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Variations in Intraoperative Fluid Administration during Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Purpose: To examine the variability of fluid administration during Cytoreductive Surgery (CRS) with Hyperthermic Intraperitoneal Chemotherapy (HIPEC).

Methods: This retrospective cohort study included consecutive patients undergoing CRS/HIPEC between 2010 to 2017 at St. George Hospital, Sydney. Anaesthetic charts were reviewed and volumes of crystalloids, albumin and blood products were extracted. Results were stratified by anaesthetist, tumour type and tumour volume as depicted by the Peritoneal Cancer Index (PCI).

Results: Twelve consultant anesthetists were involved in the surgeries of 335 patients. The median total volume of Intraoperative Fluid (IOF) administered per case was 11050 mL (range, 3000 to 45700) at a rate of 17 ml/kg/hr (Interquartile Range [IQR], 12 to 23). The median volume of blood products administered was 3330 ml (IQR, 1700 to 6400) at a rate of 5 ml/kg/hr (IQR, 3 to 9). Over 7200 units of blood products were used in all surgeries. IOF rates varied substantially with PCI. There was a clear linear relationship seen with every increase in PCI by one point resulting in an increase of 0.2 ml/kg/hr fluid ($p<0.001$). Equally, the proportion of blood products increased with increasing PCI at the cost of crystalloid and albumin administration. When comparing tumour types, the median IOF rate was almost double in colorectal cancer compared to other tumour types ($p<0.004$). There was significant variation in the rate of blood products administered between individual anesthetists ($p<0.001$).

Conclusion: To our knowledge, this is the first detailed report on the volumes and types of fluids administered during CRS/HIPEC. Outcome analyses will facilitate an informed discussion regarding standardization of treatment and fluid administration protocols for these complex patients.

Keywords: Peritoneal carcinomatosis; Cytoreductive surgery; Intraperitoneal chemotherapy; Intraoperative fluid management; Anesthetics

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Introduction

Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS/HIPEC) has emerged as an important surgical treatment option for peritoneal carcinomatosis and is now performed at multiple institutions worldwide. The surgeries are extensive and the majority of cases involve removal of most of the peritoneum, multiple visceral resections and intestinal anastomoses followed by perfusion of hyperthermic chemotherapy in the abdominal cavity [1].The extent of physical and chemical trauma results in immense fluid shifts requiring fluid and blood replacement that is hugely variable depending on the extent of surgery. This poses a complex challenge in Intraoperative Fluid (IOF) management. There is no standardized approach to IOF administration in CRS/HIPEC and so fluid and blood product administration is currently determined by the anesthetic and surgical teams based on factors such as hemodynamics, blood loss and markers of coagulation [2-4].

The impact of IOF management on patient outcomes in CRS/HIPEC is poorly understood due to a lack of well-controlled studies. The recent paradigm supported a more restrictive approach to IOF management in general surgical patients especially when administered as goal-directed therapy [5-9]. However, a more recent large-scale randomized study suggested that long-term outcomes do not differ between liberal and restrictive strategies [10]. No well-defined approach for fluid management in CRS/HIPEC exists and thus our study sought to look at the patterns of IOF patients undergoing CRS/HIPEC at a high-volume institution to help inform future discussions on how to best manage these patients.

Methods

Patient selection and data collection

All patients undergoing CRS/HIPEC between 2010 to 2017 at St George Hospital were captured in a prospectively maintained database. Anesthetic charts of the primary procedures were retrospectively reviewed and surgical cases with complete data on IOF administration identified. The anesthetist was assigned an anonymised identifier for each case. Anesthetists performing less than 5 cases during the mentioned time frame were excluded.

Preoperative data collected included age, sex, weight, American Society of Anesthesiologists (ASA) physical status classification score as well as pre-operative serum albumin and hemoglobin. Intraoperative variables collected included volumes of crystalloids, 4% albumin, Packed Red Blood Cells (PRBCs), Fresh Frozen Plasma (FFP), cryoprecipitate and platelets administered as well as tumour type and tumour volume as depicted by the Peritoneal Cancer Index (PCI) [11].

Statistical analysis

IOF administration rates were calculated in milliliters per kilogram per hour (mls/kg/hr) to control for patients' weight and operative time. Results were stratified by anesthetists and their experience in CRS/HIPEC, tumour type and tumour volume. Continuous variables were compared using Student's t-test, Wilcoxon rank sum test, one-way Analysis of Variance (ANOVA) or Kruskal-Wallis tests as appropriate. Where necessary, log-transformation of data was performed to achieve normal distribution. Differences between proportions derived from categorical data were compared using Pearson's χ^2- or Fisher's exact test where appropriate. Data is reported as median with Interquartile Range (IQR) unless denoted otherwise. All P-values <0.05 were regarded as statistically significant and all analyses were performed using R Statistical Packages [12].

Results

Patient demographics

Twelve's anesthetists were involved in the treatment of 335 patients. The mean age of patients was 54 years (range, 14 to 81) and 185 (55%) patients were women. 224 (67%) of patients had an ASA score of 3 or 4. The mean pre-operative albumin was 35 (range, 16 to 45) and hemoglobin 129 g/L (range, 74 to 165). The majority of cases were identified as appendiceal cancer, 200 (60%) patients. 76 (23%) patients had diagnoses of colorectal cancer, 30 (9%) of mesothelioma, 13 (4%) of ovarian and 16 patients had other underlying tumour pathologies. The mean PCI was 24 and the mean operative time was 9.4 h (Table 1).

Fluid administration in CRS/HIPEC

The median total volume of fluid administered per case was 11050 mL (IQR8500 to 15200) at a rate of 17 ml/kg/hr (IQR, 12 to 23). In all cases, the majority of fluid administered was crystalloid plus albumin with median volumes of 7500 ml (IQR, 6000 to 9000) at a rate of 11 ml/kg/hr (IQR; 9 to 14). A considerable volume of blood products were also administered, the median being 3330 ml (IQR, 1700 to 6400) at a rate of 5 ml/kg/hr (IQR, 3 to 9). This equated to a total of over 7200 units of blood products in all cases during the mentioned time frame.

Table 1: Patient demographics and perioperative data.

Characteristic	Value
Number of patients	335
Median age, years (IQR)	56 (46 to 63)
Sex	
Female, No (%)	185 (55%)
Male, No (%)	150 (45%)
Median weight, kg (IQR)	75 (64 to 88)
Median preoperative serum haemoglobin, g/L (IQR)	130 (119 to 140)
Median preoperative serum albumin, g/L (IQR)	37 (33 to 39)
ASA, No (%)	
1-2	104 (31%)
3-4	224 (67%)
Missing data	7 (2%)
Median total operative time, hours (IQR)	9.3 (8 to 10.7)
Type of malignancy, No (%)	
Low-grade appendiceal	81 (24%)
High-grade appendiceal	119 (36%)
Colorectal cancer	76 (22%)
Ovarian cancer	13 (4%)
Mesothelioma	30 (9%)
Other	16 (5%)
Median PCI (IQR)	24 (15 to 33)

Abbreviations: IQR: Interquartile Range; ASA: American Society of Anesthesiologists; PCI: Peritoneal Cancer Index

Relationship of intraoperative fluids administration and tumour volume

There were significant correlations between PCI and the volume and rates of different fluid types administered (Figure 1). For every increase in PCI by one point the volume of IOF administered increased by 345 ml at a rate of 0.18 ml/kg/hr (p<0.001). This increase was completely accounted for by an increase in administration of blood products of 240 ml or 0.21 ml/kg/hr with every PCI increase of one point (p<0.001). Interestingly, the rate of crystalloid plus albumin administration decreased by a small amount with increasing PCI, -0.04 ml/kg/hr per one PCI point (p=0.07). The highest PCI group (PCI>35) received a significantly higher volume and rate of blood products than all other PCI groups. For example, patients with a PCI>35 received a mean of 8000 mL of blood products at a rate of 9.9 ml/kg/hr where as patients with a PCI of 31 to 35 received a mean of 4300 mL blood products at a rate of 5.3 ml/kg/hr (p<0.003). Subsequently, in patients with a PCI>35 blood products comprised a greater proportion of the total fluid administered (47%) compared to all other patients including the PCI 31 to 35 group (35%). Table 2 and Figure 2 demonstrate the variation in volume and proportions of different fluid types administered across the PCI categories. Given

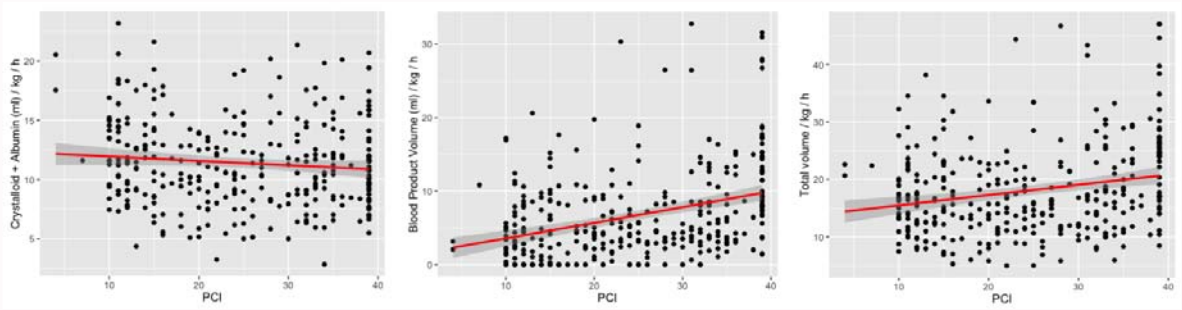

Figure 1: Variance in administration rates of different fluid types by PCI (Peritoneal Cancer Index).

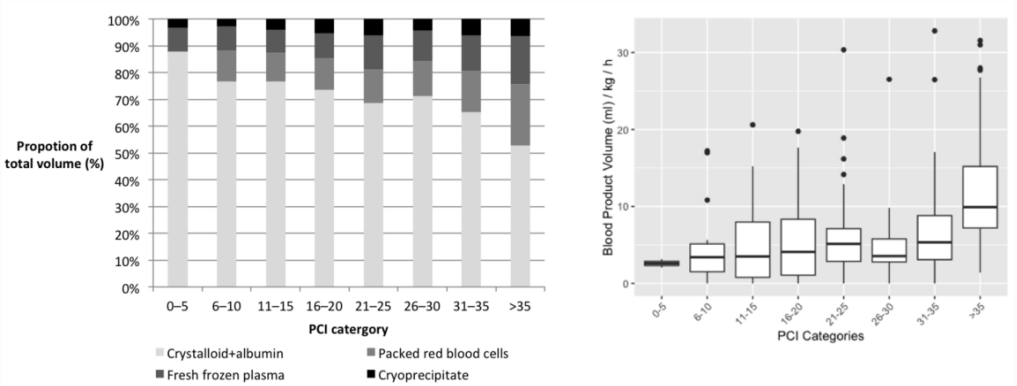

Figure 2: Proportion of fluid types administered by PCI (Peritoneal Cancer Index) category and rate of blood products administration by PCI category.

Table 2: Mean volumes (millilitres) and proportions (percent) of fluid types by PCI.

	Crystalloid+Albumin		Packed red blood cells		Fresh frozen plasma		Cryoprecipitate	
PCI	**Volume (SD)**	**% Total (SD)**	**Volume (SD)**	**% Total (SD)**	**Volume (SD)**	**% Total (SD)**	**Volume (SD)**	**% Total(SD)**
0 to 5	5000(0)	88(10)	0(0)	0(2)	500(0)	9(0)	200(200)	3(3)
6 to 10	6880(400)	78(3)	1170(250)	12(1)	970(270)	9(2)	310(110)	3(1)
11 to 15	7130(290)	76(2)	1270(150)	11(2)	970(120)	8(1)	480(70)	4(1)
16 to 20	6800(290)	74(3)	1460(280)	12(1)	1140(160)	9(1)	640(90)	5(1)
21 to 25	7500(270)	69(2)	1610(200)	12(1)	1710(270)	13(1)	770(100)	6(1)
26 to 30	6970(340)	71(2)	1450(200)	13(1)	1260(160)	12(1)	530(120)	4(1)
31 to 35	8630(260)	65(2)	2400(260)	15(1)	2050(210)	13(1)	910(110)	6(1)
>35	9970(510)	53(2)	5090(470)	23(1)	3960(380)	18(1)	1500(160)	7(1)

Abbreviations: SD: Standard Deviation; % Total: Proportion of the total fluid administered

the significant variation of IOF volumes between PCI groups we attempted to normalize fluids administration rates by PCI to assess the relationship of tumour type and anesthetic experience with IOF rates despite the level of disease.

Relationship of intraoperative fluids administration and tumour type

When comparing tumour types the median IOF rate was significantly higher in colorectal cancer once corrected for tumour volume. This was due to the median crystalloid plus albumin administration rate being significantly higher in cases of colorectal cancer (0.84 ml/kg/hr/PCI) when compared with low and high-grade appendiceal (0.38, 0.35), mesothelioma (0.44) and ovarian cancer (0.44) ($p<0.004$). In addition, higher rates of blood product administration were observed in colorectal and 'other' tumour types, but these were not statistically significant in all cases.

Variability of intraoperative fluids administration by anesthetist

The rate of crystalloid plus albumin administration between individual anesthetists was consistent however there was significant variation in the rate of blood products administered ($p<0.001$). When data was stratified into groups based on the number of cases performed by anesthetists, those anesthetists with the most experience (>45 cases) administered 1.6 ml/kg/hr less (approximately 250 mls/case) crystalloids plus albumin when compared to anesthetists with the least number of cases ($n<15$; $p<0.001$). Equally, anaesthetists with more cases tended to transfuse more blood products per case (3700 mls *vs.* 2550 mls), although this finding was not of statistical significance, when normalizing for patient weight, operative time and/or PCI (Figure 3).

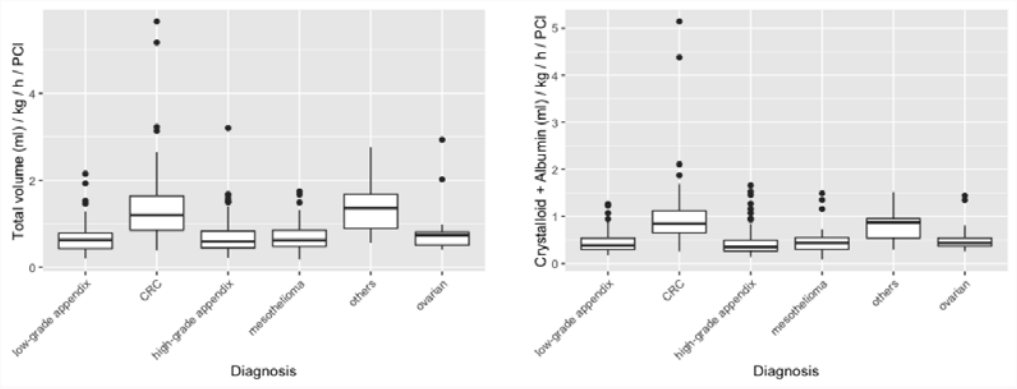

Figure 3: Variance in the rate of total fluid administered and crystalloid+albumin administered across different tumour types.

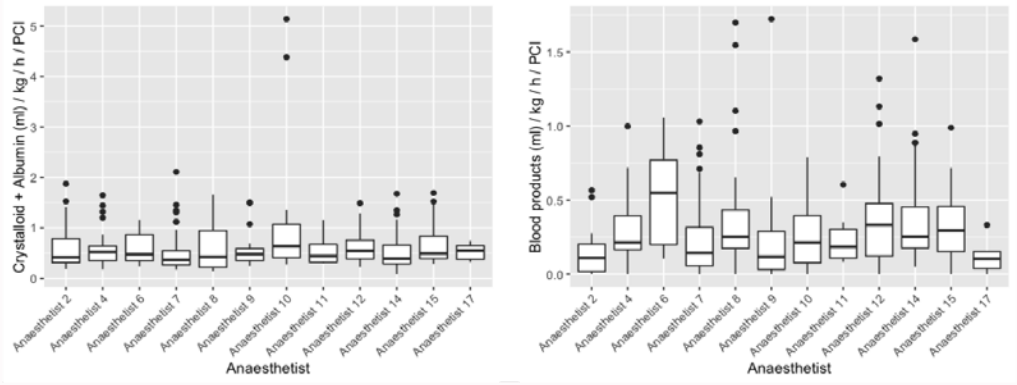

Figure 4: Variance in rates of crystalloid+albumin and blood product administration between individual anaesthetists, normalised for PCI (Peritoneal Cancer Index).

Discussion

IOF management in CRS/HIPEC is inherently challenging because the surgeries are lengthy and there is often significant blood and insensible fluid loss due to extensive tissue dissection and resection [2]. Additionally, the hyperdynamic circulatory state observed in response to chemotherapy perfusion represents unique challenge in IOF management [3]. To our knowledge, this is one of the first studies providing an in-depth description of the volumes and types of fluids administered during CRS/HIPEC in a high-volume peritoneal surface oncology referral unit.

The outcomes for patients undergoing major abdominal surgery can be heavily influenced by IOF management [7,13]. The most serious consequences of inadequate fluid resuscitation include circulatory collapse and multi-organ failure but less dramatic under-resuscitation can still be harmful. Insufficient oxygen delivery to tissues and reduced gut perfusion is associated with poorer outcomes in major surgery [14-16]. Administration of excess fluid during major surgery can be just as detrimental having deleterious effects on multiple systems. Excess fluid may increase postoperative cardiac morbidity [17,18], lead to pulmonary complications including pulmonary edema and abdominal complications such as abdominal compartment syndrome and post-operative ileus [18,19,21-24]. Holte et al. describes associations of excess perioperative fluid with decreased tissue oxygen tension leading to poor wound healing as well as impairments in coagulation [18].

Given that too much or too little fluid can have such profoundly negative consequences for patients an evidence-based approach to IOF management is crucial. Results from multiple small studies suggest that a more judicious approach to fluid management in major elective surgery leads to better outcomes. In a systematic review and meta-analysis of 12 randomized-control trials with 1397 patients, Schol et al. [7] concluded that a restrictive fluid policy in elective major surgery, when compared with a liberal fluid policy, results in a 35% reduction in the number of patients with a complication and may lower hospital length stay [7]. However, in an earlier meta-analysis of 856 patients undergoing major abdominal surgery specifically, a perioperative fluid restriction did not appear to significantly reduce the major complication rate or length of hospital stay [25]. The relief trial, the largest randomized study comparing restrictive and liberal fluid therapy for major abdominal surgery, showed no difference in disability-free survival at 1 year [10]. Conflicting evidence justifies the need for further well-controlled studies.

Despite the unique and complex challenges of hemodynamic management during CRS/HIPEC, data supporting a specific approach to IOF administration in this type of surgery is lacking. A meta-analysis of randomized-control trials investigating goal-directed fluid therapy in elective major abdominal surgeries from 1995 to 2014 did not identify any CRS/HIPEC patients in 23 studies of 2099 patients [13]. Only one randomized-control trial comparing different fluid management strategies in CRS/HIPEC exists [26]. It suggests that a restrictive fluid therapy regimen combined with goal-directed therapy reduces the incidence of major abdominal and systemic complications and length of stay. A retrospective study of 133 patients undergoing CRS/HIPEC also concluded that increased IOF was associated with an increase in perioperative morbidity [3].

With building evidence for goal-directed therapy the benefits of a standardized approach to IOF administration during CRS/HIPEC are apparent [27]. Our study supports this by identifying significant variations in the IOF that patients are receiving. Rates of IOF administration ranged from 5 to 47 ml/kg/hr (IQR, 12 to 23) reflecting huge variations in rates of crystalloid plus albumin and blood product administration. Even considering the variability in fluid requirements to maintain hemodynamic stability in a diverse group of patients does not explain the wide range of fluid administration rates. The variability may be partially explained by the differing practices between individual anesthetists as there was significant variation in the rate of crystalloid and blood product administration by individuals. More experienced anesthetists were more judicious with fluid administration. Other retrospective studies identified similar variability in IOF rates during CRS/HIPEC. Schmidt et al. [28] found that in 78 patients, the median IOF rate was 22.2 ml/kg/hr [28]. This figure differs dramatically to findings by Kajdi et al. [4] where in 54 patients the IOF rate was approximately 10 ml/kg/hr. More recently, Eng et al. [3] identified a significant spread of IOF rates among 133 CRS/HIPEC patients, the median being 15.7 ml/kg/hr (IQR, 11.3 to 18.7). The considerable variability in IOF rates in our study and others highlights the need to establish a well-defined approach to IOF management in CRS/HIPEC patients.

The type of intraoperative fluid patients are receiving has been a topic of interest in recent years with a focus on the effect of blood product administration. Most of the data associates blood products with poorer outcomes. Large-scale uncontrolled retrospective studies of general surgical patients conclude that intraoperative blood transfusions lead to increased mortality and morbidity in a dose-dependent manner [29,30]. This association appears to exist for CRS/HIPEC patients more specifically [4], with a retrospective analysis of 935 patients linking transfusion of over 5 units of PRBCs with poor perioperative outcomes including mortality and high-grade morbidity [31]. Our study concluded that patients with a higher PCI received a higher rate of blood products. Patients PCI>35 received double the volume of blood products than other patients. This suggests that more blood loss occurs per unit time in higher PCI cases but whether PCI-normalized rates of blood product transfusion also lead to worse outcomes is currently unclear. This is vital information for our institution and others, as it can help predict which patients are likely to receive more blood products and are thereby at increased risk of perioperative morbidity and mortality. It may also encourage anesthetists to be more judicious with blood products in high PCI cases and allow a permissive hypovolemia or anemia given the potential relationship between blood product administration and poorer outcomes.

Patients with colorectal cancer received crystalloid and albumin at twice the rate of patients with appendiceal cancer, mesothelioma or ovarian cancer. IOF management of different tumour types in CRS/HIPEC does not appear to have been investigated previously. Our study demonstrates a clear difference in the administration of certain fluid types depending on the diagnosis, even once adjusted for PCI. The reasons for this are not clear but one inference is that the rate of insensible fluid loss is higher during CRS/HIPEC for patients with colorectal cancer. Future prospective studies should aim to establish the IOF requirements of certain patient groups and correlate these with outcomes so that optimal perioperative fluid management can be achieved.

Limitations

As with every retrospective analysis our study is prone to limitations. Firstly, our data set was not entirely complete as information was obtained from medical documentation and thus this study is prone to selection bias. Secondly, despite being a high-volume CRS/HIPEC unit we have a large spread of anesthetists involved in each case, each of whom comes with varying levels of experience and different training backgrounds (including cardiac anesthesia, trauma, etc.) thus contributing to some of the variability seen between cases. Additionally, our unit's case-volume has steadily increased since 2010 and with that the anesthetic and surgical experience has increased dramatically. This is likely to have resulted in changing practices of IOF management and be reflected in the fact that anesthetists having performed more cases were more likely to use blood products for resuscitative purposes, although this remains hypothetical (a detailed analysis of factors contributing to blood product administration patterns is pending). However, when checking our data for variations stratified by treatment year we could not find a significant relationship with regards to type or proportion of IOF types (Figure 4). Finally, shorter cases may appear to have higher than expected IOF rates as many patients received 2000mL bolus of crystalloid at the commencement of surgery as part of established practice with many of the involved anesthetists-an aspect currently undergoing investigation given the resulting data of this contemporary IOF audit.

Conclusion

There appears to be significant variability in the IOF rates of CRS/HIPEC patients, supporting the need for a well-defined approach to this aspect of management. It would also be useful to further investigate the association between IOF rates and outcomes. The trends identified at our institution may be useful for surgeons and anesthetists to predict IOF requirements and any subsequent increase in risk of morbidity and mortality and to allow for an informed discussion on best management practices for these complex patients.

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