Editorial

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Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy: Fluid and temperature remain the culprit!

INTRODUCTION

Optimal cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are an acceptable management modality for primary peritoneal neoplasm and metastasis to peritoneum from gynaecologic or gastrointestinal malignancies.[1,2] This technique involves removal of the tumour load followed by instillation of HIPEC. Another alternative technique is pressurised intraperitoneal aerosolised chemotherapy (PIPAC) for patients with a high load of disease or HIPEC intolerable to patient. It involves delivering chemotherapeutic drugs into the peritoneal cavity as a pressurised normothermic aerosol after optimal cytoreduction.[3] These procedures require not only extensive surgical dissection associated with significant fluid shifts and blood loss but also have haemodynamic concerns related to instillation of chemotherapeutic agent in the peritoneal cavity at high temperature (41°C–43°C) or its pressurised aerosol. CRS and HIPEC require large amounts of fluids to replace ascites, longer duration, extensive surgery, blood loss and vasodilatory effects of hyperthermia.[1,2] Optimal fluid management strategy is required for a good patient outcome. The literature is scarce for a definite protocol for perioperative fluid management during CRS and HIPEC, and a consensus has yet to be reported. The initial phase of cytoreduction may lead to hypothermia due to major surgical exposure, extensive dissection and blood loss, and subsequently, HIPEC phase leads to hyperthermia. Unique concern relates to direct chemotherapeutic agent-associated nephrotoxicity in addition to haemodynamic alterations due to temperature fluctuations and its impact on renal and other vital organ functions in perioperative period.[4] These issues mandate meticulous fluid and temperature management apart from other anaesthetic management concerns for such surgical intervention.[5-9]

This issue publishes two manuscripts related to the use of intraoperative intraperitoneal chemotherapy during oncosurgery.[10,11] In a retrospective analysis, the authors have assessed factors associated with morbidity and mortality after CRS and HIPEC.[10] The other manuscript describes a case undergoing CRS and PIPAC.[11]

FLUID MANAGEMENT

Meticulous fluid management is required during CRS and HIPEC for optimal end-organ perfusion of vital organs including kidney.[12] Liberal fluid administration to replace all the fluid losses leads to fluid overload and tissue oedema, especially of the surgical site. It may also affect other systems and cause abdominal, cardiac or pulmonary morbidities. Fluid overload has been found to be associated with adverse impact on endothelial glycocalyx and consequently to adverse effects in organ function and their recovery.[13] The existing literature has shown an increased morbidity with liberal perioperative fluid management. In a retrospective analysis of 34 patients undergoing CRS and HIPEC, authors reported that, in patients with liberal intraoperative fluid replacement, a high postoperative complication rate, especially pulmonary, was observed.[14] In a recent study on 133 patients, intraoperative fluid rate was significantly associated with increased morbidity.[15] The patients receiving >15.7 mL/kg/h of intraoperative fluids experienced a 43% increase in complications as compared to those receiving less than this amount.[15] On further analysis, intraoperative fluid rate (coefficient = 0.97, $P = 0.02$) and estimated blood loss (coefficient = 0.02, $P = 0.002$) were found to be the only independent predictors of increased comprehensive complication index, an index of perioperative morbidity, particularly in patients

who receive intraoperative fluids >15.7 mL/kg/h.[15] Restricted fluid therapy has also been reported but may be of concern for optimal tissue and renal perfusion in the background of haemodynamic perturbations during phases of CRS and HIPEC.[16] Optovolaemia is required as the extent of surgery, and patient response may vary for CRS and HIPEC. Meticulous fluid management as per goal-directed therapy appears to answer these issues.[13,14] The non-invasive cardiac output monitoring and urine output appear to be an acceptable monitoring tool in such surgeries.[17] The fluid management was guided by non-invasive continuous cardiac output monitoring with FloTrac in patients with high tumour load and patient having persistent haemodynamic perturbations in the study being published.[10] Another randomised controlled trial which studied various outcomes related to CRS and HIPEC reported that the use of a goal-directed fluid therapy using the FloTrac/Vigileo was associated with improved patient-related outcome for major abdominal and systemic post-operative complications and reduced length of hospital stay.[18] The less-invasive haemodynamic monitoring devices such as the oesophageal Doppler may be useful; however, the tool and its utility though proven in other surgical interventions but has not been assessed in CRS and HIPEC.

Intraoperative measurement of urine output is a reliable, non-invasive and a surrogate marker of renal perfusion. During the phase of HIPEC, monitoring urine output is equally important, and thus utmost vigilance is required to maintain optimal urine output. The output during this phase is not well studied or reported, but a higher volume may be required at this stage to mitigate the impact of hyperthermia on vascular dilatation and hyperthermic chemotherapeutic agent on kidney. One should aim at a minimum urine output of 0.5 mL/kg/h during cytoreduction; 4 mL/kg/h during HIPEC phase and 1–2 mL/kg/h post-HIPEC.[1,2,4] Diuretic should only be given after ensuring euvolaemia and optimal renal perfusion.

The dilemma remains about the type of fluid including appropriate choice of crystalloid or colloid. Definite evidence for choice of colloids such as starches and gelatins is not available with regard to CRS and HIPEC. The fluid administration needs to be goal directed with a combination of colloids and crystalloids with a specific therapeutic end point. A balanced fluid management protocol would maintain colloid oncotic pressure and urinary output.[10] Colloids replenish intravascular volume in a ratio of 1:1 in a fluid responsive patient and may be used to maintain Optovolaemia. Such surgeries lead to protein loss owing to ascites drainage and extensive tissue handling and cytoreduction. Hypoalbuminaemia has been associated with increased morbidity after CRS and HIPEC.[6] Albumin has been shown beneficial in patients requiring extensive surgical debulking and large volume ascites drainage and may be considered with low serum protein levels.[19,20] Thus, the dynamic state of intraoperative period requires a balance between hypovolaemia and hypervolaemia and proper management of balancing fluid during the different surgical phases.[21]

Use of vasopressors and diuretics remains other concerns. The authors have used vasopressors (dopamine, noradrenaline and adrenaline) in addition to gelatin, blood products as per need.[10] The use of dopamine as the first choice with an intent to increase renal perfusion has been described in this study.[10] The loop diuretics have been used to increase urine output to mitigate nephrotoxic insult by the chemotherapeutic agent used in HIPEC. Routine use of furosemide, mannitol or low doses of dopamine to prevent renal dysfunction is not recommended as it does not affect creatinine values during cytoreductive surgery and HIPEC.[8,13] Diuretics are required only in selected cases wherein urine output is not adequate even after adequate intravascular fluid status and renal perfusion.

TEMPERATURE MANAGEMENT

Extensive procedure of cytoreductive surgery and HIPEC carries the risk of both hypothermia and hyperthermia.[4] Normothermia maintenance is an important goal in perioperative period in patients undergoing CRS and HIPEC.[13] In another study, it was seen that the core temperature significantly decreased after the cytoreductive surgery and before HIPEC than the baseline (33.5°C ± 1.7°C and 36.5°C ± 0.6°C, respectively), then significantly increased during HIPEC (38.2°C ± 1.1°C) and persisted after completion (38°C ± 0.8°C) than before this phase.[19] In the study appearing in this issue, in patients undergoing CRS and HIPEC, the authors reported that higher delta temperature was associated with a longer duration of ventilation and intensive care unit stay.[10] The sequential temperature changes exacerbate systemic effect and remain additive. Hypothermia during the initial phase of cytoreduction has marked deleterious

effects on metabolic functions, coagulation profile, cardiac morbidity and anti-inflammatory cascade. This should be managed with forced air warming with blankets and blood/fluid warmers. Hyperthermia during the HIPEC phase results in increase in the metabolic rate, resulting in increase in heart rate, end-tidal carbon dioxide, metabolic acidosis, elevated serum lactate value, ventilator induced acute lung injury, peripheral vasodilatation and increase in oxygen demand. Hyperthermia induced peripheral vasodilatation results in a reduction of the mean arterial pressure with reflex further increase in heart rate. The hyperthermia can be prevented by turning off of the warming devices, use of cold intravenous fluids and use of cooling mattress. If these measures fail and core temperature ≥39°C, then perfusionist needs to reduce the instillate temperature.

FUTURE RESEARCH

The present evidence with regard to fluid management and temperature control is based on primarily the retrospective data. Prospective randomised trials are required for various domains of CRS and HIPEC for appropriate fluid protocol, its monitoring and tool guide for fluid management and the impact of temperature fluctuations during the surgical intervention.

CONCLUSION

To conclude, anaesthesiologist has to be well aware of fluid losses and its replacement, protein losses and systemic hypo-/hyperthermia in patients undergoing CRS with HIPEC. It is essential to maintain and restore normothermia and normovolaemia to prevent morbidity. Goal directed rather than liberal or restrictive fluid infusion using appropriate haemodynamic monitoring such as cardiac output monitors and urine output is required. Balanced fluid management including crystalloids and colloids albumin appears to be appropriate. Temperature monitoring and its appropriate control during both phases of cytoreduction (hypothermia) and HIPEC (hyperthermia) are of utmost importance.

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Announcement

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