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USER'S REFERENCE FOR HA330/HA380

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Content

1. PRODUCT INTRODUCTION

1.1 Principle and Indication

HA330/HA380 is the neutral macroporous resin hemoperfusion cartridge with high bio-compatibility and no cytotoxic effect [1, 2].

The porosity structure of the adsorbing beads allows the cartridges to absorb excessive Cytokines. Thus they can regulate body immunity and hemodynamic in extracorporeal blood circulation.

In treatment with critical ill, HA330/HA380 plays an important role in reducing cytokine storm, thus to relieve the inflammation and help with patients' outcome.

During the cardiac surgery, it could reduce the extent of the cytokine response, and help with the complications such as disorientation, lung injury, and kidney dysfunction, etc.

1.2 The peak concentration theory

The peak concentration theory is a theory proposed by Prof. Claudio Ronco. It gives a clinical insight explaining how hemoperfusion works in critical ill patients.

The theory suggests that "the events associated with sepsis/SIRS may happen in sequence (the sequential or serial sepsis theory) where by pro- and anti-inflammatory mediators are alternately produced in high- or low-generation periods, thus ensuing in SIRS (Systemic Inflammatory Response Syndrome) and CARS (Compensatory Anti-inflammatory Response syndrome). In the sequential sepsis theory, temporary prevalence of SIRS should probably be treated with high-dose steroids, assuming that a timely intervention is possible thanks to an early and accurate biological monitoring. Otherwise, the therapy may overlap with the next coming period of CARS and may even favor bacterial colonization and infection dissemination. Indeed, in this period, a protective antimicrobial therapy or even an immunostimulatory therapy should be

administered. The time of intervention becomes crucial in order to prescribe the right therapy for the right disorder." Thus, "unspecific removal of soluble mediators, be they poor anti-inflammatory, without completely eliminating their effect, may be the most logical and adequate approach to a complex and long-running process such as sepsis." The concept of cutting peaks of soluble mediators, for example through blood purification method, is a paradigm that calls "the peak concentration hypothesis. [3]

1.3 Properties of HA330

Sorbent volume(ml)	330±3
Blood Volume(ml)	185±5
Adsorbent material	Styrene Divinylbenzene Copolymers
Housing material	Polycarbonate
Sterilization method	Irradiation Sterilization
Unit package	285mm(L) X 117mm(W) X 108mm(H)

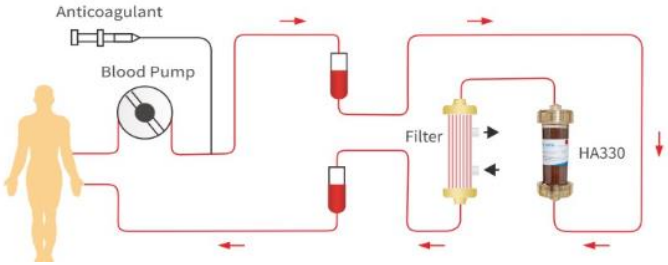
1.4 Properties of HA380

Sorbent volume(ml)	380±3
Blood Volume(ml)	150±5
Adsorbent material	Styrene Divinylbenzene Copolymers
Housing material	Polycarbonate
Sterilization method	Irradiation Sterilization
Unit package	272mm(L) X 111mm(W) X 117mm(H)

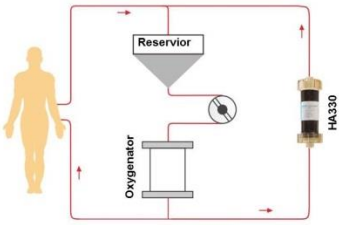
2. OPERATON GUILDLINE

2.1 Treatment modes

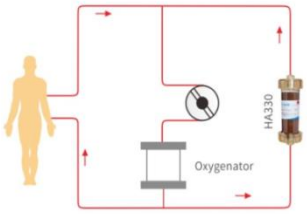
HA330/380 cartridge can be connected with HD, HDF, SLED, CVVH, ECMO and CPB.



HP+HD/HDF/CVVH/SLED



HP+CPB



HP+ECMO

2.2 Patient Selection

2.2.1 Inclusion Criteria

2.2.1.1 Sepsis:

- Patient is unstabilized clinically with conventional medical method; APACHE II score ≤30
- Present hyperinflammation: Shock happened within the last 12 hours; decrease capillary refill, cyanosis, mottling
- Development of at least one more organ dysfunction - Kidney, lung, liver, coagulation
- Systemic markers of infection:
- PCT > 3 µg/l - CRP> 10mg/dl - High IL-6, IL-8, IL-1, TNF-a levels (e.g. > 400 pg/ml)

  * High level of biomarkers can, if available, support the treatment decision, however low levels do not preclude reasonableness of treatment.

2.2.1.2 Severe Acute Pancreatitis/ Hyperlipidemia Severe Acute Pancreatitis :

- Characteristic abnormal pain, serum amylase and/or lipase ≥3 times of upper limit

of normal range; [4]

- Patients' diagnosed with severe acute pancreatitis , APACHE II≥8, C-reactive protein ≥150 mg/L; [4]
- For hyperlipidemia induced pancreatitis: TG>1000 mg/dl

2.2.1.3 Trauma, Serious Burn, ARDS, MODS/MOF etc.

2.2.1.4 Patients in Cardiac Surgery

- Patients who are going to have high risk procedures in surgical therapies due to infectious endocarditis
- Patients who could benefit from cytokine removal
- Patients with preoperative leukocytosis, high IL-6 level, or signs of organ dysfunction,
- Patients who are hemodynamically unstable or has onset of shock
- Patients who has signs of capillary leak

2.2.2 Exclusion Criteria

- Long-term use of immunosuppressant or with immune deficiency
- Severe anemia (hemoglobin≤60g/L), severe thrombocytopenia, severe pancytopenia or coagulation disorders without correct
- Malignant tumor
- Severe hepatic impairment;
- General contraindications in infusion therapy;

2.3 Priming Method

Inject 12500-25000U heparin into the cartridge (During the injection, take the needle off in case of destroying the filter in the cartridge). Shake the cartridge up and down for 20 times to make the heparin fully mixed in the solution. Cover the cap and make it static for 30 min.

Rinse with 3000ml saline at the flow rate of 200-300ml/min. Pat the cartridge and tube during pre-rinse to discharge the gas within them completely. Connect the cartridge in the circulation line and ready to initiating the treatment.

* Notes: The pre-rinsing liquid could be saline, or plasma substitutes, fresh blood, 5% albumin in order to reduce the impact of extracorporeal circulation on patients' blood pressure.

2.4 Anticoagulation use

2.4.1 For Treatment modes as HP+HD/HDF/CRRT

2.4.1.1 Heparin

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

2.4.1.2 Low molecular weight heparin

- 60 ~ 80U/kg, no additional dose

2.4.1.3 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.

2.4.2 For Treatment modes as HP+ECMO

The anticoagulant use is the same as ECMO without hemoperfusion. No additional dose is required.

2.5 Flow rate, Treatment time and Treatment frequency

2.5.1 For Treatment modes as HP+HD/HDF/CRRT

- In general condition, the blood flow rate is gradually increased from 100~150mL/min to 200~250mL/min. Hemoperfusion usually lasts 120~150 minutes.
- When this product is used in conjunction with the dialyzer, the blood flow rate can be up to 350mL/min. Hemoperfusion time can be up to 4 hours.
- When this product is used in conjunction with the CRRT, the flow rate can be up to 250mL/min. Hemoperfusion time can be up to 12 hours.
- The treatment frequency for critical ill is usually 1-2 cartridges per days, and 3-4 days per treatment [5, 8-10, 13-15].The treatment frequency should be prescribed individually for each patient by the doctor in charge according to his/her clinical experiences.

2.5.2 For Treatment modes as HP+ECMO/CPB

- When this product is used in conjunction with the CPB, the flow rate can be up to 700mL/min, and the hemoperfusion time can be up to 2.5 hours.
- When this product is used in conjunction with the ECMO, the flow rate can be up to 700mL/min, and the hemoperfusion time can be up to 6 hours.
- Treatment frequency in cardiac surgery is usually one cartridge for each surgery. The specific treatment should be determined by the clinicians according to the patient's condition.

2.6 Post-hemoperfusion

After hemoperfusion, the blood in the cartridge and tubes could be returned back to patients' body by saline. Protamine could be used to neutralize heparin when it is necessary.

3. RECORDED EFFICACY

3.1 Improvement of hyperinflammatory

- Reduce the level of IL-6 [6-7, 14, 18]、IL-8 [6, 14, 18] 、TNF-a [5-7] 、IL-1 [5, 6, 18] 、IL-2 [6]、IL-10 [6, 18] 、PCT [9], and CRP [9-11]

3.2 Stable hemodynamic condition

- Decreasing need for vasopressors [5, 9, 14]
- Stabilization of fluid balance, PH [18], HCO3 [18], decrease BUN 4, [7, 15, 18], Scr [7, 13, 15, 18]

3.3 Improvement of organ function

- Improvement in ALT, AST, MAP, PaO2/FiO2 [5, 6, 14]
- Improvement in SOFA score [5-6, 10] and APACHE II score [4-6, 9, 13, 15].
- No further increase of ventilatory support necessary [5, 16]

3.4 Benefits in ICU length of stay [4,6] and length of hospital stay [6, 12, 14]

4. CAUTIONS

4.1 **Hypotension**

Patients' temperature, pulse, blood pressure and respiration should be closely observed. Stop the treatment if the blood pressure drops significantly.

4.2 Shivering

During the first hour of hemoperfusion, shivering might appear on some patients who are hypovolemic or when the ambient temperature is low. Shivering will affect blood volume and may trigger coagulation. Once the symptom is observed, correlative treatment should be adopted. Heat preservation method should be taken to prevent the negative effects of low body temperature.

4.3 Coagulation

Coagulation may occur for reasons as follows:

- Deficiency of heparin dosage.
- Deficiency of blood flow volume. Coagulation may occur when the blood flow rate is less than 100mL/min.
- Low ambient temperature;

The efficacy of the treatment could be reduced if coagulation occurs. The treatment may even have to be stopped. A new cartridge should be used if choose to continue the treatment.

4.4 Air embolism

Strict observation must be conducted during the whole treatment to avoid the air from entering patients' body. Once occurs, hemoperfusion should be stopped immediately.

4.5 Other side effects

If patients have abnormal symptoms (such as headache, nausea, vomiting, chest tightness, abdominal pain, back pain, dyspnea, tachycardia, etc.), please handle it according to doctor's advice. For allergic patients, signs should be closely observed and appropriate measures should be adopted.

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