Unity in Diversity and the Standardisation of Clinical Pharmacy Services

Editors: Elida Zairina, Junaidi Khotib, Chrismawan Ardianto, Syed Azhar Syed Sulaiman, Charles D. Sands III and Timothy E. Welty

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Unity in Diversity and the Standardisation of Clinical Pharmacy Services

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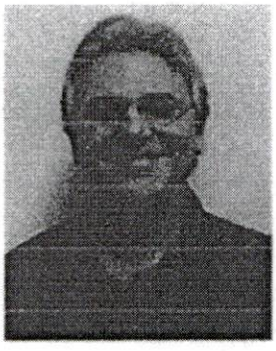

Prof. Charles F. Lacy—*Professor of Pharmacy Practice and Vice President of Roseman University of Health Sciences, Henderson, Nevada, USA*

Prof. Charles F. Lacy, Pharm.D., MS., FASHP, FCSHP, BCPP, CAATS is Professor of Pharmacy Practice and Vice-President of Roseman University of Health Sciences. He co-founded the university with his co-founders, Dr. Renee Coffman (President) and Dr. Harry Rosenberg (President emeritus). He has practiced clinical pharmacy and taught at numerous universities over the past 35 years. He was the Clinical Coordinator of Pharmacy Services at Cedars-Sinai for 20 years. He has specialized in numerous areas over the years, including psychiatric and neurologic pharmacy, oncology and informatics. He is the lead author of the renowned "Drug Information Handbook" and lead editor of the Lexi-Comp Clinical Reference Library. Dr. Lacy is a recognized leader in Pharmacy- he has worked with numerous Pharmacy & Therapeutics (P&T) Committees at the state and national level, and has lead focus groups and task-forces in the areas of pharmacoeconomics, team building, complementary medicine, and medication therapy management throughout much of the world.

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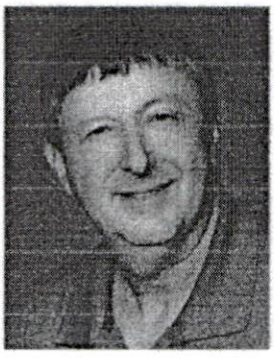
Plenary speakers

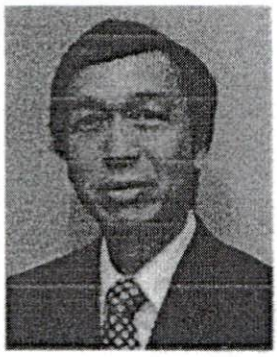


Prof. Michael D. Katz—*Professor at Department of Pharmacy Practice & Science, The University of Arizona College of Pharmacy, USA*

Prof. Michael D. Katz is Professor at the University of Arizona College of Pharmacy Department of Pharmacy Practice & Science. He practices at the University of Arizona Medical Center within the Department of Internal Medicine, His practice interests include general internal medicine, endocrinology, HIV/AIDS, infectious diseases, and evidence-based practice. Dr. Katz teaches pharmacy and medical students in both the classroom and experiential settings. He was selected in 2001 as a Dean's Teaching Scholar by the Arizona Health Sciences Center and has received numerous teaching awards. He is a Past-Chair of the American Society of Health-System Pharmacists (ASHP) Commission on Therapeutics. Dr. Katz has numerous publications and including Pharmacotherapy Principles and Practices Study Guide: A Case-Based Care Plan Approach, now in its fourth edition. Dr. Katz is the Internal Medicine PGY2 Residency Program Director and directs all residency-related activities for the College of Pharmacy. He has been involved in international education and practice for even 15 years and he serves as the College of Pharmacy's Director of International Programs. In 2010 he received the University of Arizona's prestigious Excellence in International Education Award. He has consulted and lectured extensively in Japan and many other countries regarding pharmacy education and clinical pharmacy practice and he serves as the Co-Chair of the Board of Directors of the U.S—Thai Pharmacy Consortium. Dr. Katz directs the largest program of its kind to train clinical pharmacy faculty members from Saudi Arabia.

Dr. Umi Athiyah—*A/Prof of Department of Pharmacy Practice and Dean of Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia*

Dr. Umi Athiyah is the current dean of Faculty of Pharmacy at University of Airlangga, Indonesia. Dr. Athiyah teaches various subjects including Pharmaceutical Philosophy, Community Pharmacy, Law and Ethics in Pharmacy, Management of Pharmacy Services and Logistics, Professional Communication, Pharmacoeconomics, Information Technology and Pharmaceutical Marketing. She has a research interest in Pharmacy Practice and Health Care System. She has been involved in many community based services. She has been invited as a speaker both in national and international conferences. She is one of the co-authors of a Pharmacy Management handbook.



Prof. Alan Lau – *Professor of Pharmacy Practice and Director of International Clinical Pharmacy Education at the University of Illinois at Chicago (UIC) College of Pharmacy, USA*

Prof. Alan Lau is Professor of Pharmacy Practice and Director of International Clinical Pharmacy Education at the University of Illinois at Chicago (UIC) College of Pharmacy. He obtained his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees at the State University of New York at Buffalo and then completed a clinical pharmacy residency at UIC. He pioneered the development of clinical pharmacy services for renal failure patients on dialysis. Dr. Lau had obtained many research grants for clinical and laboratory research in renal pharmacotherapeutics and clinical pharmacology, with a recent focus on mineral and bone disorder in chronic kidney disease. He has published many research papers and book chapters, including chapters in the textbooks Pharmacotherapy, Applied Therapeutics—The Clinical Use of Drugs and Basic Skills in Interpreting Laboratory Data. Dr. Lau was one of the founding members of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. In addition, he had served on the Board of Director and as Chairman of the Renal Scientific Section in the American Society for Clinical Pharmacology and Therapeutics. Dr. Lau was elected to be vice-chairman of the Nephrology/Urology Expert Committee of United States Pharmacopeia (USP) in 2007. In 2010, he was elected as a Distinguished Practitioner to the National Academies of Practice in Pharmacy. Since 2011, Dr. Lau has been working with the American College of Clinical Pharmacy on international program development and is now the International Program Director. He also has been appointed guest professor/faculty at the National Taiwan University, University of Hong Kong, University of Malta and also the Central South University in Changsha, China. Dr. Lau has been invited to give lectures on pharmacotherapy and clinical pharmacy service development in many countries, including Japan, South Korea, China, Hong Kong, Taiwan, Thailand, Vietnam, Malaysia, Singapore, Philippines, Indonesia, Saudi Arabia, Turkey and Malta.

Prof. Roger Lander – *Professor of Pharmacy Practice at Samford University, in Birmingham, Alabama, USA*

Prof. Roger Lander currently serves as Professor of Pharmacy Practice at Samford University, in Birmingham, Alabama, USA. He received his B.S.in Pharmacy and Pharm.D. from the University of Missouri-Kansas City and completed a clinical pharmacy residency program at Truman Medical Center. He then served as a faculty member at UMKC's Schools of Medicine and Pharmacy. Moving to Samford in 1986, he has developed practices in adult medicine, nutrition, ambulatory care, and pharmacokinetics. He previously served as Vice-Chair, Chair and Assistant Dean for Practice Programs. In 1994, Professor Lander helped develop a clerkship for Samford students at Guy's and St. Thomas' Hospitals in London and assisted the pharmacy there in the development of their ambulatory anticoagulation services. Professor Lander helped establish Samford's faculty/student exchange program with Meijo University in Nagoya, Japan and has traveled widely throughout Asia for information exchange and to assist colleges and hospitals in their clinical teaching and practice. He helped develop study opportunities at Samford for pharmacists from England, Japan, Korea, China, Malaysia, Indonesia, and Vietnam. Dr. Lander is one of the founders of the Asian Conference on Clinical Pharmacy. He has traveled to Indonesia at least a dozen times to assist pharmacists in their practice development.

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Dr. Surakit Nathisuwan—*Associate Professor in Clinical Pharmacy in Clinical Pharmacy Division, Department of Pharmacy, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand*

Ms. Nor Hasni Bt Haron—*Senior Principal Assistant Director Pharmaceutical Services Division, Ministry of Health of Malaysia*

Dr. Budi Suprapti—*A/Prof at Department of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga. Head of Pharmacy Department at Universitas Airlangga Teaching Hospital, Surabaya, Indonesia*

Dr. Margaret Choye—*Clinical Assistant Professor at College of Pharmacy, the University of Illinois at Chicago, USA. Clinical Pharmacist in Internal Medicine at the University of Illinois at Chicago Hospital and Health System, USA*

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Dr. Hiroyuki Kamei—*Office of Clinical Pharmacy Practice and Health Care Management, Faculty of Pharmacy, Meijo University, Nagoya, Japan*

Dr. Hanna Sung—*University of the Pacific, Thomas J. Long, School of Pharmacy and Health Sciences in California, USA*

Dr. Alexandre Chan—*Deputy Head and a tenured Associate Professor at the Department of Pharmacy, Faculty of Science at National University of Singapore (NUS) and the Duke-NUS Medical School, Singapore*

Prof. Jae Wook Yang—*Professor and Director of the Institute of Clinical Research and Practice, College of Pharmacy, Sahhmyook University & Vice President of Korean College of Clinical Pharmacy*

Prof. Dr. Syed Azhar Syed Sulaiman—*Professor at School of Pharmaceutical Sciences at University Sains Malaysia, Penang, Malaysia*

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Mrs. Fan Zhang—*Lanzhou University, a Pharmacist-in-Charge at Pharmacy Department of the First Hospital of Lanzhou University in China*

Dr. Lunawati Bennet—*Assoc. Professor of Pharmaceutical Sciences at Union University School of Pharmacy in Jackson, Tennesse, USA*

Prof. Robert D. Sindelar—*Professor and former Dean of Faculty of Pharmaceutical Sciences, University of British Columbia; and Advisor, External relations, Centre for Health Evaluation & Outcomes Sciences (CHEOS), Providence Health Care research Institute and University of British Columbia, Canada*

Dr. Baharudin Ibrahim—*School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia*

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Dr. Christine B. Teng—*Assoc. Professor of Department of Pharmacy, National University of Singapore Principal Pharmacist (Clinical), Dept of Pharmacy, Tan Tock Seng Hospital, Singapore*
Mr. Tan Wee Jin—*Principle Pharmacist at Guardian Health & Beauty, Singapore*
Dr. Ching Jou Lim—*Senior lecturer in the Discipline of Social and Administrative Pharmacy, University Sains Malaysia, Malaysia*
Mr. Mac Ardy J. Gloria—*University of the Philippines, The Philippines*
Dr. Vivian Lee Wing Yan—*Assoc. Professor of the School of Pharmacy and the Assistant Dean (Student Development) of the Faculty of Medicine, Chinese University of Hong Kong*

SYMPOSIUM 5: ADVANCED PRACTICE 2

Prof. Timothy E. Welty—*Professor and Chair of Clinical Science in the College of Pharmacy and Health Sciences at Drake University, Iowa, USA*
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Prof. Zhou Quan—*Professor and Vice Dean of Department of Pharmacy, The Second Affiliated Hospital of Zhejiang University, China*
Prof. Sukhyang Lee—*Professor of Clinical Pharmacy at College of Pharmacy, Ajou University, Korea*
Prof. Kheirollah Gholami—*Professor and Chairman at the Department of Clinical Pharmacy, College of Pharmacy, Iran*

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Prof. Michael D. Hogue—*Assoc. Dean for the Center for faith and Health at Samford University's College of Health Sciences, Birmingham, Alabama, USA*
Dr. Elida Zairina—*Senior lecturer of Department of Pharmacy Practice, Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia*
Ms. Leonila M. Ocampo—*Chairman of the Hygieian Insitute for Education, research and Training Inc, The Philippines*
Ms. Yong Pei Chean—*Senior Manager, Khoon Teck Puat Hospital and Council Member, Pharmaceutical Society of Singapore*
Drs. Saleh Rustandi—*Chairman of Himpunan Seminat Farmasi Masyarakat (HISFARMA) of Indonesia*

SYMPOSIUM 7: PHARMACY EDUCATION

Dr. Takashi Egawa—*Clinical Pharmaceutics and Health Sciences, Department of Pharmaceutical and Health Care Management, Faculty of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan*
Prof. Yolanda R. Robles—*Professor and former Dean College of Pharmacy, University of the Philippines*
Prof. Rong-sheng Zhao—*Professor in Peking University Third Hospital, China. Assistant to President, Deputy-Director in Pharmacy Department of Peking University Third Hospital, China*
Dr. Manit Saetewa—*Staff of Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Thailand*
Drs. Nurul Falah Eddy Pariang—*President of Indonesian Pharmacist Association, Indonesia*
Prof. Josepp T. Dipiro—*Dean, Professor and Archie O. McCalley Chair at the Virginia Commonwealth University, School of Pharmacy, Richmond, Virginia, USA*

SYMPOSIUM 8: ADVANCED PRACTICE 3

Dr. Daraporn Rungprai—*Academic Staff of Faculty of Pharmacy, Silpakorn University, Thailand*
Ms. Hong Yen NG—*President, 110th Council, Pharmaceutical Society of Singapore Specialist Pharmacist (Oncology), Singapore General Hospital*
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Dr. Junaidi Khotib—*Assoc. Professor of Department of Clinical Pharmacy at Faculty of Pharmacy, Universitas Airlangga, Surabaya, Indonesia*

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Dr. Wimon Anansakunwatt—*Siriraj Hospital, Thailand*

Mr. Mohammed Nazri Abdul Ghani—*Principal Pharmacist and Medication Safety Officer (MSO) of KK Women's & Children Hospital, Singapore*

Ms. Yoon Sook Cho—*Director of Pharmacy Department, Seoul National University Hospital, Korea*

Dr. Sutthiporn Pattharachayakul—*Assistant Professor at the Department of Clinical Pharmacy, Prince of Songkla University, Thailand*

Dra Mariyatul Qibtiyah—*Head of Paediatric Pharmacy Services at Dr Soetomo Hospital, Surabaya, Indonesia*

Prof. Charles F. Lacy—*Professor of Pharmacy Practice and Vice President of Roseman University of Health Sciences, Henderson, Nevada, USA*

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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

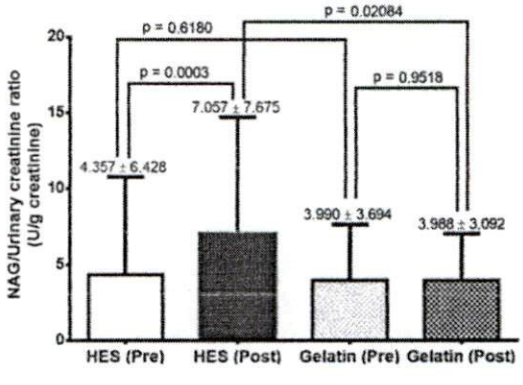

Figure 1. NAG/urinary creatinine ratio after 12 h of colloid administration.

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.

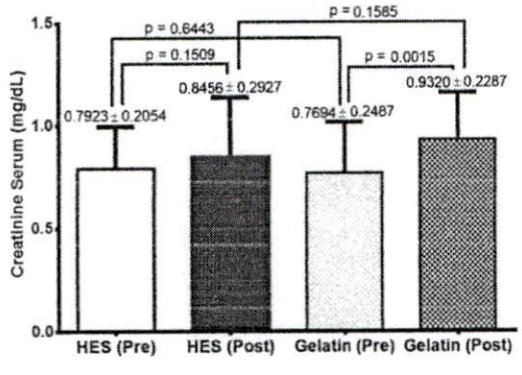

Figure 2. Serum creatinine level after 48 h of colloid administration.

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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REFERENCES

Ahsan, N. Palmer, B.F., Wheeler, D., Greenlee, R.G.Jr., Toto, R.D. 1994. Intravenous immunoglobulin-induced osmotic nephrosis. *Archives of Internal Medicine* 154:1985–7.

Al-Khafaji, A. and Webb, A.R. 2004. Fluid resuscitation. *Continuing Education in Anaesthesia, Critical Care & Pain* 4(4):127–131.

Badan POM RI. 2013. Risiko Efek Samping Kidney Injuri dan Mortalitas Pada Penggunaan Produk Obat Cairan Infus yang Mengandung Hydroxyethyl Starch (HES).:1–3.

Bamboat, Z.M. and Bordeianou, L., 2009. Perioperative Fluid Management. *Clinics in Colon and Rectal Surgery*, 22(1):28–33.

Baron, J.F. 2000a. Adverse Effects of Colloids on Renal Function. In J. L. Vincent, ed. *Yearbook of Intensive Care and Emergency Medicine Volume 2000*. Berlin: Springer: 486–493.

Baron, J.F. 2000b. Crystalloids versus colloids in the treatment of hypovolemic shock. In J. L. Vincent, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer: 443–466.

Brunkhorst, F.M., Engel, C., Bloos, F., Meier-hellmann, A., Ragaller, M., Weiler, N., Moerer, O., Gruendling, M., Oppert, M., Grond, S., Olthoff, D., Jaschinski, U., John, S., Rossaint, R., Welte, T., Schaefer, M., Kern, P., Kuhnt, E., Kiehntopf, M., Hartog, C., Natanson, C., Loeffler, M., Reinhart, K. 2008. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *The New England journal of medicine* 358(2):125–39.

Cittanova, M.L., Leblanc, I., Legendre, C., Mouquet, C., Riou, B., Coriat, P. 1996. Effect of hydroxyethylstarch in brain-dead kidney donors on renal function in kidney-transplant recipients. *Lancet* 348:1620–2.

Dehne, M.G. Mühling, J., Sablotzki, A., Dehne, K., Sucke, N., Hempelmann, G. 2001. Hydroxyethyl starch (HES) does not directly affect renal function in patients with no prior renal impairment. *Journal of Clinical Anesthesia* 13(2):103–111.

Deman, A., Peeters, P., Sennesael, J. 1999. Hydroxyethyl starch does not impair immediate renal function in kidney transplant recipients : a retrospective, multicentre analysis. *Nephrology Dialysis Transplantation* 14:1517–1520.

Demir, A., Aydınlı, B., Toprak, H.I., Karadeniz, Ü., Yılmaz, F.M., Züngün, C., Uçar, P., Güçlü, Ç.Y., Bostancı, E.B., Yılmaz, S. 2015. Impact of 6% Starch 130/0.4 and 4% Gelatin Infusion on Kidney Function in Living-Donor Liver Transplantation. *Transplantation Proceedings* 47:1883–1889.

Diehl, L.F. and Ketchum, L.H. 1998. Autoimmune disease and chronic lymphocytic leukemia: autoimmune hemolytic anemia, pure red cell aplasia, and autoimmune thrombocytopenia. *Seminars in Oncology* 25(1):80–97.

Diomi, P., Ericsson, J.L., Matheson, N.A. 1970. Effects of dextran 40 on urine flow and composition during renal hypoperfusion in dogs with osmotic nephrosis. *Annals of Surgery* 172:813–24.

DiScala, V.A., Mautner, W., Cohen, J.A., Levitt, M.F., Churg, J., Yunis, S.I.. 1965. Tubular alterations produced by osmotic diuresis with mannitol. *Annals of Internal Medicine* 63:767–75.

European Medicines Agency. 2013. *PRAC confirms that hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients*, London.

Greenblatt, D.J., Ransil, B.J., Harmatz, J.S., Smith, T.W., Duhme, D.W., Koch-weser, J. 1976. Variability of 24-Hour Urinary Creatinine Excretion by Normal Subjects. *The Journal of Clinical Pharmacology* 16(7):321–8.

Guidet, B., Martinet, O., Boulain, T., Philippart, F., Poussel, J.F., Maizel, J., Forceville, X., Feissel, M., Hasselmann, M., Heininger, A., Van Aken, H. 2012. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study. *Critical care* 16(3), p. R94.

Holte, K. 2010. Pathophysiology and clinical implications of peroperative fluid management in elective surgery. *Danish medical bulletin* 57(7), p. B4156.

James, M.F.M., Michell, W.L., Joubert, I.A., Nicol, A.J., Navsaria, P.H., Gillespie, R.S. 2011. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study : the FIRST trial (Fluids in Resuscitation of Severe Trauma). *British Journal of Anaesthesia* 107(August):693–702.

K/DOQI 2002. *Clinical Practice Guidelines For Chronic Kidney Disease: Evaluation, Classification and Stratification* New York: National Kidney Foundation, Inc.

Kumle, B., Boldt, J., Piper, S., Schmidt, C., Suttner, S., Salopek, S. 1999. The influence of different intravascular volume replacement regimens on renal function in the elderly. *Anesthesia and Analgesia* 89:1124–30.

Lang, J.D., Figueroa, M., Chumley, P., Aslan, M., Hurt, J., Tarpey, M.M., Alvarez, B., Radi, R., Freeman, B.A. 2004. Albumin and Hydroxyethyl Starch Modulate Oxidative Inflammatory Injury to Vascular Endothelium. *Anesthesiology* 100(1):51–58.

Legendre, C., Thervet, E., Page, B., Percheron, A., Noel, L.H., Kreis, H. 1992. Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. *The Lancet* 342:1–2.

Matheson, N. and Diomi, P. 1970. Renal failure after the administration of dextran 40. *Surgery, Gynecology & Obstetrics* 131(4):661–8.

Mcintyre, L.A. Hébert, P.C., Fergusson, D., Cook, D.J., Aziz, A. 2007. A survey of Canadian intensivists ' resuscitation practices in early septic shock. *Critical Care* 11(4):1–9.

Moran, M. and Kapsner, C. 1987. Acute Renal Failure Associated with Elevated Plasma Oncotic Pressure. *The New England Journal of Medicines* 317(3):150–153.

Myburgh, J.A., Finfer, S., Bellomo, R., Billot, L., Cass, A., Gattas, D., Glass, P., Lipman, J., Liu, B., McArthur, C., McGuinness, S., Rajbhandari, D., Taylor, C.B., Webb, S.A.R. 2012. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *The New England Journal of Medicine* 367(20):1901–11.

Myburgh, J.A. and Mythen, M.G 2013. Resuscitation fluids. *The New England journal of medicine* 369(13):1243–51.

Noto, A., Ogawa, Y., Mori, S., Yoshioka, M., Kitakaze, T., Hori, T., Nakamura, M., Miyake, T. 1983. Simple, rapid spectrophotometry of urinary N-acetyl-beta-D-glucosaminidase, with use of a new chromogenic substrate. *Clinical chemistry* 29(10):1713–6.

O'Reilly, D.S., Parry, E.S., Whicher, J.T. 1986. The effects of arginine, dextran and Haemaccel infusions on urinary albumin, beta 2-microglobulin and N-acetyl-beta-D-glucosaminidase. *Clinica Chimica Acta* 155(3):319–27.

Perner, A., Haase, N., Guttormsen, A.B., Tenhunen, J., Klemenzson, G., Åneman, A., Madsen, K.R., Møller, M.H., Elkjær, J.M., Poulsen, L.M., Bendtsen, A., Winding, R., Steensen, M., Berezowicz, P., Søe-Jensen, P., Bestle, M., Strand, K., Wiis, J., White, J.O., Thornberg, K.J., Quist, L., Nielsen, J., Andersen, L.H., Holst, L.B., Thormar, K., Kjældgaard, A., Fabritius, M.L., Mondrup, F., Pott, F.C., Møller, T.P., Winkel, P., Wetterslev, J. 2012. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *The New England journal of medicine* 367(2):124–34.

Simon, T.P., Schuerholz, T., Hüter, L., Sasse, M., Heyder, F., Pfister, W. 2012. Impairment of renal function using hyperoncotic colloids in a two hit model of shock : a prospective randomized study. *Critical Care* 16(1): R16.

Stainsby, D., MacLennan, S., Hamilton, P.J. 2000. Management of massive blood loss: a template guideline. *British Journal of Anaesthesia* 85(3):487–91.

Standl, T., Lipfert, B., Reeker, W., Schulteam, E.J., Lorke, D.E. 1996. Acute effects of complete blood exchange with ultra-purified hemoglobin solution or hydroxyethyl starch on liver and kidney in the animal model. *Anasthesiol Intensivmed Notfallmed Schmerzther*, 31:354–61.

The US Food and Drug Administration. 2013. *FDA Safety Communication: Boxed Warning on increased mortality and severe renal injury, and additional warning on risk of bleeding, for use of hydroxyethyl starch solutions in some settings*. Rockville.

Thomas-Rueddel, D.O., Vlasakov, V., Reinhart, K., Jaeschke, R., Rueddel, H., Hutagalung, R., Stacke, A., Hartog, C.S. 2012. Safety of gelatin for volume resuscitation—a systematic review and meta-analysis. *Intensive Care Medicine* 38:1134–1142.

Vlachou, E., Gosling, P., Moiemen, N.S. 2010. Hydroxyethylstarch supplementation in burn resuscitation—A prospective randomised controlled trial. *Burns* 36(7):984–991.