Annals of Clinical Anesthesia Research

Research Article
Published: 17 Feb, 2022

Retrospective Study to Compare Lactate Levels after Using Plasmalyte *vs*. Sterofundin Intravenous Fluid Intra-Operatively in Patients Undergoing Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Background: During HIPEC, chemotherapeutic agent is instilled in peritoneal cavity at high temperatures, causing hemodynamic alterations. This can severely compromise perfusion and oxygenation of tissues. As serum lactate is a biomarker of significant systemic tissue hypoperfusion, we have compared lactate levels after infusion of two different balanced crystalloid solutions, Plasmalyte (PL) and Sterofundin (SF).

Methodology: Records of patients who underwent HIPEC surgery (June 2018 to February 2020) were evaluated retrospectively. Parameters including age, weight, total amount of SF and PL used intra operatively; pre-HIPEC and post-HIPEC lactate levels were noted. Patients were grouped as group PL and group SF. Primary outcome was to confirm if there was a significant increase in lactate levels due to infusion of any of two crystalloids. Secondary outcomes were differences in pH and electrolyte equilibrium in the two groups.

Results: 41 patients were analyzed. More patients received PL as an intraoperative fluid (n=29) and not SF (n=12). There was no significant difference in increase in lactate levels in both groups (p=0.46). Significant difference was seen in pH post HIPEC between the two groups though both pH were within normal range. Pre-HIPEC and post-HIPEC electrolyte values were also found to be comparable.

Conclusion: Both the balanced crystalloid solutions compared are equally good in terms of perfusion of tissues during HIPEC. Both the acetate based solutions maintained the acid base balance and electrolyte homeostasis.

Keywords: HIPEC; Plasmalyte TM; Sterofundin™; Lactate; Electrolyte

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Received Date: *07 Jan 2022*
Accepted Date*: 07 Feb 2022*
Published Date*: 17 Feb 2022*

Citation:
Arora D, Shah SB, Chawla R. Retrospective Study to Compare Lactate Levels after Using Plasmalyte vs. Sterofundin Intravenous Fluid Intra-Operatively in Patients Undergoing Hyperthermic Intraperitoneal Chemotherapy. Ann Clin Anesth Res. 2022; 6(1): 1046.

Introduction

Optimal cyto-reductive surgery and HIPEC (hyperthermic intraperitoneal chemotherapy) is a standard management modality for both primary peritoneal neoplasm as well as metastasis to peritoneum from gynecologic or gastrointestinal malignancies with survival benefits [1-4]. During HIPEC phase, heated and highly concentrated chemotherapeutic agent is directly instilled in the peritoneal cavity at very high temperatures of 41°C to 43°C. Drugs can be safely given in up to 30 times of the concentration intraperitoneally as compared to intravenous route [5]. High temperature leads to killing of malignant cells locally by interfering with their RNA synthesis. This in turn increases the drug penetration of tissues. Vascular stasis in microcirculation creates an acidic environment which further accelerates tumor cell killing [6]. However, this increase in temperature also causes hemodynamic alterations and thus can have a negative impact on renal and other vital organ functions in perioperative period [7]. Also, cytoreductive surgery with HIPEC causes significant blood loss and massive fluid shifts [8].

Hence, it mandates us to have meticulous fluid and temperature management during HIPEC surgery in order to maintain optimal perfusion to tissues and vital organs. Mean arterial pressure and central venous pressure are among the parameters of macro circulation of tissues, used for hemodynamic assessment. For the purpose of assessment of global microcirculation, parameters like lactate levels and central venous oxygen saturation are frequently used [9,10]. The main disadvantages

of increasing lactate are mainly manifested in conditions of impaired micro-circulation and hypoxia in the peripheral and visceral tissues. That is why serum lactate level is the most frequently used marker for assessing tissue perfusion [11]. As serum lactate is considered as a biomarker of significant, systemic tissue hypo-perfusion [12,13], and as arterial sampling is the gold standard method for lactate determination [14], we analyzed increase in lactate level during HIPEC surgery in point of care Arterial Blood Gas (ABG) analysis. A well-balanced crystalloid solution is isotonic and contains all the ions to restore the internal environment in the appropriate ratio, maintains a stable acid-base balance and does not contain excess of any ion which could result in a disequilibrium syndrome.

The need for further research to evaluate the effect of different intraoperative fluid strategies in patients undergoing cytoreductive surgery with HIPEC was also emphasized by Shiralkar et al. [15] in their retrospective audit on patients who underwent this surgery for the treatment of pseudomyxoma peritonei. Plasmalyte™ (PL) and STEROFUNDIN™ (SF) are iso-osmolar balanced crystalloid solutions we routinely use intra operatively in our institute. However till now there is no literature comparing the effect of these two fluids on lactate levels during HIPEC surgery. A very important query that whether the clinical outcome differs with the use of these two balanced crystalloid solutions is still unanswered. Therefore, we compared the effect of these two balanced crystalloids on lactate levels, thereby indicating tissue perfusion during instillation of hyperthermic chemotherapeutic drugs in the intraperitoneal cavity.

Composition of plasmalyte and sterofundin is quite similar differing mainly in nature of metabolizable ion and presence of calcium in sterofundin [16].

Primary outcome of the study was to confirm if there is significant increase in lactate levels due to infusion of any of these two acetate based balanced solutions. Secondary outcomes included the changes in pH and electrolyte equilibrium (sodium, potassium, chloride and calcium) in the two groups.

Methods

After approval from IRB committee (RGCIRC/IRB-BHR/65/2020), we retrospectively reviewed records of patients with primary or metastatic peritoneal carcinomatosis, who were treated with CRS and HIPEC at this specialized cancer institute from June 2018 to February 2020. Data for this retrospective analysis were retrieved from our hospital medical records department and its electronic database. There were no exclusion criteria. Those patients with missing data were excluded from the analysis. All patients had pre-anesthesia check and were pre-medicated with anti aspiration prophylaxis, tab ranitidine 150 mg and tab granisetron 1 mg in the morning of surgery. All patients received thoracic epidural analgesia with bupivacaine 0.1%. Induction of anesthesia was with fentanyl 1 µg/kg to 1.5 µg/kg, propofol 1 mg/kg to 2 mg/kg and atracurium 0.5 mg/kg. Maintenance was with O_2 and N_2O with sevoflurane. Standard monitoring including electrocardiogram, non-invasive blood pressure, pulse oximetry, nasopharyngeal temperature, end-tidal carbon dioxide and agent concentration along with invasive arterial and central venous pressures was done.

Intraoperative crystalloid (PL or SF), colloid (gelaspan) and blood product administration was at the discretion of the primary anesthesiologist based on maintenance of blood pressure within 20% of the baseline and urine output >0.5 mL/kg/h. Colloid and blood products were replaced based on estimated blood loss. Normothermia was maintained with warming blankets and blood/fluid warmers. Cooling with ice packs was done as needed during HIPEC.

HIPEC was performed with a closed abdominal technique. In this technique a supra hepatic inflow cannula and a pelvic outflow cannula are connected through a recirculating perfusion circuit driven by a roller pump heat exchanger. Temperature of the perforate was elevated to and stabilized at 41°C to 43°C using a temperature control system. Total duration of HIPEC was between 60 min to 90 min. After HIPEC, abdomen was washed, anastomosis and hemostasis as required were done and abdomen closed. All patients were shifted to intensive care unit for monitoring and management.

Patients were grouped into two groups. Those who received more Plasmalyte™ intra-operatively (group PL) and those who received more Sterofundin™ intra-operatively (group SF). Parameters including age, weight, total amount of PL and SF used intra operatively, pre HIPEC and post-HIPEC lactate levels in point of care arterial Blood Gas Analysis (ABG) were recorded and compared.

Variables were presented as means ± Standard Deviations (SD). Continuous variables were compared by Student's t-test and categorical variable using Chi-square test. Fisher's exact test was used wherever applicable. ANOVA was used to compare the effects of more than two continuous variables. Data was analyzed using Statistical Package for the Social Sciences (SPSS, IBM) version 23.0™ software for windows.

Results

We analyzed total of 41 patients. Out of them 29 patients received more plasmalyte in the intraoperative period where as only 12 patients received more sterofundin. There was no difference in age (p=0.63) and weight (p=0.73) of patients between PL and SF groups. Also, no significant difference was seen in increase in lactate levels from pre HIPEC to post HIPEC ABG values in both PL and SF groups (p=0.46). Though the difference in pH post-HIPEC surgery was found to be statistically significant between the two groups, both were within the normal range clinically. Pre-HIPEC pH was comparable between the groups. Pre- and post-HIPEC levels of sodium, potassium, chloride and calcium were also found to be comparable indicating that both the balanced solutions effectively maintain the electrolyte homeostasis.

Discussion

Water constitutes 60% of the total body weight, divided between intracellular and extracellular compartments. Movement between the compartments is through membranes. Peri-operatively various mechanisms could lead to alterations in fluid homeostasis. Systemic vasodilatation caused due to hyperthermia decreases intra capillary pressure, altering the pressure gradient and therefore causing fluid shifts [17].

Surgical removal of visible tumour for peritoneal carcinoma combined with loco-regional heated chemotherapy improves the quality of life and survival of these patients. During HIPEC phase, highly concentrated, heated chemotherapeutic drugs are directly instilled in the abdomen. It requires large amount of fluids to replace ascites, long duration of surgery, massive blood loss and vasodilatory effects of hyperthermia and thus optimal fluid management strategy is required for a good patient outcome [18,19]. During cytoreductive phase, there is significant intraoperative fluid (8 mL/kg to 12 mL/kg) and blood loss [20]. However, liberal fluid administration to

replace all the fluid losses leads to fluid overload and tissue edema causing cardiac or pulmonary morbidities. Hence, meticulous fluid management is required during HIPEC for optimal end-organ perfusion of vital organs [21].

During the HIPEC phase there is increase in the metabolic rate, which in turn causes increased heart rate, raised end-tidal carbon dioxide, metabolic acidosis, elevated serum lactate value, peripheral vasodilatation and increase in oxygen demand [7]. Hyperthermia causes peripheral vasodilatation resulting in a reduction of the mean arterial pressure with reflex increase in heart rate. This requires optimization of fluid infusion without development of tissue edema. Any hypo perfusion could result in increase in serum lactate levels. In order to find out difference in perfusion characteristic of the two balanced crystalloids, we compared the serum lactate levels in the two groups.

It is to be emphasized that adequate perioperative crystalloids are needed in order to ensure optimal end-organ perfusion and to maintain hemodynamic goals without causing volume overload. Lactate values collaborate closely with global tissue hypo perfusion; therefore we have compared the lactate levels in pre and post HIPEC ABG to assess the effect on end organ perfusion of tissues. Though many patient related and operative factors have been defined to be associated with morbidity by Newton et al. [22] in the review of factors contributing to morbidity and mortality in cases of HIPEC, there was no mention on the contribution of various types of fluid. We here by attempted to find out if use of either of the two balanced solutions in intraoperative period affects micro circulation and thus adds to morbidity during HIPEC.

Balakrishnan et al. [23] in their retrospective analysis concluded that peritoneal carcinoma index, a major predictor of post-operative morbidity is associated with longer of duration of surgery, increased blood and fluid loss, increased intraoperative fluid requirement, lower MAP and increased delta temperature.

They also failed to conclude on the association of fluid infused with morbidity and the duration of ventilation and ICU stay [23]. It is not clearly mentioned till now in any type of literature regarding the type of intravenous fluid to be used in cytoreductive surgery with HIPEC. Normal saline is isotonic to plasma but it has higher chloride content which induces hyperchloremia and metabolic acidosis. Balanced crystalloid solutions, like ringer's lactate and acetate-based solutions have an electrolyte composition very similar to plasma. However, lactated ringer's solution is neither isotonic nor pH balanced. Newer crystalloids like Plasmalyte-A™ and Sterofundin™, have addressed these concerns. The use of metabolizable anions instead of chloride does not increase the plasma acidity. Also, balanced salt solutions do not reduce renal arterial blood flow and thus renal cortical perfusion, as is seen after infusion of normal saline [24]. It was believed that serum bilirubin and glucose increase with the use of plasmalyte-A due to presence of gluconate, but certain studies contradict this. Even some studies claim that plasmalyte-A is a better choice in living donors undergoing right hepatectomy and diabetic ketoacidosis. Increase in chloride and bicarbonate is seen by some with the use of sterofundin though the hyperchloremia is less compared to normal saline [25].

However, in our knowledge there is no published literature that addresses potential differences on the perfusion and acid base status between these more balanced solutions during HIPEC surgery.

We therefore have retrospectively compared the effect of these more balanced solutions on lactate levels during HIPEC. It was observed that in our institute, anesthesiologist prefer giving plasmalyte (n=29) over sterofundin (n=12). It may be because they consider one fluid to be superior to another. However, no difference was found between the two fluids in this study in terms of tissue perfusion or acid base and electrolyte equilibrium and so any of these two acetate based balanced crystalloids can be safely used intra-operatively during HIPEC.

Maurya S et al. [26] also did comparative study between two balanced crystalloid as an electrolyte priming solution (plasmalyte A and sterofundin iso) in adult patients undergoing cardiopulmonary bypass in cardiac surgery. They randomly divided sixty patients into two groups. In group A (n=30) priming of the CPB pump circuit was done with plasmalyte A. In group B (n=30) priming of the CPB pump circuit was done with sterofundin iso. Like us, they also found that both balanced crystalloid solutions are better whereas sterofundin iso has advantages over the metabolizable anions. However, in contrast to our findings, they concluded that base deficit was lesser in group B (sterofundin iso) and that it maintained adequate calcium levels on bypass.

Lactated Ringer's (RL) solution is being used in the peri-operative period as maintenance and replacement fluid. Consensus guidelines recommend the use of RL in preference to normal saline when crystalloid fluid therapy is indicated. It should be brought to notice however RL infusion is associated with increase in lactate levels which can interfere with estimation of serum lactate levels in conditions of severe hypoxia or hypo perfusion. As acetate based balanced solutions are quite similar to plasma and their use does not cause development of hyperchloremic acidosis, they drastically reduce the associated morbidity and mortality [27], so they should be the preferred solutions to be used in the intraoperative period. These plasma adapted solutions have minimal effects on acid base balance. Specifically this marked benefit is gained by replacing bicarbonate with metabolizable anions. It is now well known that these acetate based plasma adapted solutions cause fewer side effects than other colloid or crystalloids, thus shortening the hospital stay. The new generation of electrolyte solutions applies metabolism of anions in the form of acetate and/or malate in preference to lactate. Several studies quote the beneficial effects of various molecules like acetate, malate, gluconate and calcium added to the newer generation of balanced salt solutions [28].

During HIPEC, we can have severe acid base and electrolyte imbalance. It is clearly understood from our observations that both plasmalyte and sterofundin could be safely used as intraoperative fluid solutions during HIPEC. As both these balanced crystalloid solutions maintain lactate levels, tissue perfusion is also adequately achieved.

Similar to our study, Kumar AK et al. [25] compared the effect of intra-operative administration of ringer's lactate, sterofundin, plasmalyte-A and kabilyte on ionic and acid base status. They conducted a prospective monocentric double blinded randomized controlled trial for 1 year during the period of February 2015 to February 2016. The 80 patients were divided into 4 groups of 20 each randomly. The 20 were assigned to each of the four groups to receive lactated ringer's solution (Group C), sterofundin (Group S), plasmalyte (Group P) and kabilyte (Group K) respectively. As suggested by us, they also concluded that the use of balanced salt

solutions in surface surgeries of limited duration and minimal blood loss is associated with stable ionic and acid- base profile and is not associated with significant advantage over lactated ringer's solution.

All the three balanced salt solutions used in their study i.e., plasmalyte-A, sterofundin and kabilyte gave similar outcomes with respect to electrolyte and acid-base status when compared with one another. However, only those patients undergoing surgery for less than 3 h (surface surgeries of limited duration and minimal blood loss under general anesthesia were included in their study. The surgeries like HIPEC involving massive fluid shifts were not looked into in their research work.

Some studies on the use of different electrolyte solutions have shown greater benefits of solutions which in addition to appropriate proportions of electrolytes (sodium, potassium, magnesium and calcium) also contain organic anions such as acetate or malate [28]. These solutions act like a buffer for the physiological acid-base status and ion fluctuations. The energetic and metabolic effects of ringerfundin infusion were studied by Zadak et al. [29]. They compared it with plasmalyte in 14 healthy volunteers. Comparable to what we noticed in our study, they also concluded that ringerfundin was very well tolerated and did not observed any undesirable effects.

Sharma et al. [30] also found significantly higher lactate levels in ringer lactate infused group in comparison to sterofundin infused group in their comparative study on the effect of sterofundin compared to ringer lactate on acid base changes, hemodynamics and readiness for extubation in scoliosis correction surgery.

Dey et al. [31] conducted randomized controlled trial comparing the normal saline with balanced crystalloid (plasmalyte) in patients undergoing elective craniotomy for supra tentorial brain tumors. Similar to our findings, they also concluded that balanced crystalloid maintains metabolic status more favorably than normal saline in neurosurgical patients.

It is summarized that both these balanced fluids are safe to use during HIPEC surgery. Use of any of these two acetate based crystalloid solutions is better than lactate based crystalloid solutions. Perfusion of tissues is well maintained as indicated by lactate levels. Both of these solutions maintain acid base and electrolyte equilibrium.

However, this study has some limitations also. As it was a retrospective study, some of the patients were not given only one type of fluid (either PL or SF) intra-operatively, so further prospective studies are required to be done in major surgeries to evaluate and confirm the difference in effect of these balanced solutions on acid base status and ionic imbalance. More patients were infused plasmalyte, and less than half of the total patients received sterofundin, so there may be interpretation error in data.

Conclusion

During HIPEC, it is preferable to use balanced crystalloid solutions. Both the balanced crystalloids compared by us, plasmalyte and sterofundin have equally good perfusion of tissues as indicated by no significant difference in increase in lactate levels during HIPEC surgery. Also both the acetate based solutions maintained the acid base balance and electrolyte homeostasis.

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