Effect of hyperosmolar sodium lactate infusion on haemodynamic status and fluid balance compared with hydroxyethyl starch 6% during the cardiac surgery

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ABSTRACT

Background and Aim: No solution has been determined ideal for fluid therapy during cardiac surgery. Previous studies have shown that hyperosmolar sodium lactate (HSL) infusion has improved cardiac performance with smaller volume infusion, which resulted in negative fluid balance. This study compared the effects between a patent-protected HSL infusion and hydroxyethyl starch (HES) 6% on haemodynamic status of the patients undergoing cardiac surgery. Methods: In this open-label prospective controlled randomized study, patients were randomly assigned to receive loading dose of either HSL or HES 6%, at 3 mL/kgBW within 15 min, at the beginning of surgery. Haemodynamic parameters and fluid balance were evaluated, while biochemical parameters and any adverse effect were also recorded. Haemodynamic and laboratory parameters were analyzed through repeated measures analysis of variance. Statistical assessment of fluid management was carried out through Student t-test. All statistical analyses were performed using the statistical package for the social sciences® version 15, 2006 (SPSS Inc., Chicago, IL). Results: Out of 100 enrolled patients in this study (50 patients in each arm), 98 patients were included in analysis (50 in HSL group; 48 in HES group). Cardiac index increased higher in HSL group ($P = 0.01$), whereas systemic vascular resistance index decreased more in HSL than HES group ($P = 0.002$). Other haemodynamic parameters were comparable between HSL and HES group. Fluid balance was negative in HSL group, but it was positive in HES group ($-445.94 \pm 815.30$ mL vs. $+108.479 \pm 1219.91$ mL, $P < 0.009$). Conclusion: Administration of HSL solution during the cardiac surgery improved cardiac performance and haemodynamic status better than HES did.

Key words: Cardiac surgery, fluid resuscitation, hydroxyethyl starch, hyperosmolar sodium lactate

INTRODUCTION

Maximising the cardiac output (CO) by fluid infusion benefits patients undergoing cardiac surgery,\cite{1-3} but they may not tolerate large volume of fluid due to impaired cardiac performance. Hence, fluid resuscitation without or with minimal risks of fluid excess might be beneficial.\cite{4,5} Colloids are widely used in cardiac perioperative setting,\cite{4,6,7} however, higher cost and potential risks of colloids are still unresolved. Hypertonic solution infusion has been shown to benefit cardiac surgery patients\cite{8-12} and was associated with a higher excretion of body fluid excess when compared with colloid infusion.\cite{13}

Perioperative administration of lactate based hyperosmolar solutions benefited cardiac surgery patients by improving cardiac performance, oxygen
delivery and inducing negative fluid balance.\cite{14,15} Lactate was suspected to contribute to these benefits as per the findings of previous studies.\cite{16-21} We conducted this study to evaluate the effect of hyperosmolar sodium lactate (HSL) infusion on haemodynamics and fluid balance in comparison with 6% hydroxyethyl starch (HES) infusion.

**METHODS**

This prospective, randomised, open-labelled study aimed to evaluate the efficacy and the safety of a scientifically-formulated and patent-protected HSL solution (Totilac\textsuperscript{®}), manufactured by Finusolprim Farma Indonesia (for Innogene Kalbiotech Pte Ltd) compared to HES 6% (Voluven\textsuperscript{™}, Fresenius Kabi) during coronary artery bypass grafting (CABG) surgery. The composition of each solution is described in Table 1. This study was approved by institutional ethical committee.

Male and female patients, aged 18-75 years undergoing CABG surgery were enrolled. We excluded the patients who needed combined operations and intra-aortic balloon pump, patients with severe arrhythmia (ventricular tachycardia, atrial flutter with rapid response, heart block), the presence of severe haemodynamic imbalance, severe bleeding and/or re-operation, liver dysfunction as indicated by serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase >2 times normal value) and renal failure (creatinine level >180 µmol/L). Signed informed consent was obtained from all eligible patients or the next of kin if the patient was not able to comprehend or unable to accept and sign informed consent.

Patients underwent routine monitoring including 5-lead electrocardiography, radial, central venous pressure (CVP), pulmonary artery (PA) catheters, pulse oximetry, blood, urine and temperature monitoring. Following pre-medication with intravenous midazolam (2.5-5 mg), anaesthesia was induced with 3-5 mg/kgBW propofol, titrated and adjusted based on patients haemodynamic status and clinical condition and 1-2 µg/kgBW sufentanil. A dose of 0.1-0.2 mg/kgBW pancuronium bromide was administered for intubation.

Anaesthesia and haemodynamic stability during surgery was maintained with continuous infusion of 1.0-1.5 mg/kgBW of propofol as baseline hypnosis, coupled with titration of inhalational anaesthesia agent (sevoflurane). Then propofol was continued as post-operative sedation with patient warming and improvement in CO. Intravenous bolus of sufentanil was administered in case of poor analgesia and/or increase in blood pressure or heart rate at 30% or more. Nitroglycerin was continuously infused only for a tight indication, such as for patients with left main coronary artery occlusion or low ejection fraction (<40%) with multiple coronary occlusions, or if there were any signs of revascularisation injury. The infusion rate was modulated according to the blood pressure at 0.5 to 2 µg/kgBW/l. CO/cardiac index (CI), pulmonary vascular resistance (PVR)/pulmonary vascular resistance index (PVRI) and systemic vascular resistance (SVR)/systemic vascular resistance index (SVRI) were also measured and monitored intermittently by PA catheter to ensure that the haemodynamic status was normal during the infusion.

For cardiopulmonary bypass (CPB), the extracorporeal circuit consisted of a roller pump (Sarns 8000\textsuperscript{®}) and a membrane oxygenator (Capiox Sx\textsuperscript{®}). The pump flow was 2.4 L/min/m\textsuperscript{2}. During CPB, patients were cooled to 31-32°C and received intermittent antegrade normothermic blood cardioplegia, a mixture of 400-600 mL of oxygenated blood with graduated doses of potassium-magnesium solution. Standard systemic heparinisation (3 mg/kgBW) was performed and an activated clotting time of greater than 480 s was maintained during CPB. Heparin was neutralized with protamine sulphate on discontinuation.

Patients were randomised by block permutation with block size of 3. Randomisation was conducted by an independent nurse and random allocation was concealed within a thick envelope. Study drug was administered by a nurse according to random allocation; hence the investigator was blind about the treatment. Similar dose of HSL or HES solutions
were administered at 3 mL/kgBW within 15 min at the beginning of surgery (after induction and fasting fluid replacement). Additional fluid were given as needed, which was managed similarly in both groups. Types and amount of additional fluids administered were recorded.

Patients were intensively monitored during surgical procedure. The haemodynamic parameters were recorded on baseline and immediately after study fluid administration including heart rate (HR), systolic and diastolic blood pressure, mean arterial pressure (MAP), CO, CI, CVP, pulmonary capillary wedge pressure (PCWP), mean pulmonary arterial pressure, SVR and PVR. SVRI and PVRI were subsequently calculated using standard formulae. Laboratory parameters including arterial pH, PaO$_2$, PaCO$_2$, bicarbonate (HCO$_3$), haemoglobin and haematocrit levels, blood electrolytes (sodium, potassium, chloride, magnesium), blood glucose and blood lactate were recorded. Intra-operative fluid input, urine output, bleeding volume and fluid balance were also measured at the end of surgery. Any adverse event during the study period was documented.

Sample size calculation in this study was based on the anticipated minimal difference of CI between control and treatment group (delta value). Previous trials in cardiac surgery showed that hypertonic solution would result CI differences of 0.3 L/min/m$^2$ compared to isotonic crystalloid solution.$^{[15]}$ Based on a two-tailed $t$-test with 5% of significance level and assuming standard deviation of 0.4, with 10% drop-out and power 80%, we required a total of 100 patients (50 in HSL group and 50 in HES group).

Statistical assessment of haemodynamic status and laboratory parameters was carried out through repeated measures analysis of variance (ANOVA). The within-group (HSL vs. HES) changes between baseline and loading dose was evaluated using ANOVA. The multivariate analysis was conducted to see the influence of each covariate on CI. Statistical assessment of fluid management was carried out through Student $t$-test. All statistical analyses were performed using statistical package for the social sciences$^*$ version 15, 2006 (SPSS Inc., Chicago, IL).

RESULTS

One hundred patients undergoing cardiopulmonary bypass graft (CABG) surgery, 50 in HSL group and 50 in HES group, were enrolled in this study, however, only 98 (50 patients in HSL group and 48 patients in HES group) were included for analysis. Two patients in HES group were not included in the analysis due to incomplete data (1 patient) and protocol violation (1 patient). The demographics and baseline between HSL and HES group were comparable [Table 2].

Systolic and diastolic blood pressure, MAP, CVP, PCWP, PVR/PVRI showed similar changes between the two groups two groups ($P > 0.05$), while the increase of heart rate ($P = 0.024$), CO ($P = 0.002$), CI ($P = 0.001$) were higher in HSL than HES group [Table 3]. SVR/SVRI were significantly lower in HSL than HES group ($P = 0.03$ and $P = 0.002$ respectively) [Table 3]. The analysis evaluating the influence of co-ordinates

| Characteristics | HSL | HES | $P$ |
|-----------------|-----|-----|-----|
| Age (years)     | 56.49±8.42 | 56.00±6.57 | 0.747 |
| Height (cm)     | 164.51±7.44 | 164.73±6.19 | 0.873 |
| Weight (kg)     | 68.12±10.89 | 67.93±9.74 | 0.929 |
| Body mass index (kg/m$^2$) | 25.14±3.50 | 24.99±3.37 | 0.835 |
| Ejection fraction (%) | 53.58±14.15 | 53.81±15.35 | 0.938 |
| Plasma urea (mg/dL) | 31.96±13.82 | 28.72±11.14 | 0.198 |
| Creatinine (mg/dL) | 1.10±0.44 | 1.05±0.31 | 0.521 |
| SGOT (IU/L)     | 19.47±7.45 | 21.81±6.11 | 0.102 |
| SGPT (IU/L)     | 26.69±14.89 | 31.62±11.47 | 0.078 |
| Systolic blood pressure (mmHg) | 112.74±13.50 | 113.94±19.20 | 0.722 |
| Diastolic blood pressure (mmHg) | 60.04±8.49 | 60.17±9.63 | 0.945 |
| Mean arterial blood pressure (mmHg) | 76.49±10.25 | 76.51±12.93 | 0.993 |
| Heart rate (beats/min) | 63.02±12.26 | 63.13±12.73 | 0.965 |
| Cardiac output (L/min) | 3.70±0.94 | 3.82±1.16 | 0.571 |
| Cardiac index (L/min/m$^2$) | 2.12±0.50 | 2.18±0.58 | 0.583 |
| PAM (mmHg)      | 16.74±4.99 | 17.15±6.46 | 0.728 |
| PCWP (mmHg)     | 10.21±7.79 | 11.09±5.71 | 0.517 |
| CVP (mmHg)      | 7.30±3.22 | 7.19±2.94 | 0.86 |
| SVR (dyne×s/cm$^5$) | 1,567.57±453.57 | 1,495.46±435.74 | 0.422 |
| SVRI (dyne×s/cm$^5$/m$^2$) | 2641.26±648.321 | 2528.21±673.89 | 0.399 |
| PVR (dyne×s/cm$^5$) | 180.64±115.60 | 141.75±97.58 | 0.071 |
| PVR (dyne×s/cm$^5$/m$^2$) | 293.48±136.04 | 244.74±170.36 | 0.123 |
| CPB time (min)  | 101.45±32.29 | 115.73±32.89 | 0.052 |
| AOX time (min)  | 73.90±24.47 | 78.02±27.42 | 0.478 |
| Operation duration (min) | 372.47±122.82 | 380.61±82.08 | 0.733 |

BMI – Body mass index; EF – Ejection fraction; SGOT – Serum glutamic pyruvic transaminase; SGPT – Serum glutamic-oxaloacetic transaminase; PAM – Mean pulmonary artery pressure; PCWP – Pulmonary capillary wedge pressure; CVP – Central venous pressure; SVRI – Systemic vascular resistance index; PVR – Pulmonary vascular resistance; PVRI – Pulmonary vascular resistance index; CPB – Cardiopulmonary bypass; AOX – Aortic cross clamping; HSL – Hyperosmolar sodium lactate; HES – Hydroxyethyl starch; SD – Standard deviation. Values are mean±SD.
such as systolic and diastolic pressure, CVP, SVRI, PVRI, MAP, pH, HCO₃, and lactate on CI changes due to the treatment showed that SVRI was the most significant parameter related to the HSL treatment and also to the observed changes in CI between two treatment groups ($P < 0.001$). PVRI and HCO₃ levels also influenced the changes of CI between two groups ($P = 0.029$ and $0.031$, respectively).

The total fluid intake was not different between HSL and HES group although the amount of crystalloid infusion was lower in HSL than HES group (0.024) [Table 4]. The cumulative urine output was higher in HSL than HES group although it was not significant. The amount of urine output and blood loss was comparable between both groups. Hence, the total fluid output throughout the surgery was comparable between HSL and HES group. The fluid balance was more negative in HSL group (−445.94 ± 815.30), whereas the fluid balance was still positive in HES group (108.479 ± 1219.91); the difference was significant between the two groups ($P = 0.009$).

Baseline data of biochemical parameters was similar between HSL and HES group ($P > 0.05$). The changes of serum potassium, magnesium, haemoglobin, $\text{PaO}_2$, $\text{PaCO}_2$, $\text{SaO}_2$ levels, glucose level before and after study drug infusion were comparable between HSL and HES group ($P > 0.05$). Serum sodium level was higher in HSL than HES group ($P < 0.0001$). Blood lactate and pH were increased higher in HSL than HES group ($P < 0.001$). Arterial HCO₃ level increased in HSL group but decreased in HES group, the difference between both groups was significant ($P < 0.001$) [Table 5].

The number of patients requiring vasodilators and or inotropes was numerically less in HSL than HES group, although it was not statistically different [Table 6].

No adverse events related to study drug infusion was noticed in both groups during the study period.
Maximizing the CO by perioperative intravascular expansion during cardiac surgery is associated with a better improvement of tissue perfusion, reduced post-operative morbidity and length of stay.[1-3] Patients undergoing cardiac surgery may not tolerate large volumes of fluid required for haemodynamic stabilisation due to reduction of cardiac performance. Hence, small volume infusion with an adequate intravascular expansion effect and ability to remove extracellular fluid excess may benefit these patients.[4,5] Colloids have been widely used in perioperative cardiac surgery and were associated with lower net post-operative weight gain,[4,6,7] however, high cost and potential risk of colloid usage are still unsolved issues. Hyperosmolar solution infusion has been shown to be beneficial during cardiac surgery.[4,8-12] A study in cardiac surgery comparing colloid with hypertonic saline infusion found that excretion of excess body fluid was higher in hypertonic saline group than colloid and avoiding tissue oedema.[13]

In this study, we used HES 6% as a reference solution because this solution has been widely used during perioperative cardiac surgery.[4,22] Similar volumes of hypertonic sodium lactate and HES 6% was administered during cardiac surgery. Lactate plays an important role as an energy substrate for cardiac cells and many studies showed that lactate administration with a better improvement of tissue perfusion,[13] and many studies showed that lactate administration directly improved cardiac performance.[16-21] Previous studies have showed that administration of HSL for post cardiac surgery patients resulted in better cardiac performance and tissue perfusion when compared with hypertonic sodium chloride 3%.[14] Until now, we did not find any publication comparing the efficacy of HSL with colloid in cardiac surgery setting, therefore we conducted this study. The randomisation resulted in comparable baseline parameters between HSL and HES group.

This study revealed that HSL infusion resulted higher increase of CI with lower SVRI than HES infusion despite comparable intravascular volume expansion, as indicated by comparable changes in MAP and CVP in both groups. Multivariate analysis showed that the decrease of SVRI was mostly associated with the increase of CI and this finding was consistent with the previous studies.[10-15] The decrease of PVR/PVRI and also alkalinizing effect of HSL also contributed to improved cardiac performance. The increase in

### DISCUSSION

| Table 4: Laboratory parameters before and after study drugs administration |
|-----------------------------------------------|
| Laboratory parameters | Study drugs | Baseline | Loading 1 | Drug and dose interaction (P value) |
|------------------------|-------------|----------|-----------|-----------------------------------|
| Na⁺                    | HSL         | 138.80±2.799 | 141.04±2.672 | <0.0001 |
|                        | HES         | 139.22±2.904 | 139.02±3.056 | 0.687 |
| K⁺                     | HSL         | 3.65±0.333   | 3.66±0.377   | 0.687 |
|                        | HES         | 3.64±0.379   | 3.63±0.365   | 0.687 |
| Ca²⁺                   | HSL         | 1.11±0.207   | 1.03±0.199   | 0.085 |
|                        | HES         | 1.15±0.199   | 1.13±0.118   | 0.085 |
| Cl⁻                    | HSL         | 102.48±2.435 | 101.12±2.782 | <0.0001 |
|                        | HES         | 101.79±0.775 | 104.44±3.101 | 0.673 |
| Mg²⁺                   | HSL         | 1.88±0.228   | 1.95±0.352   | 0.130 |
|                        | HES         | 1.90±0.154   | 1.88±0.139   | 0.130 |
| Glucose                | HSL         | 185.92±54.489 | 169.04±65.398 | 0.085 |
|                        | HES         | 187.98±58.001 | 158.19±52.291 | 0.085 |
| Lactate⁻               | HSL         | 231.76±64.253 | 219.14±66.814 | 0.385 |
|                        | HES         | 231.76±64.253 | 219.14±66.814 | 0.385 |
| Hb                     | HSL         | 38.04±1.646  | 36.06±2.987  | 0.344 |
|                        | HES         | 39.13±2.555  | 38.36±3.865  | 0.409 |
| Ht                     | HSL         | 12.43±1.692  | 11.80±1.634  | 0.409 |
|                        | HES         | 12.73±1.662  | 11.95±1.291  | 0.409 |
| PO₂                    | HSL         | 38.04±1.646  | 36.06±2.987  | 0.344 |
|                        | HES         | 39.13±2.555  | 38.36±3.865  | 0.409 |
| PCO₂                   | HSL         | 32.94±0.223  | 28.66±0.278  | 0.673 |
|                        | HES         | 33.08±1.349  | 29.22±1.339  | 0.673 |
| pH                     | HSL         | 7.44±0.060   | 7.52±0.06    | <0.0001 |
|                        | HES         | 7.44±0.04    | 7.48±0.05    | <0.0001 |
| BE                     | HSL         | −1.006±2.222 | 1.338±2.268  | <0.0001 |
|                        | HES         | −0.925±1.664 | −1.250±1.968 | <0.0001 |
| SaO₂                   | HSL         | 96.56±1.027  | 96.35±1.062  | 0.385 |
|                        | HES         | 96.52±0.798  | 96.57±1.484  | 0.385 |
| HCO₃⁻                  | HSL         | 22.08±2.355  | 28.66±2.426  | <0.0001 |
|                        | HES         | 22.20±1.857  | 21.17±1.907  | <0.0001 |

Sodium (Na⁺); Potassium (K⁺); Chloride (Cl⁻); Calcium (Ca²⁺); Magnesium (Mg²⁺); Glucose, lactate-and bicarbonate (HCO₃⁻) are in mmol/L; Hemoglobin (Hb) is in g/L; Haematocrit (Ht) and SaO₂ are in %, PaO₂ and PaCO₂ are in torr. Data are expressed as mean±SD. Statistical comparison was carried out with Student t test.*The difference was significant between HSL and HES groups. HSL – Hyperosmolar sodium lactate; HES – Hydroxyethyl starch.

| Table 5: Fluid parameters |
|---------------------------|
| Variables (mL) | HSL | HES | P value |
| Total fluid intake  | 2409.16±656.328 | 2652.22±786.408 | 0.099 |
| Crystallloid        | 1058.00±374.896 | 1255.41±476.003 | 0.024 |
| Colloid             | 694.78±3.999.305 | 1000.00±377.965 | 0.069 |
| PC                  | 289.22±150.727 | 291.26±131.207 | 0.954 |
| TC                  | 123.15±31.632 | 131.25±68.099 | 0.635 |
| FFP                 | 270.68±25.395 | 271.05±24.262 | 0.984 |
| Total fluid output | 2865.51±879.393 | 2543.75±1036.53 | 0.112 |
| Total urine output  | 1679.00±647.922 | 1442.71±709.04 | 0.088 |
| Total bleeding      | 1176.00±686.378 | 1101.04±804.475 | 0.664 |
| Fluid balance       | −445.94±815.305 | 108.47±1219.909 | 0.009 |

HSL – Hyperosmolar sodium lactate; HES – Hydroxyethyl starch; PC – Packed red cell; TC – Thrombocyte concentrate; FFP – Fresh frozen plasma; SD – Standard deviation. Data is expressed as mean±SD. P values are obtained from the independent t test with the significant different if P<0.05.
myocardial contractility directly related to the increase in cardiac performance and lactate has been shown to improve cardiac contractility.\[14-18\] Unfortunately in this study, we did not record the cardiac contractility after study fluid infusion, but we strongly feel that the lactate contributed for the improvement of cardiac performance. The decrease of vascular resistance after hypertonic solution infusion has been attributed to its hypertonicity,\[5,11,12\] and we postulate that the same mechanism worked during HSL infusion in this study.

Previous studies have showed that the intravascular volume expansion after hyperosmolar solution infusion as indicated by the improvement of MAP and CVP contributed for increasing CI,\[11,12,23\] however the vascular expansion was comparable between HSL and HES group in this study.

In this study, lower total fluid input with comparable total fluid output resulted in a much negative fluid balance in HSL group, whereas it became positive in HES group. This finding is in accordance with previous trials.\[5,13,15\] This effect is could be due to a redistribution of interstitial fluid and mobilisation of intracellular fluid from swollen endothelial cells to intravascular space. Endothelial cell swelling and accumulation of interstitial fluid frequently occurred in major surgery patients.\[3,24-27\] Reduction of endothelial cell swelling and mobilisation of extra vascular fluid into intravascular space following hypertonic solution administration were beneficial during cardiac surgery because it would reduce tissue oedema and improve microcirculation.\[4,5,14,26,27\]

Overall, HSL could be considered as an ideal fluid in cardiac surgery due to its ability to maintain haemodynamic status and improve CI with negative fluid balance. The goal of perioperative fluid therapy is not only to maintain the effective circulatory volume, but also to avoid fluid overload whenever possible.

Tissue oedema in surgical patients should be minimised because it increases the morbidity and mortality.\[26,27\]

The infusion of HSL was well-tolerated since there was no adverse event during this study and laboratory parameters were still in normal range in both groups. Sodium level increased and chloride level decreased after HSL infusion, however the average levels were still within the normal limits. In contrast, in HES group sodium level slightly decreased and chloride levels increased. Hypernatremia, one of the potential side-effects of hyperosmolar fluid infusion, was not found in this study, as also was the case in previous studies.\[14,15\]

Osmolality and electroneutrality principles were suspected responsible for the decrease of plasma chloride level after sodium lactate infusion.\[28\]

After study drugs administration, arterial pH, HCO$_3$ and base excess reached normal levels in HSL group, whereas in HES group base excess and HCO$_3$ were almost unchanged and still below normal range. This finding indicated that HSL infusion could completely reverse tissue acidosis, whereas HES infusion did not improve the existing tissue acidosis. Reversal of tissue acidosis in this study could be due to mild alkalinisation effect of HSL. This was an expected result, considering that infusion of HSL will increase the strong ion difference as a consequence of higher sodium and lower chloride in the HL patients after lactate gets metabolised.\[14,15\]

Number of patients requiring concomitant supportive drug during cardiac surgery such as vasodilator and inotropes was numerically less in HSL group. However the difference was not significant as and the sample size might not be adequate in this respect.

Limitations of this study

This study had some limitations including lack of double-blinding as well as the absence of the data expressing cardiac contractility after HSL or HES infusion. Another limitation was that for measurement of the effect of study drugs on haemodynamic status, measurement of the extra vascular lung water also is desirable and could not be measured due to lack of suitable monitors.

CONCLUSION

This study demonstrated that HSL administration was safe and resulted in better improvement of CI and much lower vascular resistance with negative intra-operative fluid balance during CABG surgery when compared with HES infusion.
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