Combination of maintenance hemodialysis with hemoperfusion: Effects on pruritus, parathyreoid hormone and sleep quality - our experience

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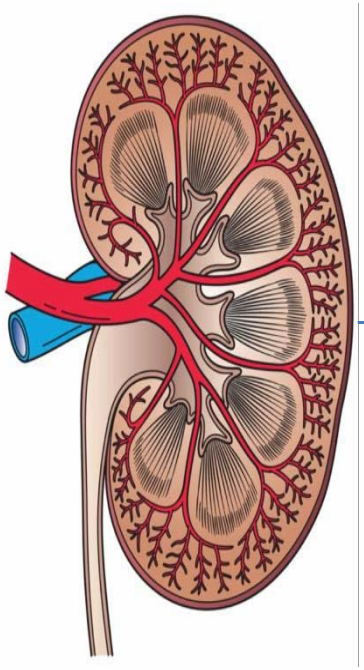
KIDNEY FUNCTION



- Reabsorption (Glucose, Amino acids, Bicarbonate, Sodium, Water…)
- Waste excretion (urea and uric acid)
- Acid-base balance
- Osmolality regulation
- Secretion (Erythropoietin, Renin and Calcitriol)

CKD

GFR categories in CKD

GFR category	GFR (ml/min/1.73 m^2)	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

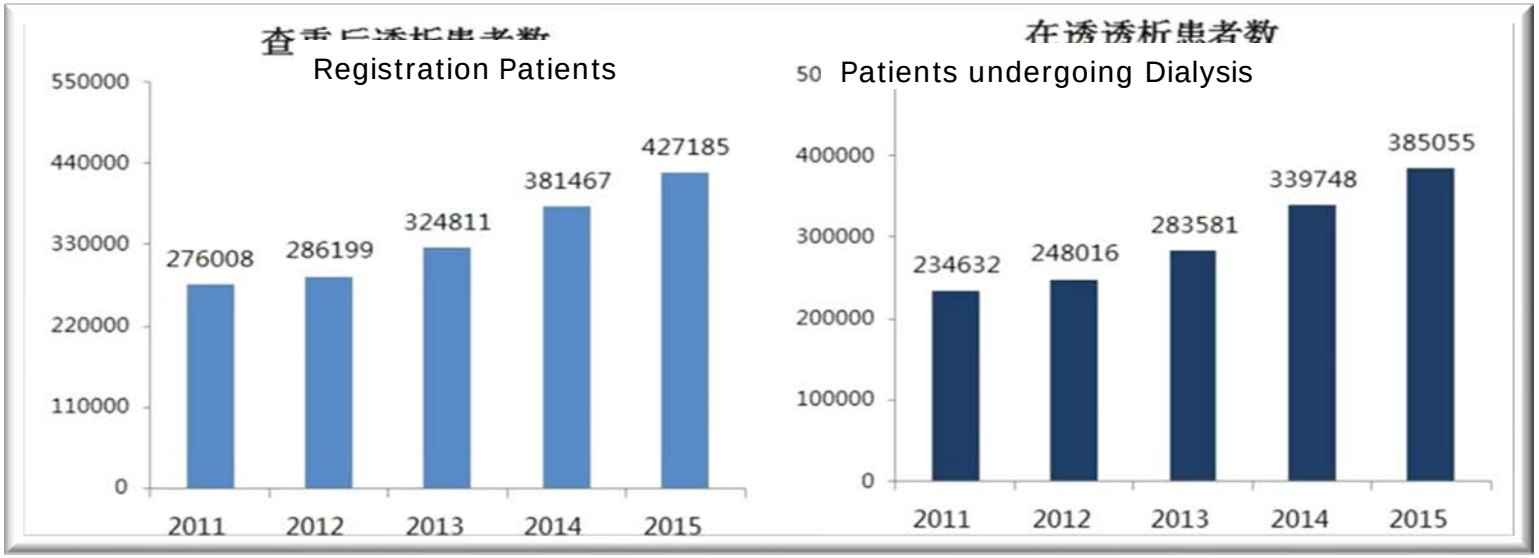
HD

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Relative to young adult level.
In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

ESRD

Kliger A S, Foley R N, Goldfarb D S, et al. KDOQI us commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD[J]. American Journal of Kidney Diseases the Official Journal of the National Kidney Foundation, 2013, 62(5):849-59.

ESRD



Data from Chinese Society of Nephrology

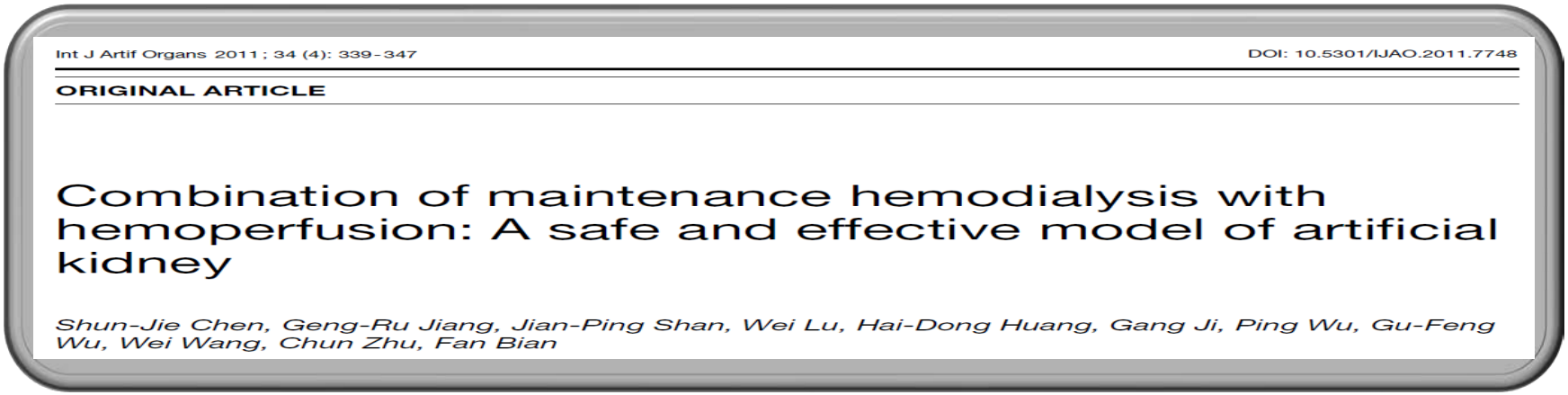
The increasing number of dialysis patients. No less than 2 Million globally.

ESRD One-year mortality: **26%.** Five-year mortality: **76%**

Rebholz C M, Coresh J, Ballew S H, et al. Kidney Failure and ESRD in the Atherosclerosis Risk in Communities (ARIC) Study: Comparing Ascertainment of Treated and Untreated Kidney Failure in a Cohort Study.[J]. American Journal of Kidney Diseases the Official Journal of the National Kidney Foundation, 2015, 66(2):231-239.

- Some of the conditions which occur in maintenance hemodialysis (MHD) patients with a high incidence, resulting in a decline in their quality of life, include malnutrition, insulin resistance, pathological changes in the peripheral nervous system, renal osteodystrophy, left ventricular hypertrophy, refractory hypertension, chronic systemic inflammation and accelerated deterioration of residual renal function.

- Studies have shown that the occurrence of mid-and longterm uremic complications is related to the low clearance rate of middle and large molecule uremic toxins when hemodialysis (HD) alone is adopted.



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ORIGINAL ARTICLE

Combination of maintenance hemodialysis with hemoperfusion: A safe and effective model of artificial kidney

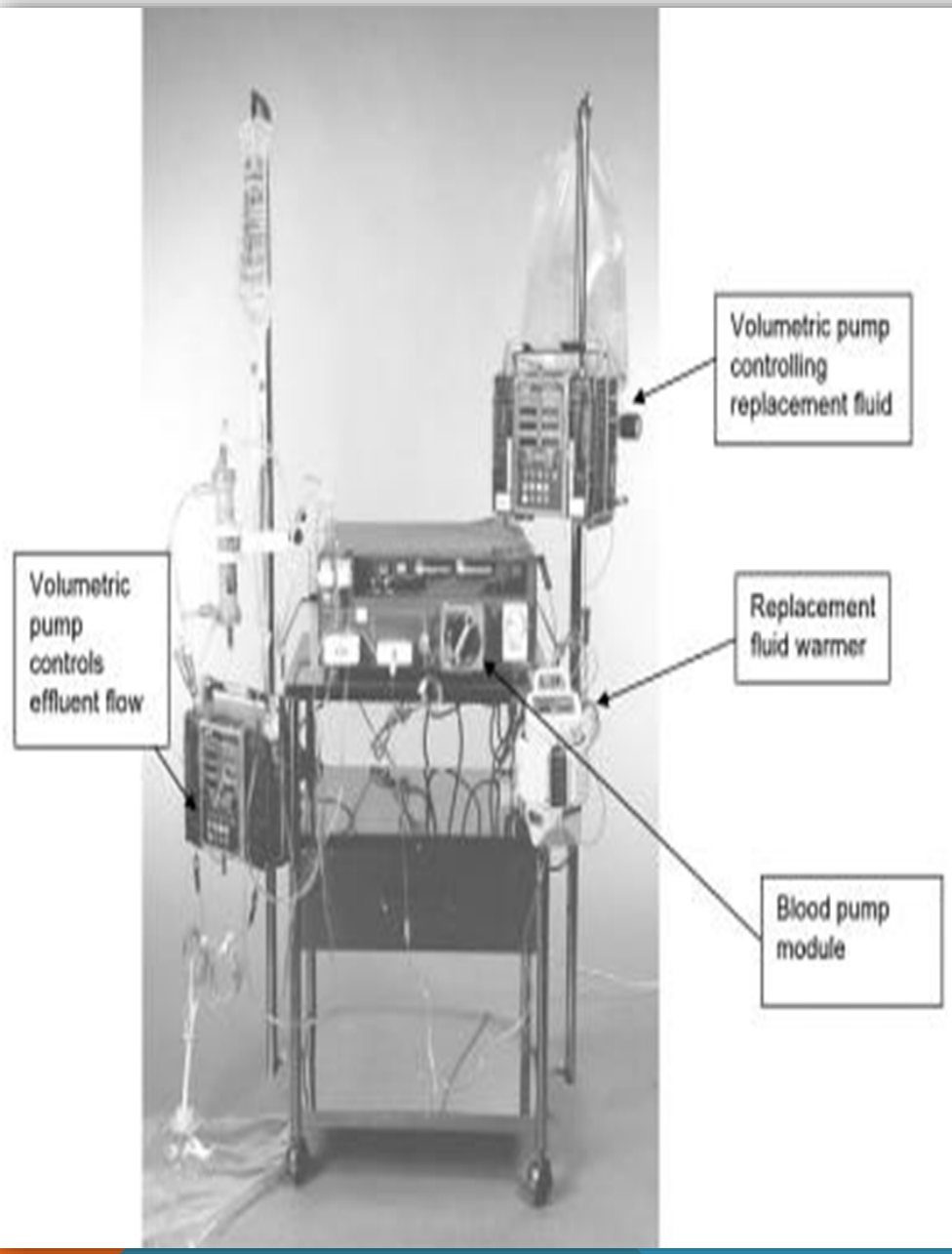
Shun-Jie Chen, Geng-Ru Jiang, Jian-Ping Shan, Wei Lu, Hai-Dong Huang, Gang Ji, Ping Wu, Gu-Feng Wu, Wei Wang, Chun Zhu, Fan Bian

- Many of these complications are irreversible and cannot be alleviated even after renal transplantation, which poses a challenge to the long-term survival of patients on dialysis.

- Clinical applications of various models of extracorporeal blood purification technology show the clearance rates of middle and large molecule uremic toxins for these models take place in the following order:

- HD + hemoperfusion (HP) > HP > bio-artificial kidney > hemodiafiltration (HDF) > hemofiltration (HF) > HD.

Bammens B, Evenepoel P, Verbeke K, et al. Removal of the protein-bound solute p-cresol by convective transport: a randomized crossover study. Am J Kidney Dis. 2004;44(2):278-285. Medline. doi:10.1053/j.ajkd.2004.04.033
Mandolfo S, Borlandelli S, Imbasciati E. Leptin and beta 2-microglobulin kinetics with three different dialysis modalities. Int J Artif Organs. 2006;29(10):949-955 Medline.


Volumetric pump controlling replacement fluid
Volumetric pump controls effluent flow
Replacement fluid warmer
Blood pump module


10 L

- Before the 1980s, low-flux dialysis was the main technology for extracorporeal blood purification in uremia treatment, which could hardly remove the middle and large molecule toxins and protein-bound toxins.
- The patients consequently led a life of poor quality with long-term complications.
- After the 1980s, with developments in the research of dialyzer membranes and dialysis machines, high-flux dialysis and online -HDF were applied. The latter was especially efficient at clearing the middle and large molecule substances.

- Therefore, largesize and high-affinity blood adsorbent was introduced into the blood purification therapy for uremic patients.

- Winchester pointed out that middle and large molecule substances displayed a multicompartmental distribution, which made them hard to be removed with traditional HD, but they could be removed to varying degrees by the use of high-flux dialyzers.

Winchester JF, Ronco C, Brady JA, et al. The next step from high-flux dialysis: application of sorbent technology. Blood Purif. 2002;20(1):81-86. Medline. doi:10.1159/000046989.

A New Series of Sorbent Devices for Multiple Clinical Purposes

- HDF was superior to HD, while HP was more effective than HD and HDF in removing middle and large molecule substances.
- For this reason we assumed that HD+HP would be the ideal choice for uremic toxin removal as a model for a hybrid artificial kidney.
- Vanholder et al reported the removal of leptin by HD+HP, stating that they found a single treatment could reduce the leptin concentration by 32% and continuous treatment for 3 weeks could reduce the concentration by 37%.

Vanholder R, De Smet R, Glorieux G, et al. Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63(5):1934-1943. Medline. doi:10.1046/j.1523-1755.2003.00924.x

- In China and other developing countries, due to the low level of economic development, low-flux dialysis is the main means of extracorporeal blood purification therapy. But it can hardly remove the middle and large molecule uremic toxins and protein-bound toxins as a result, the patients suffer from long-term complications and poor quality of life.

- In January 2007, Xinhua Hospital included an HP apparatus as an item covered by the national health insurance for the first time in China and became the first to conduct research on MHD patients with the treatment of HD combined with HP and to explore the efficacy and safety of maintenance HP.

Hemodialysis – Review Article

Blood Purif
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Blood Purification

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

Ghada Ankawi[a, b] Weixuan Fan[a, c] Diego Pomarè Montin[a] Anna Lorenzin[a, d]
Mauro Neri[a, d] Carlotta Caprara[a, e] Massimo de Cal[d] Claudio Ronco[a, d]

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.

Research Article

Blood Purif
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Published online: April 30, 2019

Blood Purification

Fluid Dynamics Analysis by CT Imaging Technique of New Sorbent Cartridges for Extracorporeal Therapies

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Giuseppe Mansi Montenegro[c] Sergio Savastano[c] Alberta Alghisi[d]
Claudio Ronco[a, b, e]

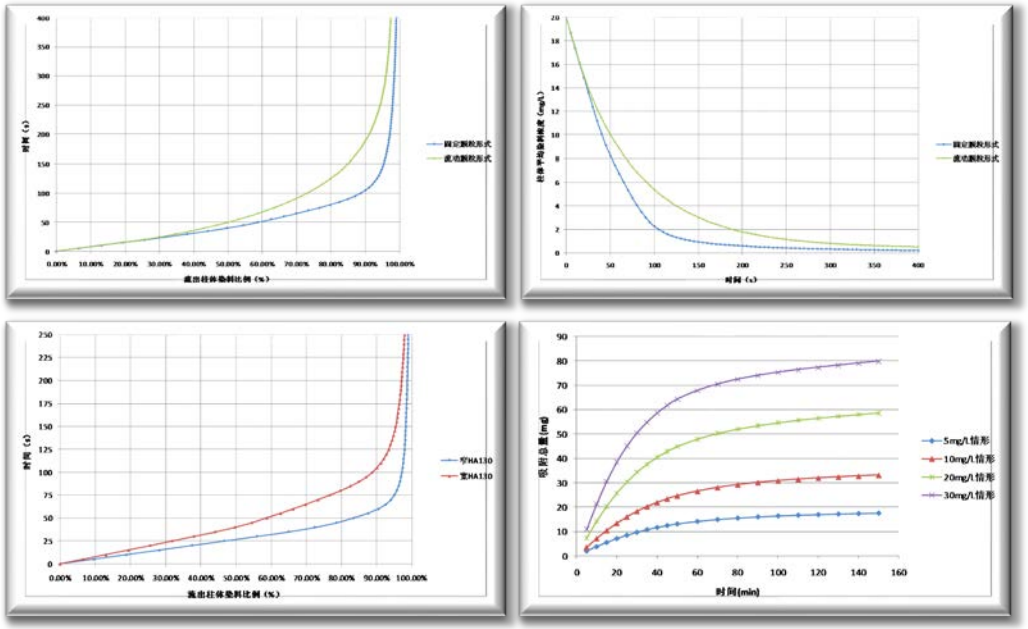
Methods:

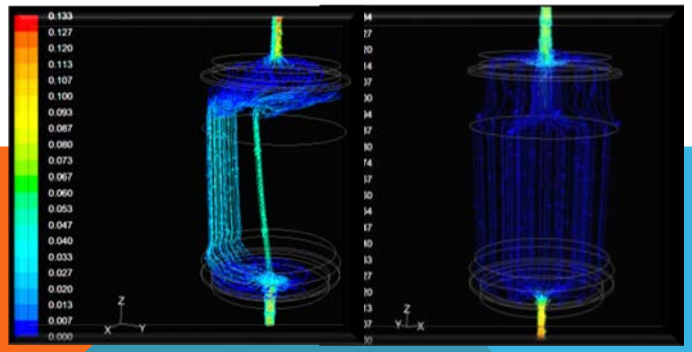
The cartridges were placed in vertical position in the CT gantry. Dye solution was circulated through the cartridges at 250 mL/min, longitudinal sections, 0.5 cm thick, were recorded for 60s.
Furthermore, an in vitro test was conducted to build pressure drop profiles. Blood was circulated at a different flow rate, 100–400mL/min, step 50 mL/min. Pre and post cartridges pressures were acquired and pressure drop calculated.

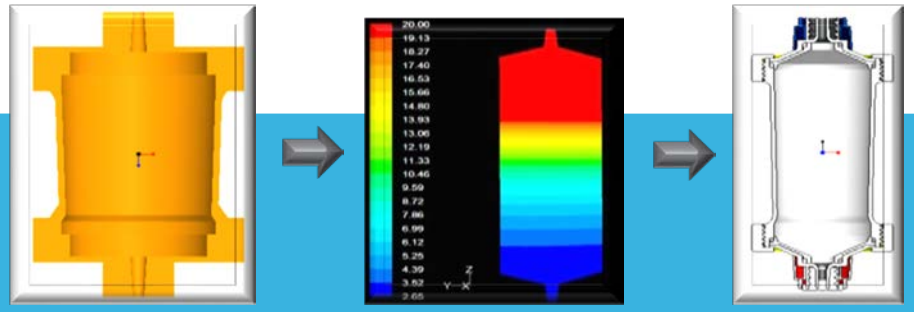
Extracorporeal Hemodynamics

Safety guarantee

- Pressure
- Blood velocity
- Temp.
- Adsorbents
- Solutes







Result:

Sequential images demonstrated an excellent distribution of the flow inside the cartridges. HA130 had a homogeneous flow profile along the entire length of the device; HA230 and HA330 showed minimal differences between central and peripheral regions. Pressure drop profiles resulted linear, increasing proportionally with blood flowrate and packing density.

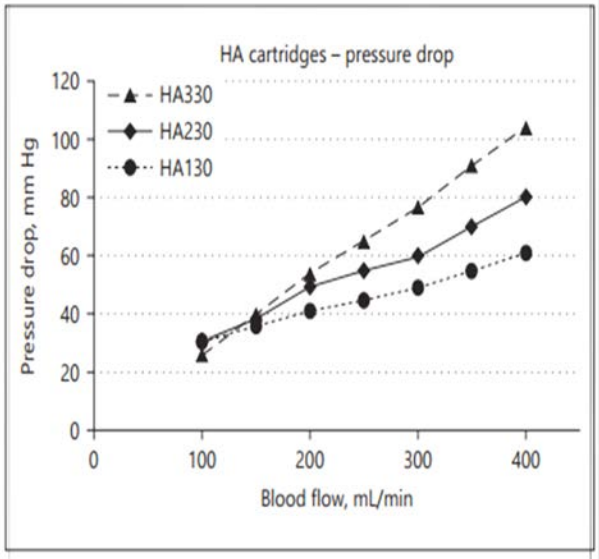


Fig. 6. Pressure drop of the 3 cartridges at different blood flow rates.

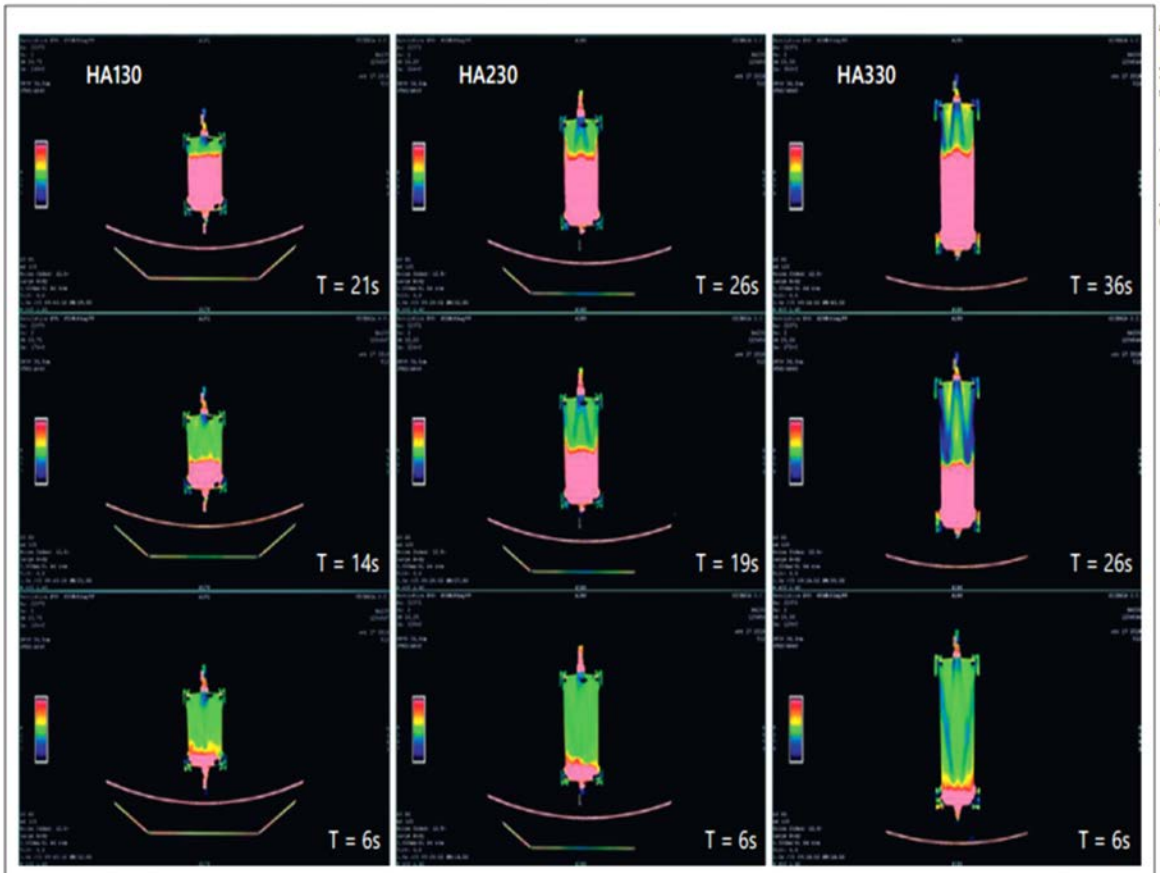


Fig. 3. Flow distribution in the 3 cartridges – HA130, HA230, HA330. From the bottom to the top, the frames show the dye progression inside the devices.

Conclusions:

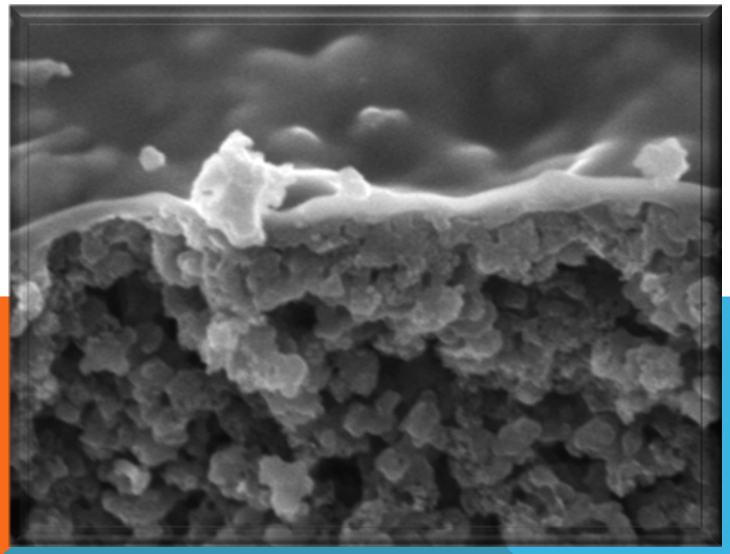
The structural and functional design of the studied cartridges is adequate for haemoperfusion with no channeling phenomena. This ensures maximum and optimal utilization of the sorbent contained in the devices.

Quality Control (*Coating*)

Coating materials

- Modified PVA TM-6,
- Modified PVA,
- Collodion,
- PHEMA,
- Heparinized Polymer,
- Grafted PVP

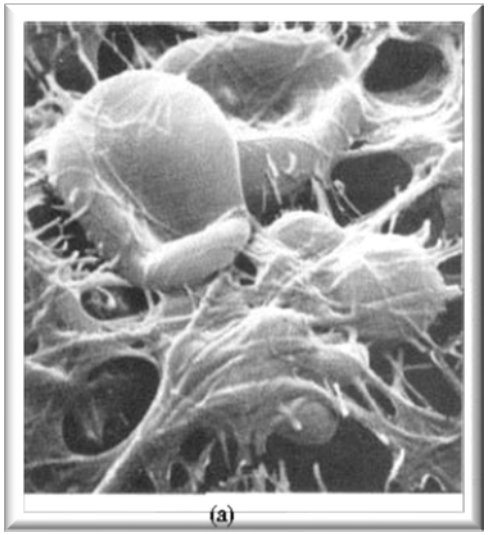
We have most of the coating technology !

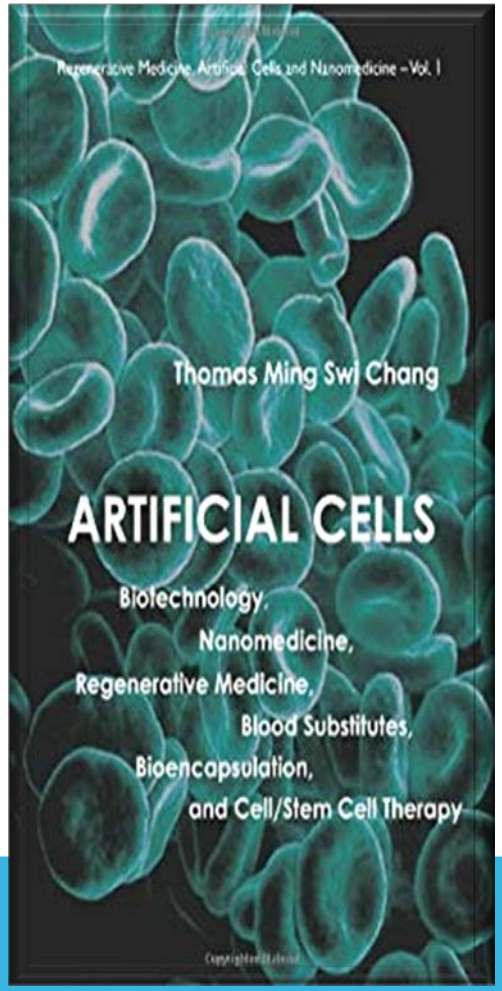


Benefit of coating

- Increase mechanical strength
- Reduce particle producing
- Improve blood compatibility
- Improve anticoagulant properties
- Reduce the breaking of blood components

Quality Control (*Coating*)





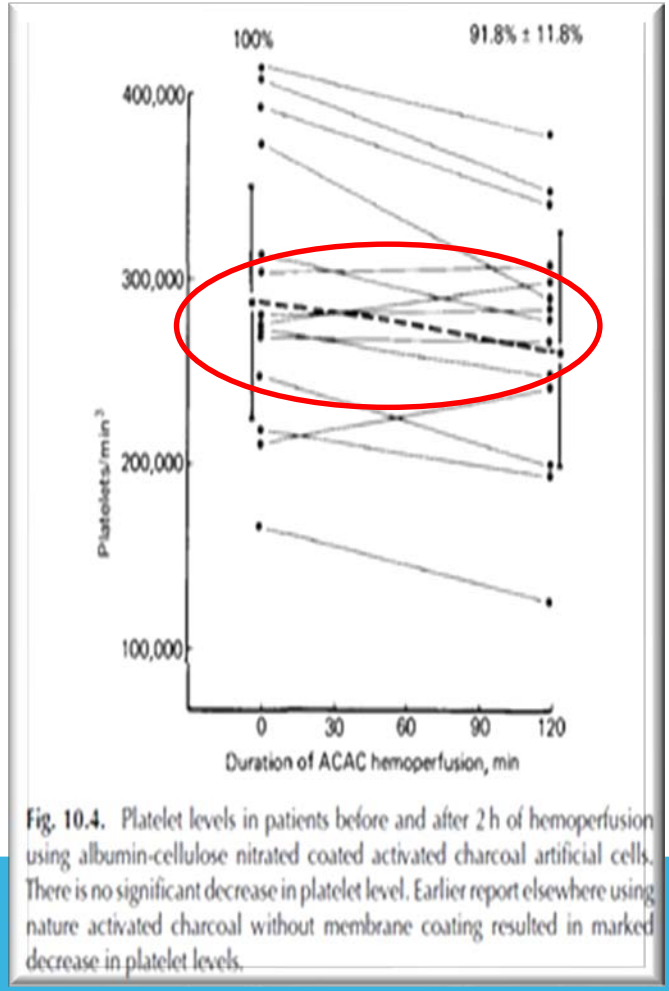


Fig. 10.4. Platelet levels in patients before and after 2 h of hemoperfusion using albumin-cellulose nitrated coated activated charcoal artificial cells. There is no significant decrease in platelet level. Earlier report elsewhere using nature activated charcoal without membrane coating resulted in marked decrease in platelet levels.

Thomas Ming swi Chang et al. Regenerative Medicine, Artificial Cells and Nanomedicine[M]. World Scientific Publishing Co. Pte. Ltd,2007.

Evaluation Methods

Original created evaluation method

- pH Test
- Cytotoxicity Test
- Intracutaneous Irritation Test
- Sensitization Test
- Acute Toxicity Test
- Complement Activation Test
- Thrombosis Test
- Resin Strength Test
- Reducing Substances Test
- Metal ion Test
- Evaporation Residue
- UV Absorption
- Platelet Adhesion Test
- Pro-thrombin Time Test
- Chemical Residues Test

Original Paper

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Published online: June 8, 2018

Blood Purification

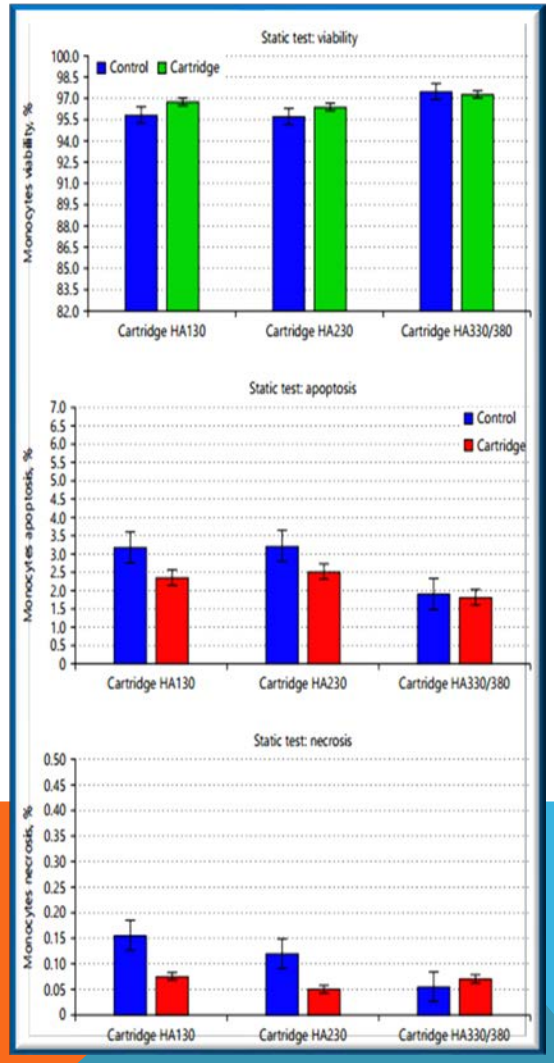
Biocompatibility and Cytotoxic Evaluation of New Sorbent Cartridges for Blood Hemoperfusion

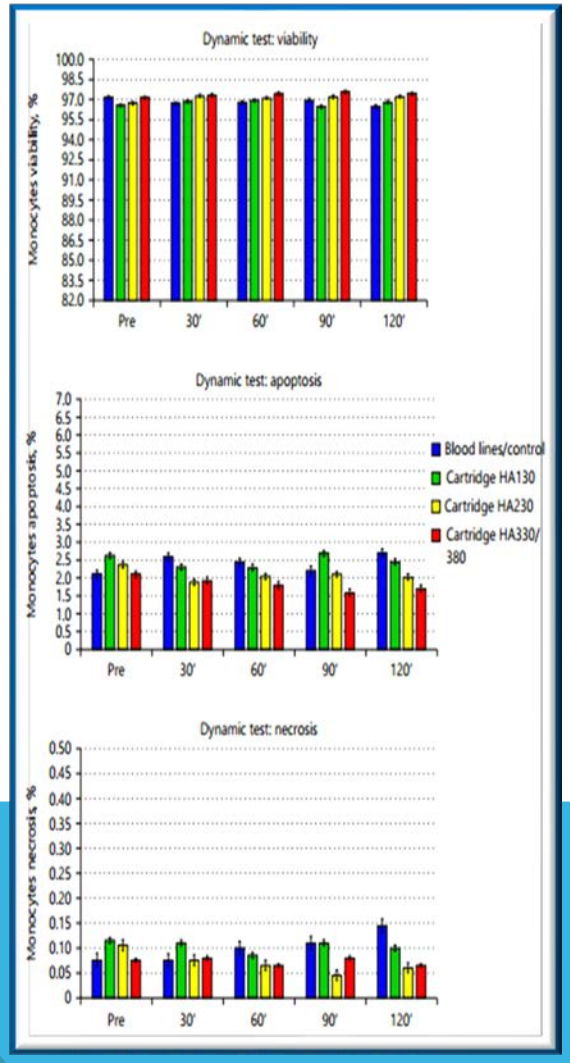
Diego Pomarè Montin[a] Ghada Ankawi[a, b] Anna Lorenzin[a, c] Mauro Neri[a, c]
Carlotta Caprara[a, d] Claudio Ronco[a, c]

Methods:

1. Monocytes were exposed to the sorbent material in static and dynamic manners.
2. In static test, cell medium samples were collected after 24 h of incubation in the cartridges.
3. In dynamic test, HP modality has been carried out and samples at 30, 60, 90, and 120 min were collected.

Safety of Jafron Cartridges





Results:

Compared to control samples, there was no evidence of increased necrosis or apoptosis in monocytes exposed to the cartridges both in the static and dynamic tests.

Conclusion:

Our in vitro testing suggests that HA cartridges carry an optimal level of biocompatibility and their use in HP is not associated with adverse reactions or signs of cytotoxicity.

Indications of Hemoperfusion

ESRD & Complications
(Encephalopathy, Pruritus, Cardiovascular disease…)

Poisoning
(Drug overdose, Pesticide, Biotoxin…)

Immune Disease
(Allergic purpura, Pemphigus…)

ICU
(Sepsis, ARDS, Cardiac surgery…)

Hepatic Failure
(Hepatitis, Jaundice, Pre& Post liver transplant…)

Hyperbilirubinaemia & Hyperbileacidemia

SLE

UREMIC TOXINS

- **Small water soluble compounds**
  - <500D
  - Easily removed by whatever type of dialysis
  - E.g.: Urea
- **Large middle molecules**
  - >500D
  - Partly removed by dialyzers with large pore(high flux)
  - E.g.: β2-microglobulin
- **Protein bound compounds**
  - <500D
  - Difficult to be removed by whatever type of dialysis
  - E.g.: Indoles, phenols

RESTRICTION OF FILTERS

Int J Artif Organs 2014; 37 (00): 000-000 DOI: 10.5301/ijao.5000354

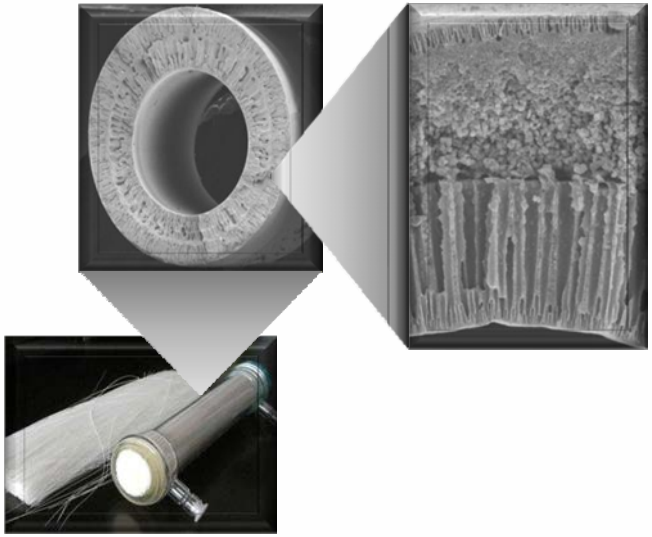
ORIGINAL ARTICLE

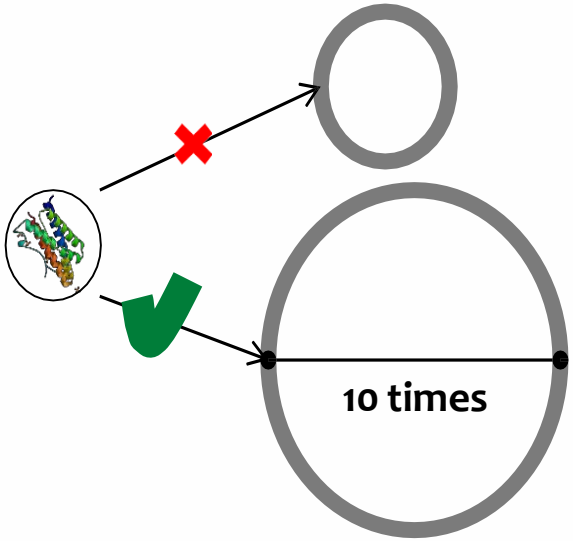
Pore size – a key property for selective toxin removal in blood purification

Stephan Harm, Dieter Falkenhagen, Jens Hartmann

Department for Health Sciences and Biomedicine, Danube University Krems, Krems - Austria

The pore size of high-flux dialyzer is not large enough for middle molecules.

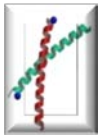
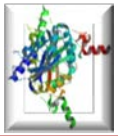


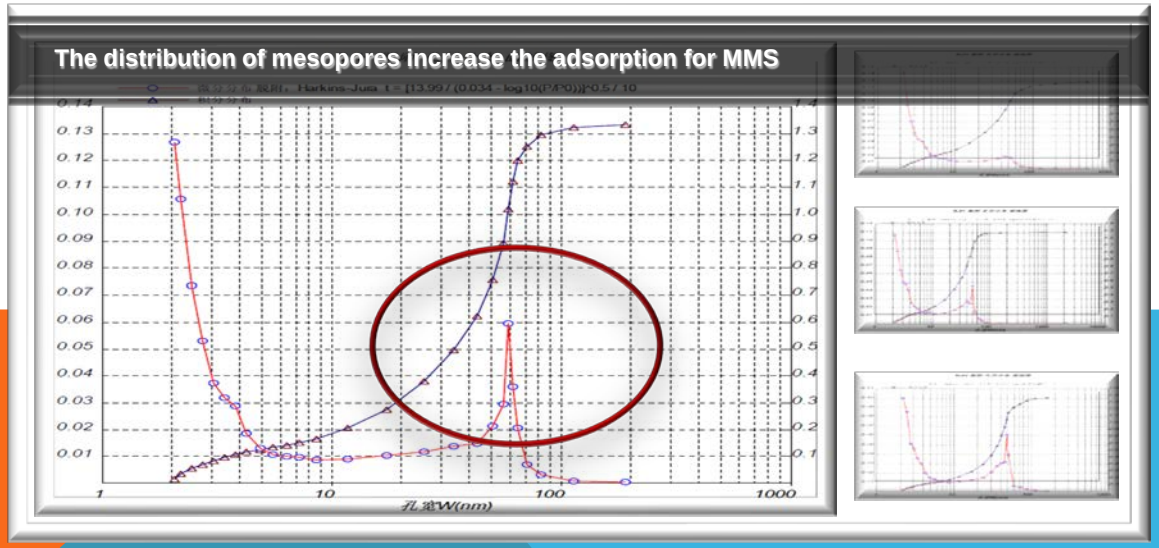


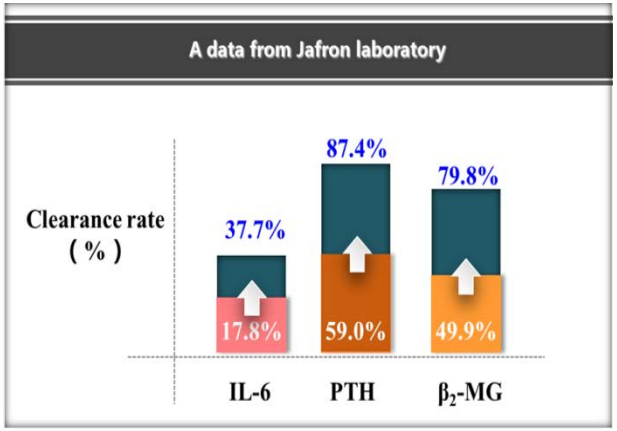
β_2-MG:3.442nm

Pore size:20-50nm

Sorbent Designing *(Porosity Regulation Technology)*

Pathogenic substances	PTH	β2-MG	IL-6	TNF-α
molecular conformation				
Molecular size (narrowest)	3.018nm	3.442nm	4.632nm	10.652nm
Target molecular Passway: 10 times of itself				





Accurately control the pore size
Improve the efficacy

1. Three times weekly treatment may not be enough to remove middle uremic toxins or protein bound uremic toxin;

2. If enlarge the pore size on the membrane, there will be a risk of inflammation and loss of nutrition.

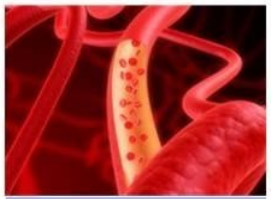
COMPLICATIONS AND RELATED TOXINS

Uremic toxins	Long-term dialysis complications
Parathyroid hormone （PTH）	Renal Osteopathy, Ectopic Calcification, Uremic Pruritus
β2-microglobulin（β_2-MG）	Amyloidosis and Carpal Tunnel Syndrome
Renin, Angiotensin	Refractory Hypertension
Advanced Glycation End Products （AGEs), Homocysteine （Hcy）	Risk Factors of Cardiovascular Diseases
Leptin	Malnutrition, Hypertension, Insulin Resistance, Affecting Immunoreaction
Tumor necrosis factor （TNT), Interleukin （IL), C-reactive protein （CRP）	Chronic Inflammatory Reaction, Malnutrition, Anemia
Advanced oxidation protein products (AOPP）	Atherosclerosis

HEMOPERFUSION ON UREMIC TOXIN

More than 100,000 ESRD patients are using HA130 globally.

1. Removal of large middle uremic toxins
2. Removal of protein bound toxins
3. Release complications
4. Improving life quality
5. Benefit survival

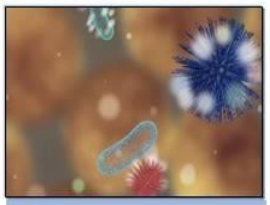

Cardiovascular Disease


Renal Osteodystrophy

Hypertension

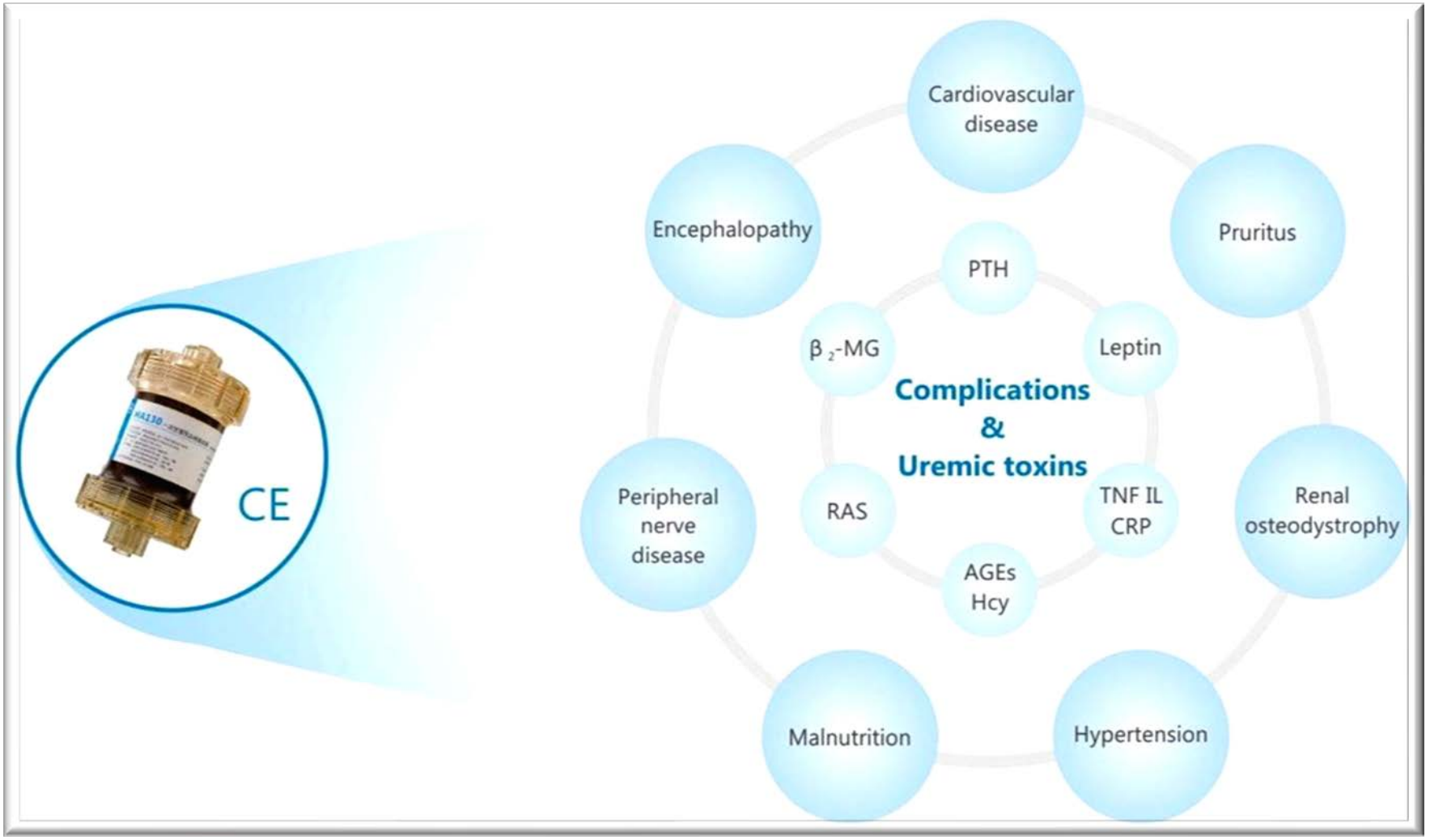

Skin Itching


Malnutrition

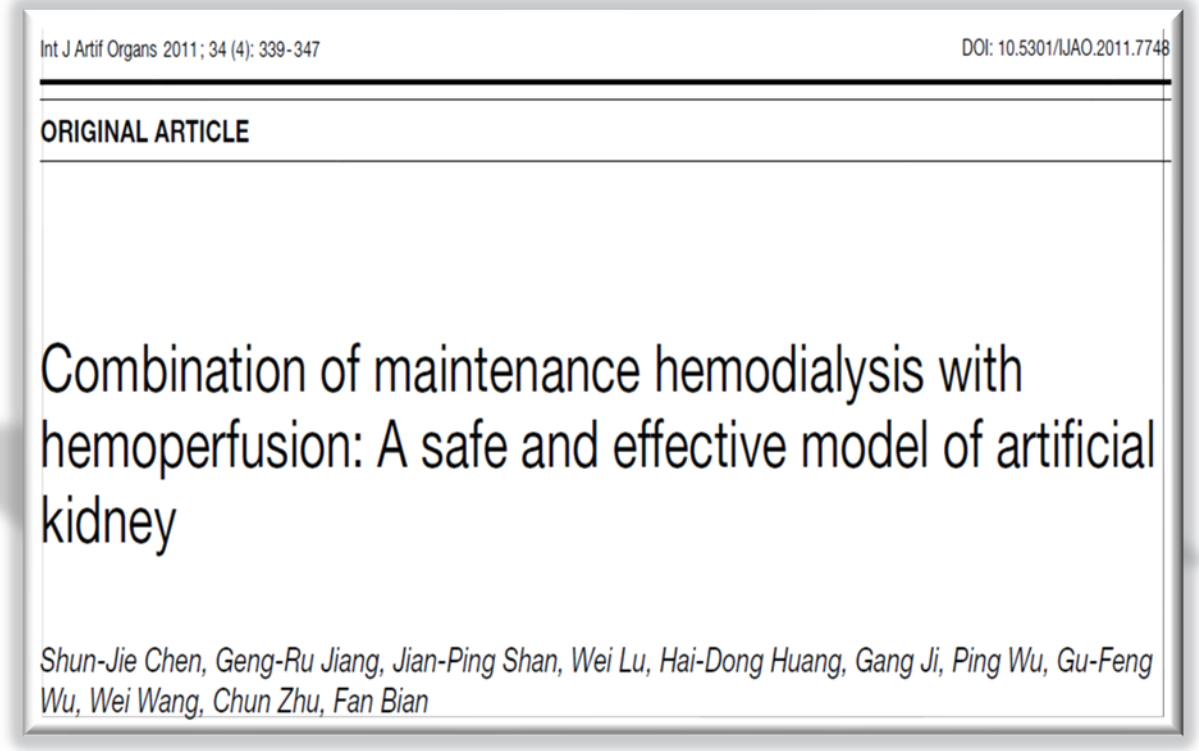

Inflammatory Response

Jafron

APPLICATION OF HEMOPERFUSION ON ESRD



HD+HP Clinical RCT



Int J Artif Organs 2011; 34 (4): 339-347 DOI: 10.5301/IJAO.2011.7748

ORIGINAL ARTICLE

Combination of maintenance hemodialysis with hemoperfusion: A safe and effective model of artificial kidney

Shun-Jie Chen, Geng-Ru Jiang, Jian-Ping Shan, Wei Lu, Hai-Dong Huang, Gang Ji, Ping Wu, Gu-Feng Wu, Wei Wang, Chun Zhu, Fan Bian

Design

A prospective randomized, parallel controlled analysis.

N=101

HP Group (51)
Control Group (50)

Follow-up:

2 Years

Outcome

- Middle Molecular Toxin
- SF-36 Score
- Survival

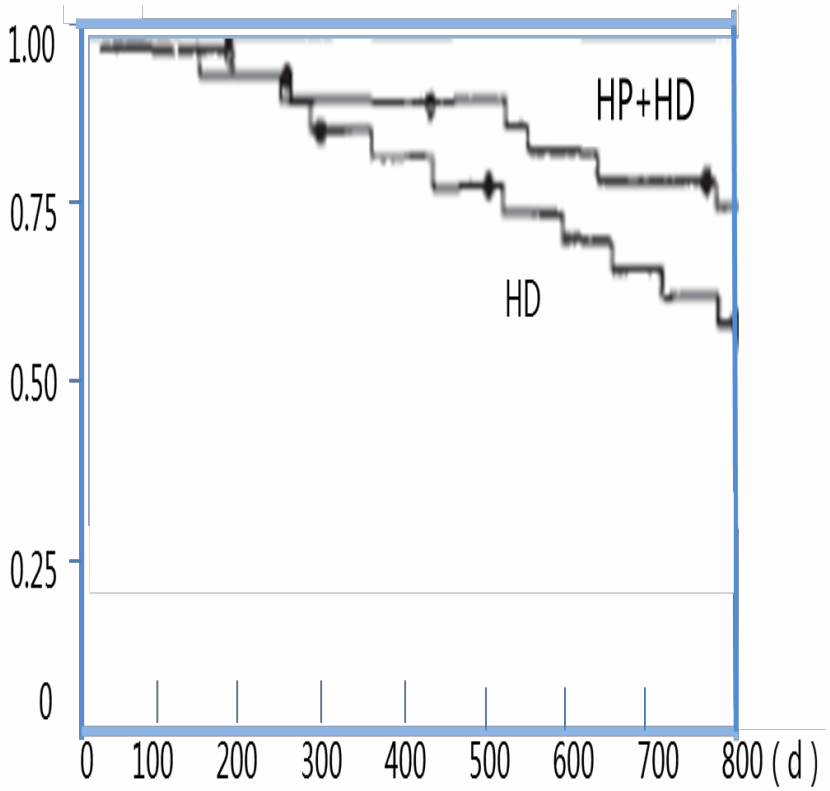
Method

HP+HD once a week
Regular hemodialysis

HD + HP CLINICAL RCT

Total score in 8 aspects of SF-36(life quality)

Item	HP+HD (n=41)	HD (n=30)	P value
Physiological function	58.48±20.05	57.32±19.45	0.8028
Physiological ability	38.64±21.84	36.56±19.43	0.6703
Body pain	64.62±27.54	44.31±21.45	0.0009
General health	48.48±18.29	40.43±10.78	0.0415
Activity	56.82±21.59	49.36±20.11	0.0321
Social function	58.69±15.74	55.35±12.57	0.0641
Emotion	56.88±15.19	51.16±12.22	0.0257
Mental health	65.09±20.24	55.23±21.47	0.0463
Total score	59.76±19.46	41.09±15.52	0.0069



Improving life quality and survival advantage

Chen Shunjie, et al, Chinese Journal of Nephrology, 2011,27(1):7-11.

HP FOR ESDN

Effect of Hematodialysis plus Hemoperfusion on Insulin Resistance and Nutritional Status of Patients with End-Stage Diabetic Nephropathy

Antony Raine, Daniel Cordonnier*, Eberhard Ritz
Section of Nephrology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Design: A prospective randomized, parallel controlled analysis
Method: Group A: n=28, HD 3 times/week
Group B: n=30, HD twice/week combined with HDF once/week
Group C: n=28, HD+HP once/week, routine HD twice/week
Follow up: 12 weeks

Table 2 Changes of Inflammatory Factors in Three Groups Before and After treatment ($\bar{x} \pm s$, ng/L)

Groups		Time	CRP	TNF-α	IL-6
Group A (n=28)	HD	Before treatment	15.71±4.48**	829.02±89.52**	155.94±36.48**
		12 weeks after treatment	15.49±4.67**	803.17±96.94**	146.31±37.23**
Group B (n=30)	HD+HDF	Before treatment	15.47±3.18**	842.19±77.68**	161.02±34.70**
		12 weeks after treatment	13.03±4.19**△	754.28±82.53**△	127.89±31.34**△
Group C (n=28)		Before treatment	15.42±4.03**	828.14±83.87**	153.47±35.66**
	HD+HP	12 weeks after treatment	10.86±3.96**△△▲	687.56±87.42**△△▲▲	109.38±35.34**△△▲
Control group (n=24)		-	3.69±1.68	55.12±30.27	41.67±16.82

Compared with control group, **P<0.01; Compared with treatment before, *P<0.05, **P<0.01; Compared with group A, △P<0.05, △△P<0.01; Compared with group B, ▲P<0.05, ▲▲P<0.01.

HD+HP effectively decreased inflammatory factors.

Antony Raine, et,al. J Int Transl Med, 2015, 3(3):180-184

HP FOR ESDN

Table 4 Change of Nutritional Status in Three Groups Before and After Treatment ($\bar{x} \pm s$)

Groups	Time	Hb (g/L)	Alb (g/L)	BMI (kg/m²)
Group A (n=28) HD	Before treatment	104.06±13.45	32.18±2.69	21.62±1.83
	12 weeks after treatment	104.82±12.36	33.02±3.81	22.60±2.58
Group B (n=30) HD+HDF	Before treatment	104.23±13.17	32.64±4.27	22.02±2.47
	12 weeks after treatment	104.98±13.79	33.57±3.79	22.73±1.69
Group C (n=28) HD+HP	Before treatment	103.98±12.76	32.75±4.38	21.98±2.28
	12 weeks after treatment	113.31±12.94$^{**\Delta}$	35.73±3.71$^{**\Delta}$	24.30±1.51$^{**\Delta\Delta}$

Compared with treatment before, $^{**}P<0.01$; Compared with group A, $^{*}P<0.05$, $^{**}P<0.01$; Compared with group B, $^{\Delta}P<0.05$, $^{\Delta\Delta}P<0.01$.

Conclusion: HD combined with HP can effectively remove the mid- and macro-molecular inflammatory mediators, alleviate IR, and ameliorate the nutritional status compared with HD+HDF and conventional HD therapy in the patients with ESDN.

Antony Raine, et,al. J Int Transl Med, 2015, 3(3):180-184

HD + HP FOR ESRD PATIENTS

IJAO The International Journal of Artificial Organs

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Original Research Article

Additional hemoperfusion is associated with improved overall survival and self-reported sleep disturbance in patients on hemodialysis

Yan Hong Gu[1,*], Xiu Hong Yang[1,*], Li Hua Pan[1,*], Xiao Li Zhan[1], Li Li Guo[2] and Hui Min Jin[1]

- Totally **158** dialysis patients
- Dialysis age ≥3months
- Age≥18
- Follow up 2years
- *Group HD (N=80)*
- *Group HP+HD (N=78)*
- HP 1-2 times biweekly additional to regular HD
- Outcome: **overall survival and improvement of sleep disorders**

Improving Pruritus & Sleep

	Baseline		P	End of treatment		P
	HD	HD + HP		HD	HD + HP	
Patients (n)	80	78		68	75	
Age (years)	62.5 ± 11.5	63.9 ± 12.8	NS	64.1 ± 10.6	65.6 ± 11.8	NS
Male (%)	41.25	43.56	NS	42.65	41.33	NS
Diabetes (%)	40	39.74	NS	41.18	40.0	NS
HD duration (years)	4.4 ± 0.5	4.8 ± 0.6	NS	6.3 ± 0.7	6.5 ± 0.8	NS
Low-incomes (%)	28.75	14.10	<0.05	25.0	12.0	<0.05
Pruritus score	7.3 ± 1.5	7.2 ± 1.4	NS	7.2 ± 0.9	5.9 ± 1.1	<0.01
Sleep medication	37	34	NS	28	19	<0.05
Laboratory parameters						
CRP (mg/L)	13.1±0.7	12.7±0.8	NS	12.7±0.5	9.6 ± 0.4	<0.01
Albumin (g/dL)	31.1±1.5	31.0±1.6	NS	30.0±2.1	31.4±1.5	NS
Hemoglobin (g/dL)	9.8 ± 2.3	9.2 ± 2.7	NS	10.6±0.6	10.8±0.7	NS
Hypercalcemia (%)	8.75	8.97	NS	8.82	1.33	<0.05
Hyperphosphatemia (%)	75.0	76.9	NS	63.2	42.7	<0.05
iPTH (pg/mL)	601 ± 23.9	607 ± 23.5	NS	618 ± 29.4	449 ± 27.3	<0.01
Sleep parameters						
Sleep duration (min)	360 ± 16.6	370 ± 15.1	NS	368 ± 25.2	418 ± 22.7	<0.05
Sleep efficiency (%)	76 ± 5.5	78 ± 6.9	NS	78.5±5.4	88.2±3.5	<0.01

Tab. 1 Characteristics of the HD versus HD + HP groups at baseline and at the 2-year follow-up.

A 2-year hemoperfusion therapy was associated with improvement of clinical parameters, such as **pruritus score, CRP, hypercalcemia, hyperphosphatemia and iPTH.**

IMPROVING SURVIVAL & MELATONIN LEVEL

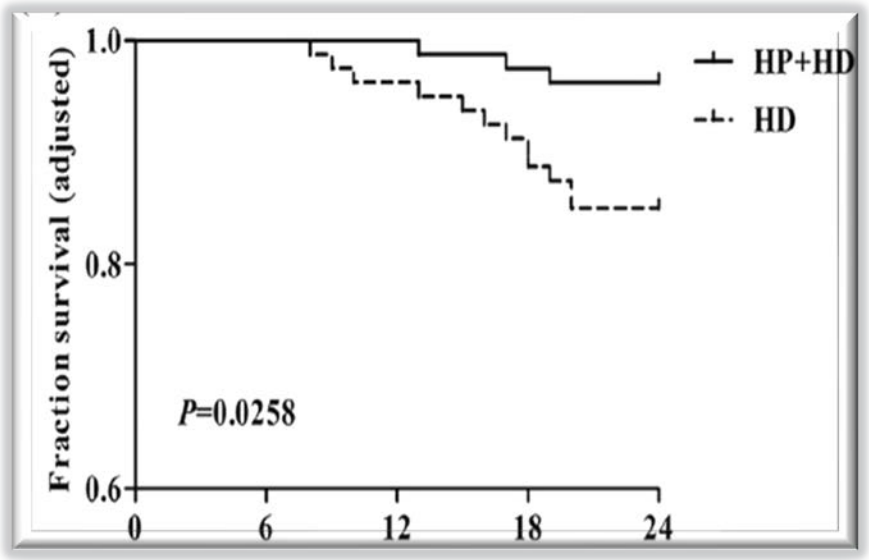


Fig.1 Kaplan–Meier survival curve in two cohorts after 24 months of observation adjusted survival curve for age, sex, coexistence of diabetes, and low income

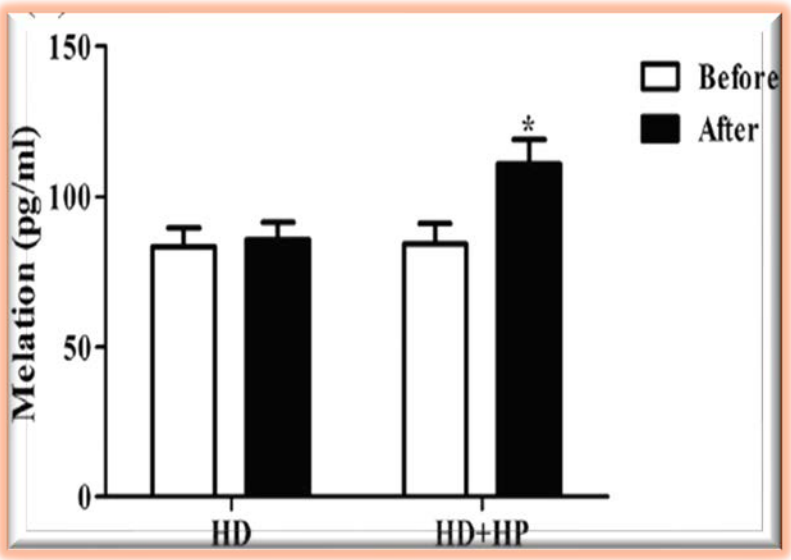


Fig.2 Comparing nocturnal melatonin value between HD and HD + HP groups before and after 24-month follow-up period

Conclusion: The results indicate that **additional HP (HA130)** is associated with

- ✓ *reduction of pruritus scores and parathyroid hormone*
- ✓ *an increase in nocturnal melatonin concentration secretion*
- ✓ *improved sleep disorders*
- ✓ *Improvement in the overall survival rate .*

HP FOR REFRACTORY HYPERTENSION

Design : A prospective randomized, parallel controlled analysis.
Method: HDF Group: HD twice a week & HDF once a week;
HP+HDF Group: HP twice a month & treatment for HDF Group

N(HP+HDF)=45 N(HDF)=30
Follow up : 12 months

The evolution of RA, Ang Ⅱ, aldosterone, blood pressure and use of hypotensor in HDF and HDF+HP (n=75)

		RA (ng/ml)	AngⅡ (pg/ml)	Aldosteron(pg/ml)	SBP (mmHg)	DBP (mmHg)	Hypotensor
0M	HDF (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)
	HP+HDF(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	HDF (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)
	HP+HDF(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	HDF (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)
	HP+HDF(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	HDF (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)
	HP+HDF(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

Lu sheng et al Chin J Blood Purif, May,2015,Vol.5,No.14

THERAPEUTIC REGIMEN

1. **Intensive program : 4 times/month**
   Recommended for long-term (＞1 year) hemodialysis patients with complications (like pruritus, malnutrition and hypertension)

2. **Maintenance program : 1-2 times/month**
   Recommended for short-term (＜1 year) hemodialysis patients, with no complications or patients whose status are under control after intensive therapy.

3. **Individualized program**
   Based on patients conditions, clinical treatment could be personalized.

1.Chen Xi, Zhou Rong etc. The efficacy of short-term high frequency hemoperfusion combined with hemodialysis on skin pruritus irregular hemodialysis patients[J]. Chinese Journal of Blood Purification,2015,14(02):97-99
2. Wei L U, Xie Y, Huang L S, et al. Observation of medium and long term efficacy of hemodialysis combined with hemoperfusion in the treatment of maintenance hemodialysis patients with resistanthypertension[J]. Chinese Journal of Blood Purification,2015.

OPERATION GUIDANCE - PRE-RINSING

Before connection

1.1HA130 Rinsing

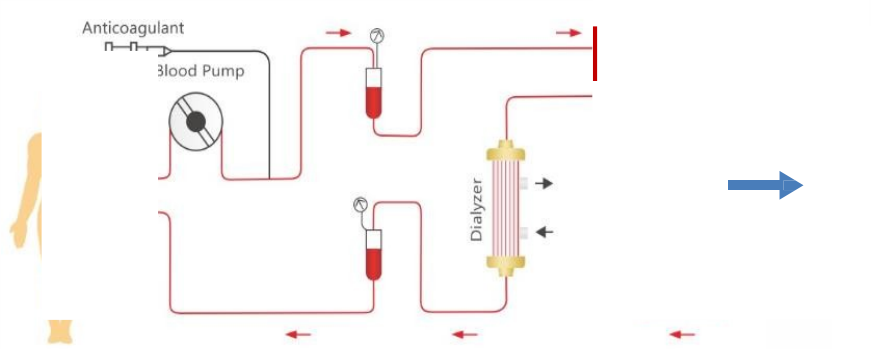
Use 5ml syringe (without needle) to inject 1 pc of heparin (12500u/pc) into the cartridge

Turn cartridge upside down for 20 times

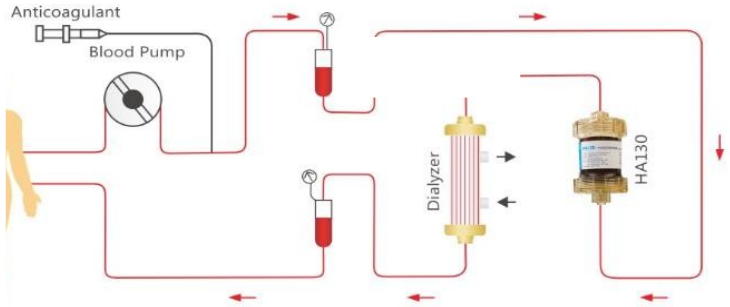
30min statically

OPERATION GUIDANCE - CONNECTION OF HA130 & DIALYZER

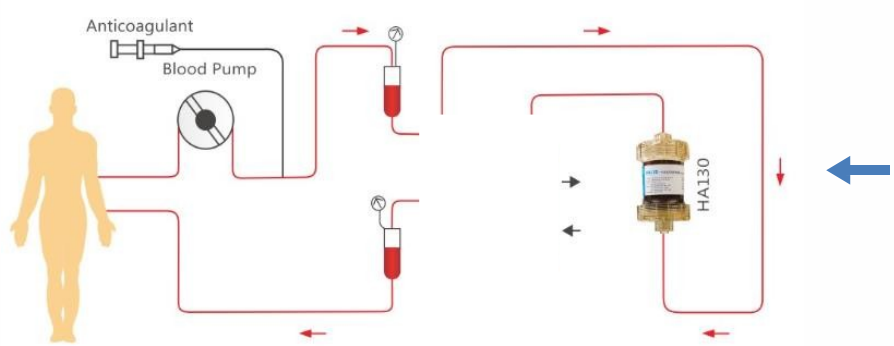
Dialyzer connection



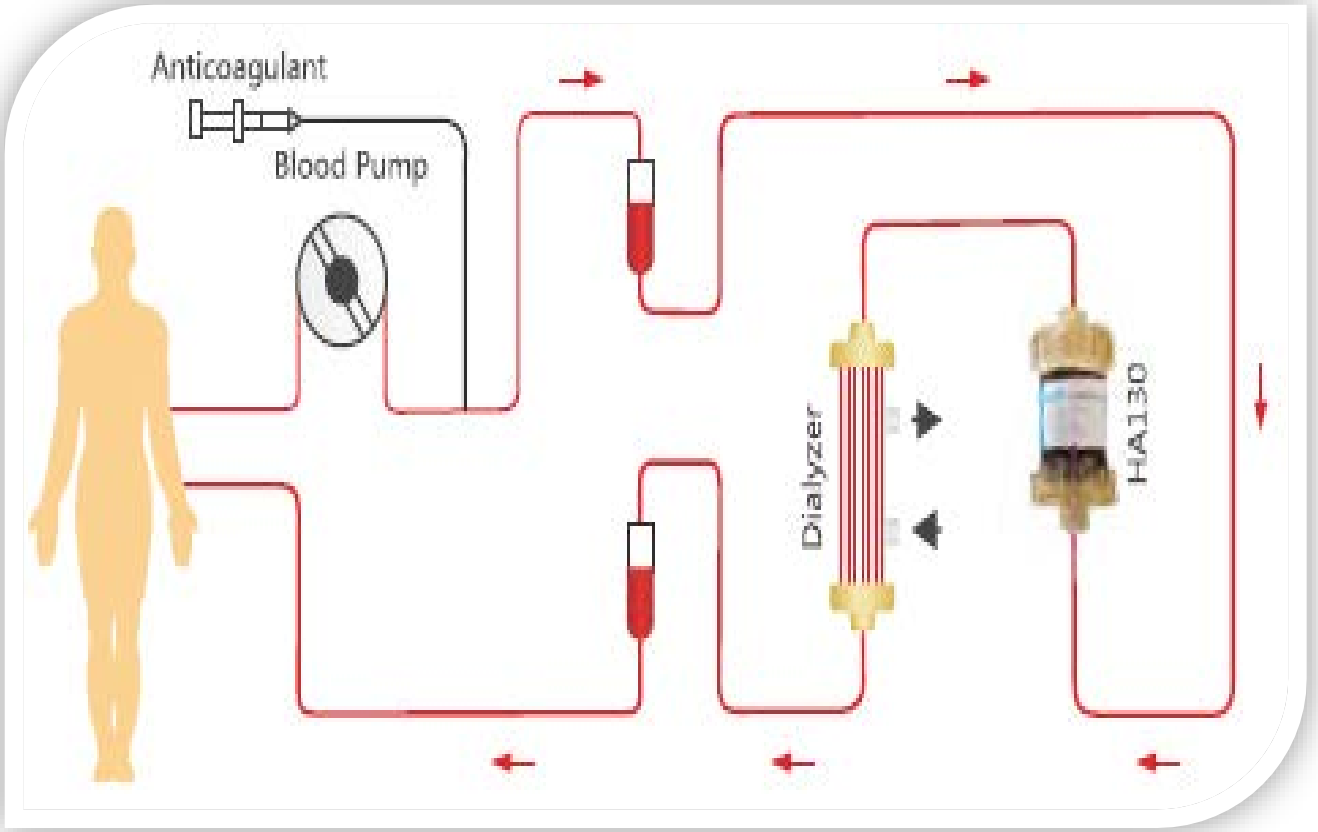
HA130 connection



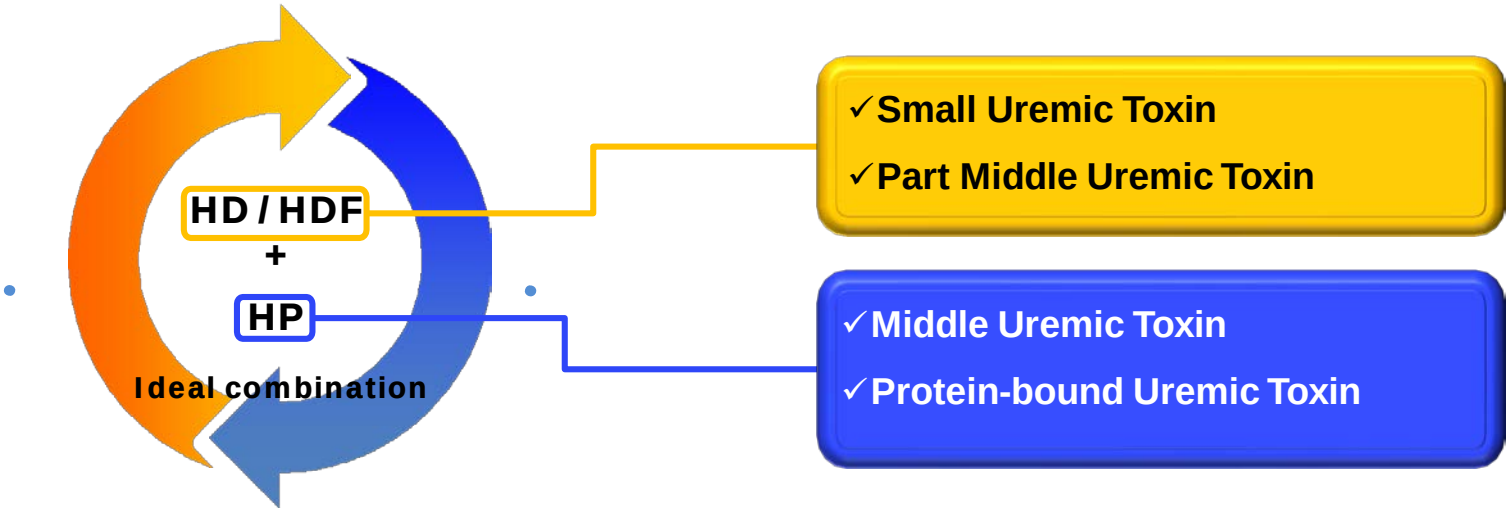
Extension tube

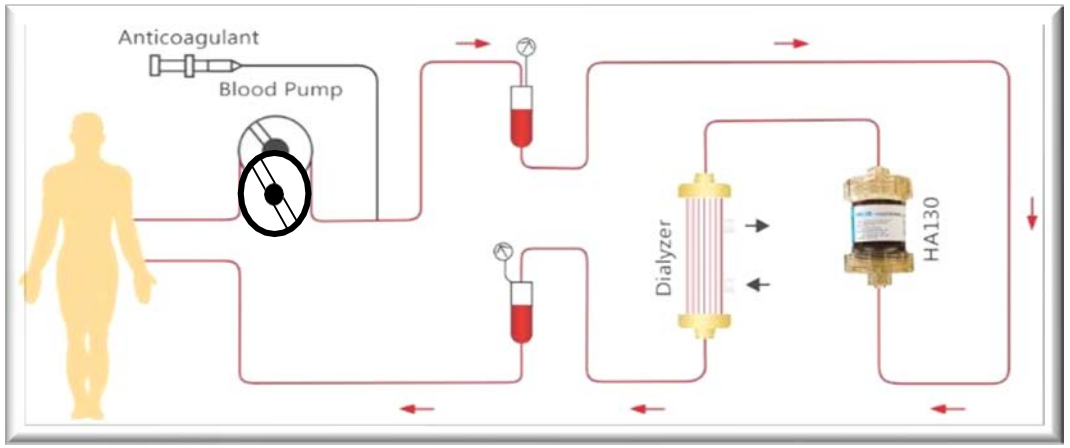


HA130: CONNECTION WITH DIALYZER



COMBINED ARTIFICIAL KIDNEY (HA130+HD/HDF)





OPERATION GUIDANCE - BLOOD FLOW SETTING

Flow setting

Flow range of directing blood

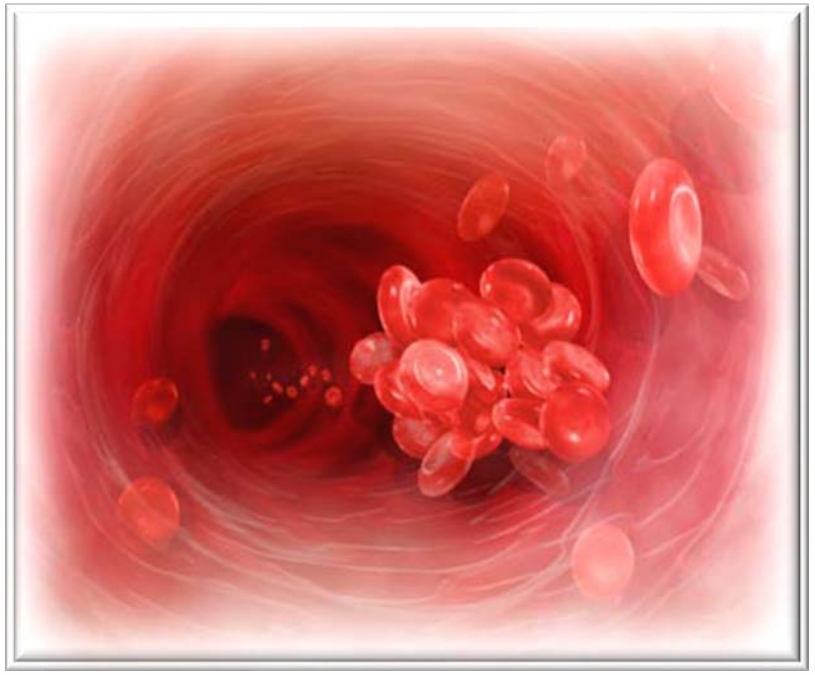
50-100 ml/min

Flow range of treatment

150-300 ml/min

Flow range of blood return

80-100 ml/min



OPERATION GUIDANCE ANTICOAGULANT DOSE

Recommended anticoagulant dose

Heparin

1. first-dose: 62.5~125U/kg
2. additional dose: 1250～2500U/h

LMWH

60～80U/kg, no additional dose

Citrate

4% sodium citrate 100-250ml/h input from the artery, keep ACT within 200～250s.

Adjust the flow rate of calcium to keep free calcium within 0.20-0.40mmol/L in vitro and 1.00-1.20mmol/L in vivo.

The dosage is subject to specific clinical practice.

NO ANTICOAGULATION

In some circumstances, risks to the patient complicates the use of any anticoagulant.

These circumstances may include, but are not limited to:

- Active bleeding
- Increased aPTT
- Increased international normalized ratio (INR)
- Liver failure
- Low platelet count

COMPLICATIONS

Vascular access

- Vascular spasm (initial BFR too high).
- Movement of catheter against vessel wall.
- Improper length of hemodialysis catheter inserted.

Fluid volume deficit

- Excessive fluid removal without appropriate fluid replenishment.

COMPLICATIONS

Hypotension

- Intravascular volume depletion
- Underlying cardiac dysfunction

Electrolyte imbalances

- High ultrafiltration rates (high clearance)
- Inadequate replenishment of electrolytes by intravenous infusion

COMPLICATIONS

Air embolus

- Leaks or faulty connections in tubing
- Line separation

Cardiac arrest

- Hypotension/hypertension
- Hemolysis
- Air embolism
- Circulatory overload
- Arrhythmias

Objectives

When to start ?

What Modality ?

HOW can we do it ?

HD+HP 130 - OUR EXPERIENCE

- We started in june 2019.
- We had only one patient
- Now, we have seven patients working HDF + HP

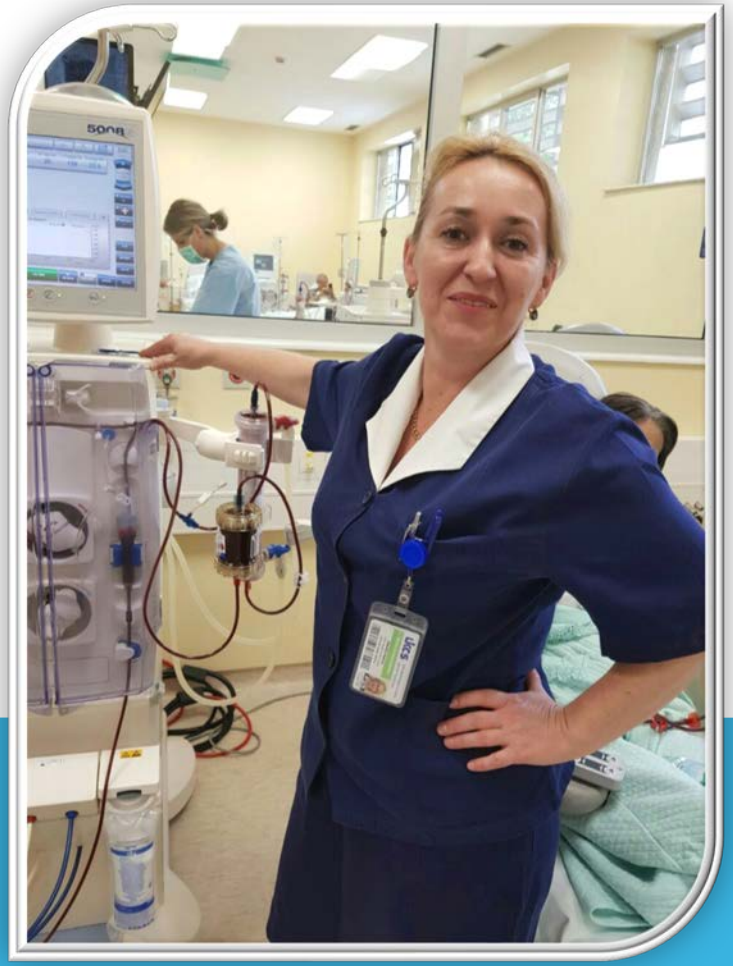


Table 1. Clinical characteristics of group of HD patients before and after applying of HP

HD + HP	HD
Characteristics of patients	
HD patients (n) 7	7
Male / Female (f) 5 / 2	5 / 2
Age in years (M ± SD) 36,86 ± 7,68	36,86 ± 7,68
HD months (M ± SD) 154,89 ± 74,22	150,99 ± 72,22
Diseases caused by renal failure (f / %)	
cGN 3 (42,85%)	3 (42,85%)
DM 0 (0,00%)	0 (0,00%)
HBP 0 (0,00%)	0 (0,00%)
ADPKD 1 (14,28%)	1 (14,28%)
Unknown 3 (42,85%)	3 (42,85%)

CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; Alb = serum albumin; Hb = Hemoglobin; Ca^{2+} = serum calcium; P^{3+} =serum phosphorus; iPTH = immunoreactive parathyroid hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Vascular access for dialysis (f / %)

AVF	6 (85,71%)
6 (85,71%)	
CVK	1 (14,29%)
1 (14,29%)	

Complications (f / %)

CAD	0 (0,00%)
0 (0,00%)	
CHF	2 (28,57%)
2 (28,57%)	
PVD	1 (14,28%)
1 (14,28%)	
Stroke	0 (0,00%)
0 (0,00%)	
COPD	1 (14,28%)
1 (14,28%)	
HTA	4 (57,14%)
4 (57,14%)	

CAD = Coronary artery disease; COPD = Chronic obstructive pulmonary disease; Alb = serum albumin; Hb = Hemoglobin; Ca^{2+} = serum calcium; P^{3+} =serum phosphorus; iPTH = immunoreactive parathyroid hormone; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Laboratory data (M ± SD)

CRP (mg/L)	
3,06 ± 2,22	2,00 ± 2,75
Alb (g/L)	
38,57 ± 6,29	41,50 ± 2,08
Hb (g/L)	
109,39 ± 23,14	110,09 ± 20,86
Ca^{2+} (mmol/L)	
2,31 ± 0,28	2,34 ± 0,13
P^{+3} (mmol/L)	
2,51 ± 0,72	1,20 ± 0,41
iPTH (pg/mL)	
1296,70 ± ± 1094,05	1391,50 ± 971,90 !!!
SBP (mmHg)	
150,00 ± 23,80	128,57 ± 6,90
DBP (mmHg)	
87,14 ± 11,13	81,43 ± 6,90

Improvement in laboratory data, especially in lower CRP and P, but unfortunatelly not iPTH.

Table 2. Sociodemographic characteristics and parameters related to SQ of group of HD patients before and after applying of HP

	HD		HD + HP
Sociodemographic characteristics of patients			
HD patients (n)	7		7
Male / Female (f)	5 / 2		5 / 2
Age in years (M ± SD)	36,86 ± 7,68		36,86 ± 7,68
Married / Single (f)	1 / 6		1 / 6
Employed / Unemployed (f)	1 / 6		1 / 6
HD months (M ± SD)	150,99 ± 72,22		154,89 ± 74,22
Complications related to SQ (%)			
Pruritus	4 (57,14%)	Less complications after applying HP	2 (28,57%)
RLS	1 (14,29%)		0 (0,00%)
SAS	0 (0,00%)		1 (14,29%)
Snoring	3 (42,86%)		4 (57,14%)
Breathing problem	5 (71,43%)		3 (42,86%)
Pain	4 (57,14%)		3 (42,86%)
PSQI components scores related to SQ			
Subjective SQ (M ±SD)	1,43 ± 0,53	Better components of SQ after applying HP	1,00 ± 0,58
Sleep latency (M ±SD)	1,29 ± 0,49		1,00 ± 0,58
Sleep duration (M ±SD)	1,71 ± 0,95		1,14 ± 0,69
Sleep efficiency (M ±SD)	0,57 ± 0,79		,43 ± 0,53
Sleep disturbance (M ±SD)	1,00 ± 0,00		1,00 ± 0,00
Use of sleep medication (M ±SD)	1,14 ± 1,21		1,00 ± 1,41
Daytime dysfunction (M ±SD)	0,57 ± 0,79		0,43 ± 0,53
Global PSQI score (M ±SD)	7,57 ± 2,88	Better GS of SQ !!!	5,86 ± 2,73

Lower PSQI components scores meaning better result;
Global PSQI score more then 5 – "Bad sleepers"

- When HP was combined with HD, the complementary use of the two different methods of blood purification was able to fully remove the metabolites, toxins and pathogenic factors as well as regulate water, electrolyte and acid-base balance in patients, rapidly improving the patients sleep and appetite while alleviating itchy skin symptoms, which in turn would prevent the recent and long-term complications in patients, improve quality of life and prolong life.

Morena MD, Guo D, Balakrishnan VS., et al. Effect of a novel adsorbent on cytokine responsiveness to uremic plasma. Kidney Int. 2003;63(3):1150-1154. doi:10.1046/j.1523-1755.2003.00839

- Maintenance HD combined with HP not only ensured the thorough clearance of small molecule toxins, but was also able to remove the medium and large molecule toxins, which would help alleviate the systemic inflammation of uremic patients and increase the effect of the treatment of uremic anemia more effective than HD alone.

Wang JY, Hotta T, Murate T, et al. Growth inhibition of erythroid colonies by autologous sera and the clinical effect of erythropoietin in chronic renal disease. Rinsho Ketsueki. 1989;30(7):975-979. Medline.

- One of the most important causes for uremic anemia is the decrease in the production of EPO by renal interstitial cells.
- Another important cause is that uremic patients have had systemic inflammatory response syndrome (SIRS) for a long time. The functional iron deficiency of patients in an inflammatory state can cause the decline of reticulocyte hemoglobin content (CHr), which will in turn lead to lower responsiveness of EPO.
- In addition, medium and large molecule toxins such as hsCRP, iPTH, IL-6 and TNF-α accumulated in the patient's body will directly inhibit the maturation of erythrocytes.

Thomas C, Thomas L. Biochemical markers and hematologic indices in the diagnosis of functional iron deficiency. Clin Chem. 2002;48(7):1066-1076. Medline.
Hackeng CM, Beerenhout CM, Hermans M, et al. The relationship between reticulocyte hemoglobin content with C reactive protein and conventional iron parameters in dialysis patients. J Nephrol. 2004;17(1):107-111. Medline.

- In spite of the fact that active control of complications is a thorny task, this study suggests that this model of artificial kidney may be an important means for improving the quality of life of MHD patients and the rate of their mid and long-term survival.

CONCLUSIONS

- HD+HP was superior to HD in regularly eliminating middle and large molecule uremic toxins accumulated in the body.
- These findings suggest a potential role for HD+HP in the treatment to improve the quality of life and survival rate of MHD patients.