THE USE OF HYDROXYETHYL STARCH 200/0,5 AS PLASMA SUBTITUTES IS SAFE IN HYPOVOLEMIC PATIENTS AS INDICATED IN CHANGES OF N-ACETYL- -GLUCOSAMINIDASE AND CREATININ SERUM PARAMETERS

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ABSTRAK

Hydroxyethyl Starch (HES) merupakan senyawa yang efektif untuk memperbaiki volume intravaskular dengan cepat tanpa menyebabkan edema jaringan. Namun, HES juga memiliki profil keamanan pada ginjal yang masih menjadi perdebatan. Berdasarkan pengalaman klinik di RSUD Dr. Soetomo, frekuensi kejadian gagal ginjal akut setelah pemberian HES 200/0,5 pada dosis kurang dari 20 ml/kg BB (dosis maksimum) sangat jarang. Tujuan penelitian ini adalah mengevaluasi pengaruh pemberian infus HES 200/0,5 pada dosis kurang dari 20 ml/kg BB pada pasien yang mengalami perdarahan selama operasi, dengan parameter rasio N-acetyl-b-D-Glucosaminidase (NAG) per kreatinin dan serum kreatinin. Penelitian ini dilakukan secara observasional dan prospektif pada pasien yang menjalani operasi elektif di GBPT RSUD Dr. Soetomo, yang memerlukan terapi resusitasi HES 200/0,5 dan memenuhi kriteria inklusi dan eksklusi. Selain itu, penelitian ini juga mengobservasi pasien-pasien yang hanya mendapatkan terapi kristaloid sebagai kelompok kontrol. Parameter yang diamati, yakni NAG, diukur pada sebelum operasi dan 12 jam sesudah pemberian terapi cairan. Sedangkan serum kreatinin diamati sebelum operasi dan 48 jam sesudah resusitasi. Penelitian ini dilakukan selama 3 bulan, dan diperoleh 50 subyek yang terbagi menjadi 2 kelompok. Kelompok kristaloid dan kelompok HES 200/0,5. Data demografi dan karakteristik dasar tidak berbeda antar kelompok, kecuali total volume perdarahan. Total perdarahan pada kelompok HES 200/0,5 lebih besar dibandingkan dengan kelompok kristaloid (p<0,0001). Rerata volume cairan yang diterima subyek kelompok HES 200/0,5 sebesar 2042,0 ± 673,9 mL, lebih besar jika dibandingkan dengan kelompok kristaloid yang rata-rata mendapatkan cairan sebesar 910,0 ± 592,0 ml. Dosis HES 200/0,5 yang diterima subyek sebesar 8,31 ± 4,86 ml/kg BB. Pengukur an rasio NAG/kreatinin dan serum kreatinin menunjukkan peningkatan yang signifikan pada kedua kelompok, tetapi masih dalam rentang normal. Selain itu, nilai kedua parameter tersebut tidak berbeda antar kelompok. Sebagai simpulan, HES 200/0.5 dengan dosis kurang dari 20 ml/kg aman digunakan pada pasien yang mengalami hipovolem akibat perdarahan, yang tanpa riwayat gangguan ginjal sebelumnya. ***(FMI 2015;51:228-233)***

Kata kunci: *hyroxyethyl starch, gagal ginjal akut, n-acetyl-β-d-glucosaminidase, serum kreatinin*

ABSTRACT

Hydroxyethyl Starch (HES) is a compound that improves intravascular volume effectively and rapidly without causing tissue edema. However, HES also has renal safety profile which is still being debated. Based on clinical experience in Dr. Soetomo Hospital, the frequency of acute renal failure following HES 200/0.5 administration at a dose of less than 20 ml/kg (maximum dose) is very rare. The purpose of this study was to evaluate the effect of HES 200/0.5 at a dose of less than 20 ml/kg in patients undergoing surgery. N-acetyl-b-D-Glucosaminidase (NAG) per urine creatinine ratio and creatinine serum were used as main parameter to assess renal injury. This research was observational and prospective design in patients undergoing elective surgery at Gedung Bedah Pusat Terpadu, Dr. Soetomo Hospital, who requiring resuscitation therapy with HES 200/0.5 and met the inclusion and exclusion criteria. NAG was measured prior to surgery and 12 hours after administration of fluid therapy, while creatinine serum was observed before surgery and 48 hours after resuscitation. This study was conducted for three months, and obtained 50 subjects divided into 2 groups, crystalloid group and HES 200/0.5 group. Demographic and baseline characteristics did not differ between groups, except the total bleeding volume. Total bleeding in HES 200/0.5group was higher than crystalloid group (p <0.0001). The mean volume of fluid received in HES 200/0.5 group was 2042.0 ± 673.9 mL, higher when compared with that of crystalloid group (910.0 ± 592.0 ml). Doses of HES 200/0.5 received was 8.31 ± 4.86 ml/kg. Measurement of the of NAG/creatinine ratio and creatinine serum showed significant increase in both groups, but still within the normal range. In addition, the value of these two parameters did not differ between groups. In conclusion, HES 200/0.5 in a dose of less than 20 ml/kg is safe to use in patients who suffered from hypovolemic hemorrhage, without prior history of renal impairment. ***(FMI 2015;51:228-233)***

Keywords: *hyroxyethyl starch, acute renal failure, n-acetyl-β-d-glucosaminidase, creatinine serum*

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INTRODUCTION

A successful of fluid resuscitation in shock conditions is essential to prevent organ failure and death (Stainsby et al 2000, Al-Khafaji & Webb 2004). Therefore resuscitation fluids that have efficacy and good safety profile is required to prevent those condition. Hydroxy-ethyl Starch (HES) is a colloidal fluid that has a high effectiveness in hypovolemia management. HES is derived from amylopectin and produced by replacing glucose residue anhydroxyethyl with hydroxy-ethyl group at position C2 and C6. This makes the substitution of HES are more stable to amylase hydro-lysis in the blood, thereby extending their shelf life (Spaniol et al 2007, Myburgh & Mythen 2013). These compounds can increase the circulating volume rapidly through increased oncotic pressure without causing tissue edema that often arise in the administration of crystalloid fluids (Macintyre et al 1985, Morisaki et al 1994, Moggio et al 1983, Munsch et al 1988).

However, behind its high effectiveness, HES has a renal safety profile that remains debatable. HES is said to induce renal damage through several mechanisms. These fluids can alter renal function by increasing oncotic pressure in the glomerular capillaries, thereby opposing glomerular filtration as well as the deposition of these compounds in cells that lead to cell lysis and formation of osmotic nephrosis-like histological lesions (Legendre et al 1993, Hauet et al 1998). Some studies suggest HES increases the risk of kidney damage and death within 90 days (Schortgen et al 2001, Brunkhorst et al 2008). However, some other studies found contradictory findings, in which the use of HES is safe and does not cause acute kidney damage (Kumle et al 1999, Dehne et al 2001, Guidet et al 2012). The difference is due to the dose and duration of HES use in those studies. Based on clinical experience in Dr. Soetomo Hospital, the frequency of acute kidney failure after administration of HES 200/0.5 with therapeutic doses are rare. Maximum volume of HES 200/0.5 that administered is 10-20 ml/kg BW per day and for 1 day. While the dose used in those study reached 2000 ml to 4000 ml. Therefore, it needs to be observed carefully the onset of acute renal failure in patients with bleeding requiring HES 200/0.5 fluid administration with standard dose therapy. The purpose of this study was to analyze the effect of infusion of HES 200/0.5 maximum dose of 20 ml/kg in patients with bleeding during surgery on NAG/creatinine ratio and creatinine serum.

MATERIALS AND METHODS

This study was conducted observationally and prospect-ively in patients underwent elective surgery at Gedung Bedah Pusat Terpadu (GBPT), Dr. Soetomo Hospital, with bleeding and required resuscitation fluids and met the inclusion criteria: receiving resuscitation fluid HES 200/0.5 with a maximum dose of 20ml/kg based on the doctor's diagnosis, physical status of ASA I-II, bleeding conditions 15-30% Estimated Blood Volume (EBV), aged 18-45 years, and are willing to sign the informed consent of study. Exclusion criteria of this study are patients who had been treated with HES or other colloids within 24 hours, a history of renal impairment, serum creatinine >1.2 mg/dl, a history of liver disease, a history of diabetes mellitus and hypertension.

Before surgery, blood and urine samples were taken from the subjects for measurement of creatinine serum and NAG/creatinine urine ratio. During surgery, subjects received crystalloid therapy or combination of crystalloid and HES 200/0.5 in accordance with the conditions of each subject. Twelve hours later urine was retrieved for examination of NAG/creatinine ratio, and 48 hours after resuscitation for creatinine serum analysis.

Creatinine serum was used as a parameter of acute renal damage. Based on KDIGO, acute renal impairment is defined as an increase in serum creatinine of 0.3 mg/dL (26.5 mol/l) in 48 hours. While N-acetyl-β-D-glucosa-minidase (NAG) is a biomarker of acute kidney damage that can detect early kidney damage, ie 12 hours after the onset of the damage. In addition, NAG is also a biomarker that is robust and stable to storage.

All data was analyzed with the use of SPSS software and GraphPad Prism 6. Parameter NAG/creatinine ratio and serum creatinine, each were compared by means of paired t-test when the data fit normal distribution and Wilcoxon test when the data were not fit normal distribution. ANCOVA was used to compare the value of each parameter in the HES group and crystalloid group and to eliminate covariate bleeding volume if the data were homogenous. If the data were not homogen-ous, analysis were carried out using linear regression test.

RESULTS

Patients' characteristics

Fifty patients were obtained for three months observation in Gedung Bedah Pusat Terpadu, Dr. Soetomo Hospital, and were divided into 2 groups. Twenty-five patients were in the control group, who only used crystalloid fluids during surgery. The other 25 patients were in colloid group, ie patients who used combination of liquid crystalloid and colloid fluid HES

200/0.5 during the operation. Demographic and baseline characteristics between groups of crystalloid and groups of HES 200/0.5 showed no significant differences in the parameters of gender, age, body weight, and baseline serum creatinine (Table 1).

The basic characteristic that differed significantly was total bleeding during surgery (p <0.0001), which is subjects in group HES 200/0.5 had was severe bleeding (844.0 ± 444.0 ml; EBV 23.18 ± 13.18%) compared to crystalloid group (300.4 ± 180.1 ml; EBV 8.36 ± 4.78%). All patients obtained in this study had no history of kidney disorders, liver disorders, diabetes mellitus, and hypertension. Before surgery, all patients were given fluid loading Ringer's lactate (RL) or a combined RL and NaCl 0.9% of 1000 ml.

The average cumulative amount of fluid received during the operation was 2152.0 ml (± 669.2) in crystalloid group and 2972.0 ml (± 773.8) in HES 200/0.5 group (Table 2). The average dose of HES fluid received was 8.31 ± 4.86 ml/kg. This dose was still below the recommended maximum dose, 20-33 ml/kg (Novikov & Smith 2008). Of the 25 subjects of HES 200/0.5 group, there were two subjects who also received gelatin infusion with an average dose of 7.79 ± 0.77 ml/kg, and 11 patients received whole blood transfusions. The number of subjects in HES 200/0.5 group who received blood transfusions was quite high, therefore statistical test is carried out to assess if there was the effect of transfusion addition on parameter changes.

Table 1. Patients' demography and characteristics in crystalloid group and HES 200/0.5 group

Variables	Cristalloid group (n = 25)	HES 200/0,5 group (n = 25)	p value
Sex			
Male	2 (8.00%)	5 (20.0%)	p = 0.4174
Female	25 (92.0%)	20 (80.0%)	
Age (years)			
mean ± SD	42.2 ± 11.3	43.8 ± 8.1	p = 0.5507
Body weight (kg) mean ± SD	55.3 ± 8.5	58.4 ± 9.0	p = 0.2155
Creatinin serum (mg/dL)			
mean ± SD	0.77 ± 0.18	0.79 ± 0.16	p = 0.6257
Total bleeding during operation			
Volume (ml)	300.4 ± 180.1	844.0 ± 444.0	< 0.0001***
EBV (%)	8.3 ± 4.7	23.1 ± 13.1	< 0.0001***

Table 2. Total amount of fluid intake during surgery

Notes	Control group (n = 25)	HES 200/0.5 group (n = 25)
Total fluid (ml)	2152.0 ± 669.0	2972.0 ± 773.8
Cristalloid (ml)		
NaCl 0.9%	478.6 ± 141.0	466.6 ± 223.3
RL	1085.4 ± 488.5	1046.0 ± 386.2
Colloid volume (ml)		
HES 200/0.5	-	470.0 ± 252.0
Gelatine (2 subjects)	-	500.0 ± 0.0
Colloid dose (ml)		
HES 200/0.5	-	8.31 ± 4.86
Gelatine (2 subjects)	-	7.79 ± 0.77
Blood product (ml)		
WB (11 subjects)	-	468.1 ± 258.1

Table 3. Results of measurement of N-acetyl-β-D-glucosaminidase and creatinine serum

Parameters	Groups	Pre	Post	p value	
NAG/creatinine (U/g creatinine) ratio mean ± SD	Cristalloid	1.229 ± 0.811*	2.119 ± 1.513	$p = 0.0160^{\#}$	$p = 0.7997^{\times}$
	HES 200/0.5	3.086 ± 2.803*	4.569 ± 3.385	$p = 0.0147^{\#}$	
Creatinine serum level (mg/dL) mean ± SD	Cristalloid	0.74 ± 0.17	0.88 ± 0.20	$p = 0.0008^{\#}$	$p = 0.296^{\times}$
	HES 200/0.5	0.78 ±0.20	0.94 ± 0.20	$p = 0.0008^{\#}$	

#*NAG/creatinine ratio before resuscitation in crystalloid group compared to that in HES 200/0.5 group was significantly different ($p = 0.0245$)
#comparison of parameter values between before and after resuscitation in each group
×comparison of the difference in parameter values in crystalloid group and HES 200/0.5 group

The results showed significant increase in the average NAG/creatinine ratio, from 1.229 ± 0.811 U/g creatinine to 2.119 ± 1.513 U/g creatinine ($p \leq 0.05$) after 12 hours post resuscitation in crystalloid group (Table 3). Similar results were also obtained in HES 200/0.5 group, where the average of NAG/creatinine ratio before resuscitation was 3.086 ± 2.803 U/g creatinine increased significantly to 4.569 ± 3.385 U/g creatinine ($p \leq 0.05$). HES 200/0.5 group had a tendency to increase NAG/creatinine ratio higher (1,483 ± 3,333 U/g creatinine) than that of crystalloid group (0.970 ± 1.689 U/g creatinine). In linear regression statistical tests comparing the difference in NAG/urinary creatinine ratio between the groups, after eliminating covariates bleeding, significant difference ($p = 0.632$) was not found. In addition, NAG/creatinine ratio after resuscitation was still within normal values, ie <5 U/g creatinine. Similar results were also obtained on creatinine serum levels (Table 3), where the increase in creatinine serum levels did not differ significantly ($p = 0.296$) between groups. Nevertheless, mean creatinine serum level of in crystalloid group and HES 200/0.5 group increased significantly, from 0.74 ± 0.17 mg/dL to 0.88 ± 0.20 mg/dL ($p \leq 0.05$) (crystalloid group) and 0.78 ± 0.20 mg/dL to 0.94 ± 0.20 mg/dL ($p \leq 0.05$) (HES 200/0.5 group).

DISCUSSION

Caution about the side effects of HES on renal function was first coined by Legendre et al, who reported an association between exposure to HES on organ donation and osmotic nephrosis-like lesion (OL) in transplant recipients (Legendre et al 1993). The same histological lesions were reported after aggressive administration of HES hemodilution in anesthetized dogs. This condition is caused not only by HES, but also by resuscitation fluids such as dextran, mannitol, immunoglobulins, and iodinated contrast agent (DiScala et al 1965, Standl et al 1996, Diomi et al 1970, Ahsan et al 1994). The first randomized study assessing HES side effects on renal function was performed by Cittanova et al comparing HES 200/0.6 and gelatin. The results of that study suggest that the use of HES on kidney donors leads to impaired renal function in donor-recipient with an increase in serum creatinine concentration and incident hemodialysis (Cittanova et al 1996). However, Deman et al. failed to prove the adverse effects of HES on kidney function through the parameters need for dialysis in the first week after kidney transplantation (Deman et al 1999).

Compared to this study, we found no significant differences in the difference between NAG/creatinine ratio between the groups after eliminating the covariate, bleeding. This means that the addition of HES 200/0.5 fluid does not provide a different effect on increasing NAG/creatinine ratio in the group that did not receive colloidal liquid HES. In addition, the average increase of NAG/creatinine ratio in both groups were still within normal values, ie <5 U/g creatinine.

This finding confirms a previous study by Dehne et al (2001) which examined patients who underwent middle ear surgery and got intravenous fluids RL, HES 200/0.5, HES 200/0.6 and HES 450/0.7 and measured the parameters of renal damage commonly used and the biomarkers of acute kidney damage, one of which was the NAG. At 24 hours after surgery, NAG/creatinine ratio increased in all groups, but did not differ between groups (Dehne et al 2001).

The same was found in the study by Guidet et al (2012), which examined the effectiveness and safety of HES compared with NS in patients with severe sepsis. Urinary biomarker NAG was observed up to 8 days and found that HES did not induce acute kidney damage. Likewise, mean serum creatinine levels between the two groups of crystalloid and HES showed almost the same graphs all the time observation (Guidet et al 2012). Compared to this study, an increase in serum creatinine levels did not differ significantly ($p = 0.296$) between

groups. Effect of HES fluid administration on therapeutic doses was no different from effect of crystalloid fluid on changes in serum creatinine levels. Nevertheless, mean creatinine serum level in crystalloid group and HES 200/0.5 group increased significantly

Meta-analysis conducted by Mutter et al (2013) concluded differently. HES has the potential to increase the risk of acute kidney damage. Similar result was also obtained by Zarychanski et al (2013), in which HES is associated with significant increase in the risk of death and acute kidney damage. Differences in these results are influenced by many factors, the volume of fluid administered, duration of exposure, as well as the difference in treatment.

The total volume of colloid fluid infused on the subject, either HES 200/0.5 used alone or in combination with other colloids, was 1000 to 1500 ml. This amount is not as high as the average HES dose in a lot of studies, where HES was given ranging from 1.2 L (1 day) to 70 ml/kg (14 days) (Diehl et al 1982, Brunkhorst et al 2008). In addition, the accumulation of colloid molecules, which is hypothesized to be one of the mechanisms of kidney damage by HES only occur if HES is given in high doses or in repeated administration and the use of HES in high concentration (10%) (Baron 2000b, Baron 2000a). With an average dose of HES 200/0.5 only 8.31 ml/kg (41% of the maximum dose) and a concentration of 6%, the risk of damage to the kidney is also low. However, different findings were put forward by Neff et al (2003) who were investigating the repeated dose administration of HES 130/0.4 (up to a dose of 70 ml/kg), a combination of HES 200/0.5 and albumin (HES 200/0.5 dose of 33 ml/kg) + albumin maximum of 70 ml/kg in patients with head trauma. Neff et al. found that renal function did not differ between both groups and was safe to use up to 5-7 days. Nonetheless, this study had limitation in regard with few number of patients (Neff et al 2003).

Crystalloid fluid administration before, during, and after the operation also plays a role in maintaining renal function. As previously known, HES may cause increased oncotic pressure in the glomerulus. Glomerular filtration rate depends on the balance between hydrostatic pressure that drives fluid displacement to Bowman chamber and oncotic pressure that inhibits fluid displacement. When there is an increase in oncotic pressure due to the addition of a colloid, glomerular filtration will be disrupted. It can happen to all compounds that are osmotically active and hard to be filtered (Moran & Kapsner 1987). Therefore, the provision of an amount of crystalloid fluids will prevent urine hyperviscosity from colloidal application (Kumle et al 1999).

Overall patients included in this study did not show any abnormalities in kidney function at the beginning. Therefore, although the kidney function was not affected by the HES 200/0.5, the existing data could not conclude whether the regiment of HES 200/0.5 resuscitation fluids administration was still safe when there is impaired renal function before. In addition, risk factors such as hemodynamic instability, vascular obstructive disease, dehydration, and kidney disorders, have a high predisposition effect on the incidence of acute renal failure in comparison to the type of colloid administered (Matheson & Diomi 1970, Baron 2000a).

CONCLUSION

There was a significant improvement in parameters of NAG and serum creatinine in crystalloid group and HES 200/0.5. group. However, the increase was still within normal limits. The increase in both parameters was not significantly different when compared between crystalloid group and HES 200/0.5 group, so that HES 200/0.5 fluid in a dose of less than 20 ml/kg is safe to use in patients with hypovolemia due to bleeding who had no previous history of kidney disorders.

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