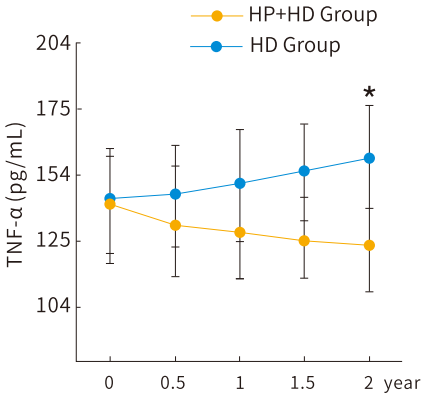


Fig.3 Changes of TNF-α, *p < 0.05[11]

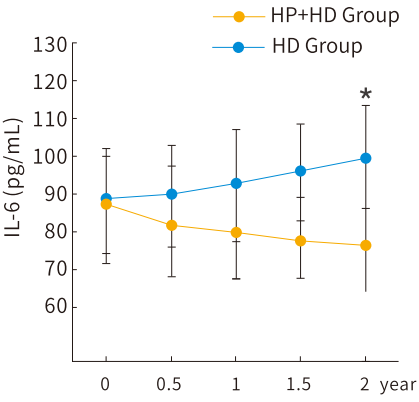


Fig.4 Changes of IL-6, *p < 0.05[11]

Relieve Uremic Pruritis

The significant improvement of uremic pruritis and pruritis score as a result of using HA130+HD in the patients with long-term dialysis has been reported in the previous studies when compared to conventional hemodialysis alone, and the possible mechanism is that the combination of HA130 and HD could benefit of clearing PTH, β_2-MG, phosphorus as well as the inflammatory mediators which are associated with the incidence of uremic pruritis[11-14].

Ameliorate Dialysis-related Amyloidosis

HA130+HD showed a significant removal of β_2-MG as well as the inflammatory mediators such as IL-6 and TNF-α when compared to conventional HD alone, which may reduce the bone pain and may prevent further progress such as Carpal Tunnel Syndrome (CTS)[11,12].

Improve Sleep Disorders

HA130+HD is associated with significant improvement of sleep disturbances as well as sleep efficiency in dialysis patients when compared to HD alone. The possible mechanism is that HP+HD leads to the reduction of uremic toxins, improvement of uremic pruritus and melatonin levels (Fig. 5,6)[13].

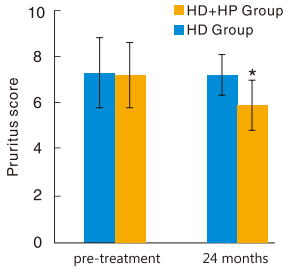


Fig.5 Changes of pruritis score, *p < 0.05[13]

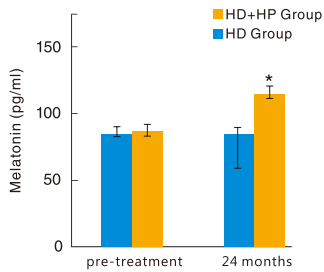


Fig.6 Changes of melatonin level, *p < 0.05[13]

Control Resistance Hypertension

The application of HA130 can significantly reduce the levels of Rennin (RA), Angiotensin-II (Ang II), Aldosterone, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) as well as reduce the number of antihypertensive agents used in HP treatment group compared to control group (Table 1), thus might reduce the occurrence of cardiovascular related events[15,16].

Table.1 Comparison of RA, Ang II, aldosterone, blood pressure and antihypertensive drugs in each treatment stage between HP treatment group and control group ($\bar{x}\pm s$)[16]

	Group	RA(ng/ml)	AngII(pg/ml)	Aldosterone(pg/ml)	SBP(mmHg)	DBP(mmHg)	Hypotensor
0M	Control Group (n=30)	2.22±0.61	834.85±219.50	497.55±217.06	175.10±8.67	98.50±7.77	4(3,5)
	Observation Group(n=45)	2.20±0.62	856.72±305.33	491.37±256.88	176.38±10.07	98.51±6.75	4(3,5)
	T value	0.138	−0.338	0.108	−0.569	−0.007	
	P value	0.891	0.736	0.914	0.571	0.995	0.394
3M	Control Group (n=30)	2.26±0.52	805.56±218.20	460.10±161.48	172.83±7.90	98.57±5.52	4(3,5)
	Observation Group(n=45)	2.21±0.58	829.09±262.03	477.57±209.17	175.40±8.04	97.29±6.14	4(2,5)[1)]
	T value	0.398	−0.407	−0.387	−1.364	0.919	
	P value	0.692	0.686	0.700	0.177	0.361	0.301
6M	Control Group (n=30)	2.15±0.49	850.98±158.76	489.91±155.50	168.03±7.77	95.60±17.59	3.5(2,5)
	Observation Group(n=45)	1.29±0.43	747.26±209.76	421.59±168.16	153.04±7.16	87.64±5.01	2(0,4)[1)]
	T value	8.118	2.302	1.776	8.579	2.872	
	P value	0.000	0.024	0.080	0.000	0.005	0.000
12M	Control Group (n=30)	2.14±0.48	851.06±157.66	490.98±159.84	169.40±7.53	96.37±17.57	4(2,5)
	Observation Group(n=45)	1.27±0.41	736.10±199.64	412.61±156.45	152.93±7.08	87.73±5.60	2(0,4)[1)]
	T value	8.462	2.649	2.107	9.620	3.079	
	P value	0.000	0.010	0.039	0.000	0.003	0.000

[1)]Compared with 0 M, p < 0.01

Alleviate Secondary Hyperparathyroidism (SHPT)

SHPT is a common complication of chronic kidney disease characterized by elevated parathyroid hormone levels secondary to derangements in the homeostasis of calcium, phosphate, and vitamin D, which is associated with increased cardiovascular morbidity and mortality. HA130 combined with conventional HD could significantly reduce the PTH and phosphorus levels when compared to the control group, thus may improve the symptoms and prevent the progression of the SHPT[11-13].

Reduce Protein-bound Toxins

Protein-bound toxins such as homocysteine, indoxyl sulphate, and p-cresyl are associated with the progression of cardiovascular events in dialysis patients. The latest clinical reports illustrated that HA130 combined with HD could significantly reduce the levels of these toxins and may reduce the risk of cardiovascular events compared to those with HD alone (Fig. 7)[18,19].

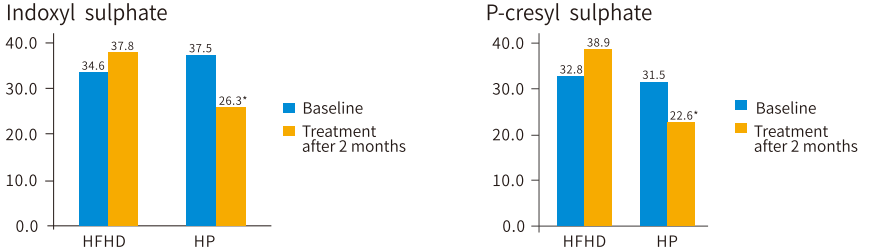


Fig.7 Changes of protein-bound uremic toxins, *p < 0.05[18], (* Unpublished Data)

Regulate Intestinal Microbiota

Hemoperfusion using HA130 in chronic dialysis patients demonstrated significant results in regulating intestinal microbiota by reducing inflammatory status and regulating the expression of Lactobacillus acidophilus as well as Escherichia coli when compared to patients in the control group[17], however, further investigations are needed.

Support Nutrition

Uremic malnutrition is one kind of syndrome distinct from malnutrition caused by inadequate nutrient intake and ineffective nutrient utilization, which can contribute to nutritional disorders in CKD patients. Compared to the control group, the HA130 treatment group showed benefits in reducing leptin levels, EPO needs, and increasing hemoglobin levels and BMI[11,12]; however, further investigations are needed.

Improve Quality of Life (QoL)

The findings of HA130+HD compared to HD alone suggested a potential role in improving the quality of life by improving pruritis, body pain, general health, vitality, total QoL score etc. (Fig. 8)[11,12].

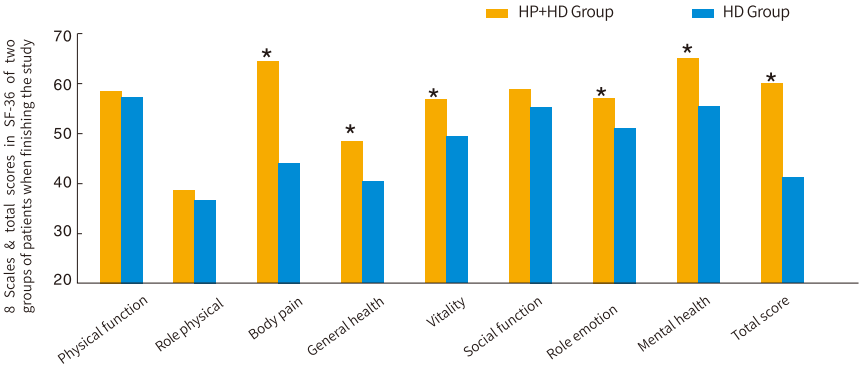


Fig.8 SF-36 scores for HA130+HD vs HD, *p < 0.05[12]

Improve Survival Rate

Previous studies showed significant benefits in reducing the cardiovascular events and improving survival rate in the HA130+HD group compared to conventional dialysis (Fig. 9,10)[11,13].

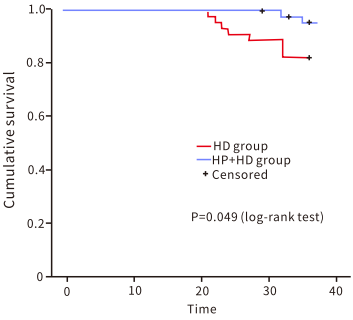


Fig.9 Survival curve after 36 months of observation, p = 0.049[11]

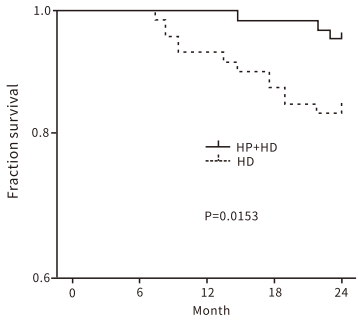


Fig.10 Survival curve after 24 months of observation, p = 0.0153[13]

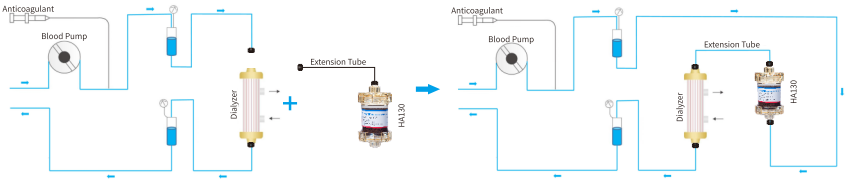
Treatment Procedures

A. Heparinization

- Unscrew one cap of the cartridge (1).
- Use 5 ml needle-free syringe to inject 12500U ~25000U of heparin into the cartridge (2).
- Tighten the cap back to cartridge (3).
- Shake and rotate the cartridge slightly for 10 sec to mix the heparin with adsorbents (4).
- Put the cartridge statically in sterile towel for 30 min (5).

B. Priming (Washing)

- Fill the arterial tube of the circuit with saline, then connect it with the arterial end of the cartridge to fill the cartridge with saline.
- Connect the venous end of the cartridge with the intravenous tube of blood circuit.
- Fix the cartridge on rack vertically with the venous end upwards and arterial end downwards.
- Flush the whole set with 3000mL of normal saline at the flow rate of 200-300 mL/min.
- Pat the cartridge and tubes during the whole priming process to remove the air bubbles as shown in the next steps.



Dialysis circuit before HA130

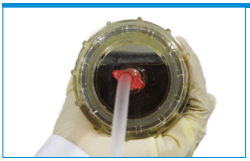
Dialysis circuit after integrating HA130

C. Air Exhausting (Deaerating)

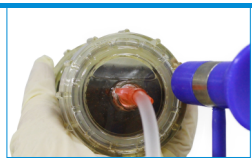
During the whole set rinsing with 3000 mL of saline, exhaust the air bubbles as the following steps:

- Hold the cartridge horizontally and hit the bottom surface of the arterial end at 0-3 o'clock with a frequency of 2-3 times/s, and total 10 sets (Step I).
- Hold the cartridge vertically and hit the edge of upper side with frequency of 2-3 times/s, and total 2 sets (Step II).
- Hold the cartridge at 30° from the horizontal and hit the bottom edge of the arterial end at 11-13 o'clock with a frequency of 2-3 times/s, and total 10 sets (Step III).

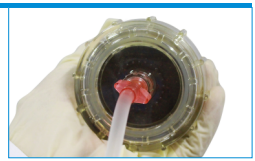
Step I



Pre-deaerating arterial end



During deaerating arterial end



Post-deaerating arterial end

Step II

Pre-deaerating vein end

During deaerating vein end

Post-deaerating vein end

Step III

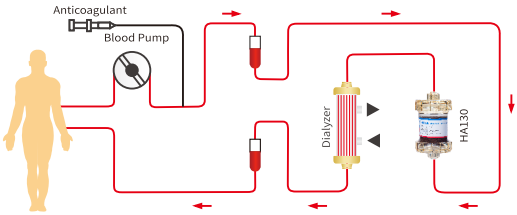
Pre-deaerating residual bubble

During deaerating residual bubble

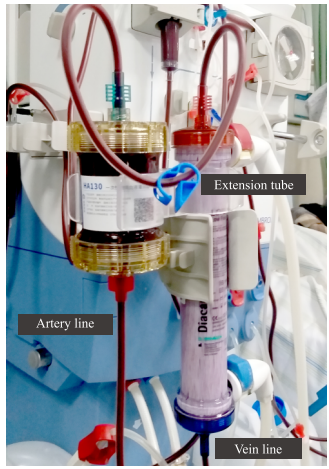
Deaerating completed

D. Connecting to Patient

- Disconnect the saline and connect to the arterial end of the patient.
- Disconnect the waste bag end and connect to the vein end of the patient.
- Start the treatment.



HA130+HD/HDF/HF



Treatment Recommendations

Recommended Treatment Regimen: 4 times/month for intensive program, 1-2 times/month for maintenance program, 4 hours for each, and it could be adjusted according to the patients' conditions.

Treatment Mode: HA130+HD/HDF/HF

Patient Anticoagulation:

1) Heparin: loading dose: 62.5~125 U/kg, additional dose: 1250 ~2500 U/h;

2) LMWH: 60~80 U/kg, no additional dose.

(*Anticoagulant could be adjusted according to patients' coagulation status.)

Cautions: The possible side effect of blood purification may occur during the treatment, including the hypotension, coagulation and allergy, and it should be managed according to the related clinical recommendations.

Therapy Evaluation

- Relief of the complications of ESRD such as uremic pruritis, sleep disturbances, resistance hypertension etc[11–16].
- Improvement of related markers such as PTH, β_2-MG, CRP, etc[10,11].
- Improvement of pruritis score, blood pressure, sleep efficacy and quality of life score[11–13,16].

Basic Parameters

Basic Parameters of HA130			
Adsorbent Volume (mL)	130	Sterilization Method	γ-radiation
Biocompatibility	Tested as Required in ISO10993	Treatment Period	4 h
Adsorbent Material	Double crosslinked Styrene-divinylbenzene Copolymers	Target Molecular Weight	5-30 kDa
Housing Material	Polycarbonate (PC)	Adsorption Surface (m^2)	18,000~20,000

FAQ

1. Why do we need HA130 for chronic hemodialysis patients?

HA130 aims to reduce the middle uremic toxins with molecular weight 5-30 KDa and protein-bound toxins to prevent or reduce the incidence of ESRD related complications, such as uremic pruritis, CTS, refractory hypertension etc.

2. What are the common reasons for blood clotting during the treatment?

The main causes which may lead to clotting formation are insufficient amount of priming heparin, patient's insufficient anticoagulant dose, patient's hypercoagulable state (high blood lipids and high blood viscosity), and low blood flow rate (recommended blood flow rate is less than 320 mL/min. Close observation during the treatment is recommended.

3. Is there a cost-effectiveness study on hemoperfusion treatment?

The cost-effectiveness study with 1,407 patients recruited to the HD/HP trial from 30 clinical centes with two years follow-up period demonstrated that the[20]:

- Use of HP+HD extends the patients' life year (LY) by 2.87 years and the patients' quality-adjusted life-year (QALY) by 1.32 years.
- HP+HD is cost-effective as the incremental cost-effectiveness ratio (ICER) of HP + HD is 25,251 USD per QALY, which is lower than 30,778 USD, willingness-to-pay threshold of three times GDP set by WHO standard.
- HP+HD reduces the incidence of severe CVD events and subsequent CVD deaths.

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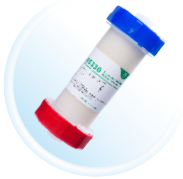
HA230

HA130

HA380

HA280



BS330

HA330-II

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- 30 years of research and clinical experience in hemoadsorption industry
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*Contraindications, warnings and more detailed information, please refer to Instructions For Use

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