Unity in Diversity and the Standardisation of Clinical Pharmacy Services

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Hydroxyethyl starch or gelatin, which is safer for the kidneys?

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ABSTRACT: The aim of this study was to compare the effects of HES 200/0.5 and gelatin in the kidneys with a dose of < 20 ml/kg/day. This is an observational study conducted in patients who underwent elective surgery at Dr. Soetomo Hospital with the bleeding condition being 15–30% of EBV (Estimated Blood Volume) and a resuscitation fluid of HES 200/0.5 or modified fluid gelatin. The observed parameters were the ratio of NAG/urinary creatinine and serum creatinine. The results indicated that there was a significant increase in the NAG/creatinine ratio in the HES 200/0.5 group ($p = 0.0004$), with no significant increase in modified gelatin. By contrast, the gelatin group showed a significant increase in serum creatinine ($p < 0.0001$) compared with the HES group. However, the increase in the NAG/urinary creatinine ratio and serum creatinine in both groups was within the normal limits. HES 200/0.5 or modified gelatin at a dose of < 20 ml/kg/day in surgery patients does not lead to changes in kidney function.

1 INTRODUCTION

Liquid resuscitation is an important part in the treatment of hypovolemic shock. A long hypovolemic shock is associated with a high risk of death from organ failure and disseminated intravascular coagulation (DIC). The objective of fluid resuscitation is to increase the volume of intravascular fluid, in order to enhance cardiac output and improve tissue perfusion. Increase of the circulating fluid volume is generally achieved by rapid infusion of crystalloid or colloid fluids. Failure of resuscitation will lead to multiple organ failure (MOF) and even death (Al-Khafaji & Webb 2004, Stainsby et al. 2000).

The widely used resuscitation fluid is of two types, namely crystalloid and colloid fluids. Volume-sparing effects are a major advantage of colloids compared with crystalloids in maintaining intravascular volume, which is usually described as a 1:3 ratio (colloid:crystalloid). In addition, colloids have a lower risk of pulmonary and systemic edema (Al-Khafaji & Webb 2004, Myburgh & Mythen 2013).

Although colloid fluids can effectively increase the intravascular volume, its risk on kidney function cannot be ignored. HES potentially induces kidney damage due to an increase in plasma oncotic pressure and accumulation in tissues. Studies on the safety aspects of HES administration on renal function have been performed, but the results are still contradictory. A study conducted by Kumle et al. (1999) on the use of HES (6% HES 70/0.5 and 6% HES 200/0.5) and gelatin 35000D in the perioperative period of geriatric patients showed no difference in the increase in a significant marker of kidney damage. Three fluid regimens are determined to be safe to administer (Kumle et al. 1999). Guidet et al. (2012) also examined the effectiveness and safety of HES compared with NS in patients with severe sepsis. From these studies, it was stated that HES does not induce acute kidney injury (AKI) and damage to tubular and glomerular function, observed through urine biomarkers, alpha-1-microglobulin, N-acetyl-beta-glucosaminidase (NAG), and neutrophil gelatinase-associated lipocalin (NGAL). In addition, there was no significant change in serum creatinine compared with baseline values, with peak serum creatinine levels observed at 1.757 ± 1.230 mg/dL (HES group) and 1.722 ± 1.195 mg/dL (group NS) (Guidet et al. 2012).

Recent studies have shown different results comparing HES with crystalloid fluid products in patients in critical conditions. Three studies have shown that patients with severe sepsis treated with HES have a higher risk of kidney damage. In addition, two studies have shown that HES-treated patients had a substantial mortality risk (Brunkhorst et al. 2008, Myburgh et al. 2012, Perner et al. 2012).

Recently, the European Medicines Agency (EMA) has recommended reevaluating and

discontinuing distribution permit of HES in July 2013. The same is also recommended by the US Food and Drug Administration (FDA). National Agency of Drug and Food Control of the Republic of Indonesia has also initiated an appeal regarding the security aspects of HES under limited conditions (Badan POM RI 2013, The US Food and Drug Administration 2013, European Medicines Agency 2013). As a result, the trends of the use of colloid fluids shift to the use of the latest generation of gelatin, which is claimed to be safer. By contrast, a systematic review and meta-analysis study was conducted by Thomas-Rueddel et al. (2012) on the safety of gelatin use in all RCTs involving adult and acute hypovolemic patients due to surgery, trauma, severe infection, or critical illness receiving gelatin, albumin, or crystalloid fluid as resuscitation fluid. The results of this study stated that the safety of gelatin under all clinical conditions cannot be confirmed. Further investigation is needed to establish its security profile (Thomas-Rueddel et al. 2012).

On the basis of clinical experience at several hospitals in Surabaya, the frequency of acute renal failure after HES 200/0.5 is low. In addition, the maximum dose of HES solution is 10–20 ml/kg BW per day and is given for only one day, while the cumulative dose used in previous studies was 2000–4000 ml (Mcintyre et al. 2007, Vlachou et al. 2010, James et al. 2011). Therefore, it is necessary to observe carefully the safety aspects of its use in patients requiring HES 200/0.5 fluid administrations with the appropriate doses and comparing it with modified fluid gelatin.

2 METHODS

2.1 *Patients*

This study was observational and prospective, conducted using nonrandom sampling technique. The study participants were patients who underwent elective surgery at GBPT Dr. Soetomo Hospital, Surabaya. The inclusion criteria were:

a. Obtain a resuscitation fluid of HES 200/0.5 or modified fluid gelatin based on physician diagnosis
b. Physical status of ASA I-II
c. Bleeding condition 15–30% of Estimated Blood Volume (EBV)
d. Age 18–45 years
e. Willing to sign informed consent

The exclusion criteria were:

a. Treated with HES or other colloids within 24 h
b. Serum creatinine > 1.2 mg/dl
c. History of renal disease (renal impairment)
d. History of diabetes mellitus and hypertension

2.2 *Procedures*

Standard fluid treatment in patients undergoing was carried out by a combination of crystalloid and colloid fluids. Before surgery, each patient will receive 500–1000 ml of crystalloid fluid, which will be continued during the surgery. Administration of fluid loading before surgery aims to correct fluid deficits due to fasting, prevent occurrence of hypotension due to spinal anesthesia, and to prepare for fluid loss from bleeding during surgery (Bamboat & Bordeianou 2009, Holte 2010). When bleeding persists or when blood pressure decreases, a colloid resuscitation fluid of HES 200/0.5 or modified gelatin at the dose of 20 ml/kg BW was added. Blood products, whole blood or packed red cell, would also be added, if required, depending on patient condition.

2.3 *Laboratory analysis*

To evaluate changes in renal function, we used the NAG/urinary creatinine ratio before and 12 h after administration of HES 200/0.5 and modified gelatin. NAG can be used to detect acute kidney damage within 12 h of onset of damage. To eliminate the bias due to changes in urine tonicity that depend on the amount of incoming fluids, drugs, and time, the urine creatinine concentration is used as a denominator of urine biomarker (K/DOQI 2002). In principle, creatinine excretion is relatively constant for a day and almost equally among individuals, so the NAG/urinary creatinine ratio at any given time will describe NAG excretion (Greenblatt et al. 1976).

NAG activity in urine was measured using a colorimetric method, which uses sodium 4-nitrophenyl N-acetyl-β-D-glucosaminide (NP-GlcNAc) as the substrate to be hydrolyzed by NAG contained in the urine sample. This reaction will produce a yellow-colored p-nitrophenol compound through ionization reaction, so it can be measured using a spectrophotometer at a wavelength of 405 nm (Noto et al. 1983).

The changes of serum creatinine were also taken as one of the criteria for acute renal impairment. On the basis of the RIFLE criteria, the AKI is defined by an increase in serum creatinine 1.5 to 3 times the initial value after 24 h. In this study, blood was drawn before and after 48 h of HES 200/0.5 or modified gelatin administration for measurements of creatinine serum level.

2.4 *Statistical analysis*

Data were analyzed using GraphPad Prism 6, and all results were presented as mean ± standard deviation (SD). After verifying normal data distribution, effects of fluid replacement solution

were statistically analyzed by *t*-test. Statistical significance was set at $p < 0.05$.

A three-fold increase in the NAG or NAG level > 5 U/g urinary creatinine was regarded as clinically relevant. The increase in serum creatinine 1.5 to 3 times the initial value after 24 h based on RIFLE criteria is defined as AKI.

3 RESULTS AND DISCUSSION

3.1 *Demographic data*

We observed colloid fluid infusion of HES 200/0.5 and gelatin (modified gelatin) in patients undergoing elective surgery at GBPT Dr. Soetomo Hospital during January to July 2015 and obtained 104 samples. A total of 53 patients received HES 200/0.5, and the remaining 51 patients received modified fluid gelatin.

Most of the study participants were female (Table 1). Patients undergoing gynecological and orthopedic surgery formed the majority of the study population. Body weight, initial serum creatinine, and bleeding condition (volume and % EBV) during surgery did not differ significantly between the groups.

The average cumulative amount of fluid received by patients during surgery was not significantly different (2314 ± 1208 ml vs. 1869 ± 623.2 ml; Table 2). The average dose of HES fluid received by the patient is 9.8 ± 5.0 ml/kg. The dose is still below the recommended maximum dose, that is, 20–33 ml/kg BW (Novikov & Smith 2008). This was not significantly different from the dose of the modified gelatin group, which was 9.1 ± 3.0 ml/kg BW.

Table 1. Baseline characteristics of the patients.

Parameter	HES 200/0.5	Modified gelatin	p
Sex			
Male	7 (13.2%)	26 (51%)	
Female	46 (86.8%)	25 (49%)	
Body weight (kg)	57.8 ± 12.6	56.22 ± 11.96	0.5085
Serum creatinine (mg/dl)	0.79 ± 0.19	0.82 ± 0.19	0.6443
Bleeding volume (ml)	879.8 ± 514.4	693.0 ± 263.8	0.1313
EBV (%)	24.4 ± 15.4	19.7 ± 8.0	0.3908

Table 2. Total amount of fluids administered during surgery.

Parameters	HES 200/0.5	Modified gelatin	p
Total fluid amount (ml)	2314 ± 1208	1869 ± 623.2	0.1371
Total colloid amount (ml)	539.1 ± 257.8	515.9 ± 144.2	0.9981
Colloid dose (ml/kg BW)	9.8 ± 5.0	9.1 ± 3.0	0.9567

3.2 *Renal function*

Side effects of HES on renal function were first studied by Legendre et al, who reported an association between HES exposure to organ donors and osmotic nephrosis-like lesion (OL) in transplant recipients (Legendre et al. 1992). The same histologic lesions were also reported after the aggressive administration of HES hemodilution in an anesthetized dog. This condition is due to not only HES but also other resuscitation fluids such as dextran, mannitol, immunoglobulin, and iodinated contrast agents (DiScala et al. 1965, Diomi et al. 1970, Ahsan et al. 1994, Standl et al. 1996). The first randomized study to explore the side effects of HES on renal function was performed by Cittanova et al. (1996) by comparing HES 200/0.6 and gelatin. The results suggest that the use of HES in renal donors leads to impaired renal function in donor recipients with elevated serum creatinine concentrations and hemodialysis events. However, Deman et al. (1999) failed to prove the adverse effects of HES use on renal function through parameters of need for dialysis in the first week after renal transplantation (Cittanova et al. 1996, Deman et al. 1999).

In this study, we found a significant increased in NAG/urinary creatinine ratio before and after treatment in the HES 200/0.5 group ($p = 0.0004$) (Figure 1). The findings confirm the results of other studies by Dehne et al. (2001). Dehne et al. studied patients undergoing middle ear surgery and

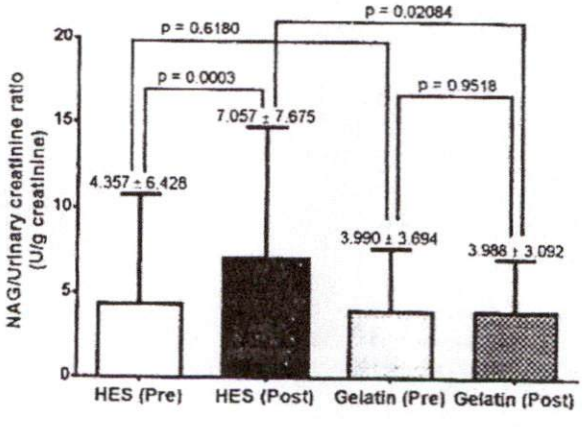

Figure 1. NAG/urinary creatinine ratio after 12 h of colloid administration.

obtained RL, HES 200/0.5, HES 200/0.6, and HES 450/0.7 infusion fluids by measuring commonly used kidney damage parameters as well as changes in biomarkers of acute kidney damage, one of which is NAG. At 24 h after surgery, the NAG/urinary creatinine ratio increased in all the groups but did not differ between the groups (Dehne et al. 2001). A study conducted by Simon et al. (2012) showed that the HES 200 group significantly elevated acute tubular necrosis and interstitial bleeding compared with the other groups, indicating tubular injury, thereby explaining the increased NAG (Simon et al. 2012). This is because HES preparation with a high molecular weight (6% HES 670 kD) has no intrinsic non-thiol-dependent anti-inflammatory properties in vitro. It is indicated that HES preparations may have pro-inflammatory effects (Lang et al. 2004). Meanwhile, different results are found in a study conducted by Guidet et al. (2012), which investigated the effectiveness and safety of HES compared with NS in patients with severe sepsis. The urine biomarker NAG observed for up to 8 days shows that HES does not induce acute kidney damage.

In contrast to the HES 200/0.5 group, in the modified gelatin group, the NAG/urinary creatinine ratio before and after treatment did not differ significantly ($p = 0.9518$). The result of this study is different from that of the study conducted by O'Reilly et al. (1986). There was an increased urinary excretion of NAG at 2 h and a second peak at 21–24 h after gelatin infusion. Hypothetically, this increase in NAG was mainly due to an increase in the endocytosis rate of tubular cells, not due to structural damage to the tubular cell (O'Reilly et al. 1986).

Despite a significant increase in NAG values, the HES group did not show an increase in serum creatinine level ($p = 0.1509$). A significant increase in serum creatinine was observed in the modified gelatin group ($p = 0.001$; Figure 2). The study conducted by Demir et al. (2015) also produced similar results. In the gelatin group, there was a significant increase in serum creatinine compared with baseline values (Demir et al. 2015). However, changes in serum creatinine concentrations in all colloid groups were within the normal range, below 1.2 mg/dL, and no increase more than 1.5 times of its initial level.

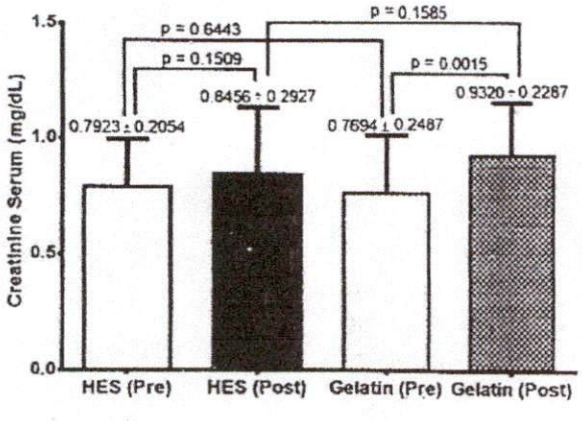

Figure 2. Serum creatinine level after 48 h of colloid administration.

The total volume of colloid fluid infused in the patients in the two colloid groups was 100–1500 ml (539.1 ± 257.8 ml for the HES 200/0.5 group and 515.9 ± 144.2 ml for the modified gelatin group). This amount is not as high as the average dose of HES in many studies, where HES is given from 1.2 L (1 day) to 70 ml/kg BW (14 days) (Diehl & Ketchum 1998, Brunkhorst et al. 2008). In addition, the accumulation of colloid molecules, hypothesized as one of the mechanisms of renal impairment by HES, occurs only when HES is given in high doses, repeatedly, and in high concentrations (10%) (Baron 2000a, Baron 2000b). With an average dose of HES 200/0.5 9.8 ml/kg BW and 6% concentration, the risk of kidney damage is also low.

Administration of crystalloid fluids before, during, or after surgery also plays a role in maintaining kidney function. HES can cause increased oncotic pressure in the glomerulus. The rate of glomerular filtration depends on the balance between the hydrostatic pressure that drives fluid transfer to the Bowman capsule and the oncotic pressure that inhibits fluid transfer. When there is an increase in oncotic pressure due to the addition of a number of colloids, the glomerular filtration will be disrupted. This can occur in all active osmotic and difficult-to-filter compounds (Moran & Kapsner 1987). Administration of a number of crystalloid fluids will prevent the occurrence of urinary hyperviscosity due to colloid administration (Kumle et al. 1999).

The baseline condition of the study subjects had no history of renal impairment or increase in serum creatinine. Therefore, although renal function is not affected by HES 200/0.5 and modified gelatin infusion, it cannot be concluded from the available data whether the HES 200/0.5 or modified gelatin regimen remains safe when there is previous renal function impairment. In addition, risk factors such as hemodynamic instability, vascular obstruction, dehydration, and renal impairment have a large predisposing effect on the incidence of acute renal failure compared with the given colloid type (Matheson & Diomi 1970, Baron 2000a).

4 CONCLUSION

HES 200/0.5 or modified gelatin with a dose of <20 ml/kg/day in patients underwent surgery did

not lead to changes in kidney function. Both colloid fluids should be used with some reservations in terms of renal damage and monitored for kidney function periodically.

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