High intra-abdominal pressure during hyperthermic intraperitoneal chemotherapy (HIPEC) following cytoreductive surgery (CRS) for peritoneal surface malignancies

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ABSTRACT

Objective: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) represent a mainstay of treatment for peritoneal malignancies. There is evidence that HIPEC using high intra-abdominal pressure (IAP) results in increased tissue penetration, although its safety profile remains relatively unknown. We thus aim to evaluate differences in intra- and post-operative outcomes in patients undergoing CRS-HIPEC with different levels of IAP.

Methods: This pilot prospective cohort study was conducted from January 2020 to February 2021 with patients undergoing CRS-HIPEC. Low IAP during HIPEC was defined as <18 mmHg and high IAP as ≥18 mmHg. Data was collected on patient and tumor characteristics, intra-operative clinical and biochemical parameters, and immediate post-operative outcomes.

Results: 40 patients underwent CRS-HIPEC (n low = 20, n high = 20). Median IAP in the low and high IAP groups were 12.0 and 19.0 mmHg respectively. During HIPEC, both groups experienced increase in heart rate, central venous pressure, end tidal CO2, temperature, and serum glucose, with decrease in mean arterial pressure and base excess. There were no significant differences in hemodynamics between the 2 groups. Mild electrolyte derangements and a decrease in hemoglobin were noted in the high IAP group but were of small magnitude. Post-operatively, high IAP did not result in increased rate of complications, time to full feeds, ICU or total hospital stay.

Conclusions: High IAP in HIPEC is well tolerated and did not result in additional adverse events.

Introduction

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is a treatment that is increasingly being employed in the treatment of peritoneal carcinomatosis (PC), such as those arising from mesothelioma, colorectal, appendiceal, and ovarian cancer [1]. It involves the surgical removal of macroscopic tumor via systematic peritonectomies and resection of associated visceria, followed by the direct intraperitoneal administration of heated chemotherapy to target any residual microscopic disease [2]. It is therefore able to circumvent the limitations of conventional systemic chemotherapy of inadequate penetration through the plasma-peritoneal barrier. This allows for more favorable pharmacokinetics with the administration of higher doses of chemotherapeutics direct to the peritoneal cavity with limited systemic toxicity, before the development of any post-operative adhesions that have been shown to be a milieu for entrapment of cancer cells eventually giving rise to disease recurrence [3].

Several studies have shown that the application of HIPEC at higher intra-abdominal pressure (IAP) can increase local drug uptake into tumor and peritoneal tissues, in terms of both depth of penetration as well as total drug concentration, without a concomitant rise in systemic absorption [4–6]. Such an effect was demonstrated to be the most pronounced when used in combination with hyperthermia, suggesting a possible synergistic effect [7]. In a murine model of PC, high IAP was further shown to be associated with increased survival [4]. The mechanism of action is thought to involve overcoming high interstitial fluid pressures in solid tumors through the establishment of a hydrostatic gradient [8]. Should it also prove its effectiveness in human trials,
high IAP may represent a strategy that augments currently accepted methods of HIPEC.

However, the potential of high IAP needs to be balanced with its impact on hemodynamic and respiratory parameters, which could render the procedure unsafe. Traditionally, raised IAP beyond 12 mmHg has been considered to constitute intra-abdominal hypertension, with progression to abdominal compartment syndrome as IAP reaches 20 mmHg and above with new onset organ failure [9]. High IAP, particularly if arising acutely or of a significant magnitude, is thought to have a detrimental effect on organ perfusion and function that can affect multiple intra- and extra-abdominal systems. Therefore, the aim of the current pilot study is to evaluate the safety of high IAP by assessing its effect on intra-operative parameters as well as post-operative outcomes in patients undergoing CRS-HIPEC before the commencement of a full scale randomized controlled trial.

Methods

Study design

This prospective cohort study has been approved by the Singapore Health Services Centralized Institutional Review Board, with informed consent obtained from all included participants. Patients with isolated and histologically proven peritoneal carcinomatosis undergoing treatment with CRS-HIPEC at the National Cancer Center Singapore were prospectively recruited from January 2020 to February 2021. Additional eligibility criteria included complete cytoreduction with residual disease <2.5 mm, an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, as well as fitness for surgery on pre-operative assessment. Those with distant metastases evaluated on computed tomography (CT) or positron emission tomography-CT were excluded. Data collected included demographic and clinical characteristics, intra-operative parameters as well as post-operative outcomes.

CRS and HIPEC

CRS was performed using the Sugarbaker technique, with systematic peritonectomies and resection of macroscopic disease and involved viscera to achieve complete cytoreduction. The extent of disease was measured using the Peritoneal Cancer Index (PCI) and the completeness of cytoreduction (CC) by the CC score. HIPEC was administered for 60 min using the closed abdomen technique via either the Belmont Hyperthermia Pump (Belmont Instrument Corporation, Billerica, MA, USA) or the RanD Performer HT (RanD, Medolla, Italy) through a single inflow catheter, with drainage through four intra-abdominal drains. Temperature was monitored using probes attached to the inflow and outflow catheters with the circuit maintained at 42°C. Either cisplatin or mitomycin-c (dosed using a body surface area based regimen) was used with peritoneal dialysate as carrier solution, depending on primary tumor histology.

IAP during HIPEC was measured with the modified Cheatham and Safcsak intra-vesical method [10]. Briefly, three three-way stopcocks were connected serially between the Foley catheter and its drainage tubing, each connected to a standard intravenous infusion set with 1 litre normal saline, a 60 ml syringe, and a pressure transducer via a rigid pressure tubing. The system was flushed with normal saline and the transducer was zeroed at the symphysis pubis. IAP measurements were taken by clamping the urinary draining tubing and instillation of 100 ml of normal saline into the bladder to create a conductive fluid column. A high IAP protocol was instituted from the 21st patient onwards where we maintained IAP at a target level between 18 to 22 mmHg by increasing the volume of perfusate. For purpose of analysis, low IAP was defined as <18 mmHg and high IAP as ≥18 mmHg. These cutoff values had been derived from previous similar works in this area [5].

Intra-operative anesthetic management and continuous parameters monitoring were performed by the dedicated anesthetist. General anesthesia was typically induced using propofol, rocuronium and a target-controlled infusion of remifentanil, then maintained using a volatile anesthetic such as desflurane with remifentanil and as-needed atracurium. Parameters of interest in the current study include heart rate (HR), mean arterial pressure (MAP), central venous pressure (CVP), respiratory rate (RR), end tidal CO2 (ETCO2), as well as temperature. For analysis, data was collected at 7 time points—the first and second time points at the start and end of CRS, 4 subsequent time points in 15 min increment during HIPEC, and the final time point 15 min post-HIPEC. Blood gas analysis and serum chemistry were obtained via arterial blood samples before and after HIPEC administration, and included that of hemoglobin, sodium, potassium, calcium, glucose, pH, pO2, pCO2, as well as bicarbonate.

Patients were transferred to the surgical intensive care unit (ICU) or high dependency unit post-operatively for monitoring, with subsequent transfer to the general ward at the discretion of the surgeon and intensivist in charge. 30-day post-operative morbidity was graded using the Common Terminology Criteria for Adverse Events Version 5.0 classification [11].

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics Version 23 (IBM Corporation, Armonk, NY, USA). Independent-samples t-tests were used for comparisons between continuous variables and chi-square tests for comparisons between categorical variables. Paired-samples t-tests and linear mixed models were used to analyze within and between groups of repeated measures for the assessment of intra-operative parameters at different time points. IAP was reported as median with interquartile range and compared using the Mann-Whitney U test due to a bimodal distribution.

Sample size calculation

Assuming a morbidity rate in CRS-HIPEC of around 40% [12], at least 20 patients per arm were required to detect a two-fold increase in complications rate in the high IAP group at
80% power with a one-sided type I error rate of 5%. While this is a fairly large estimated effect size, we note that the impact of a high IAP on post-operative complications has not been adequately described in clinical studies and the variance in our single center study was expected to be relatively modest. As this is a pilot study, we were also limited by the availability of funding, study duration, as well as the annual CRS-HIPEC caseload at our institution.

### Results

A total of 40 patients underwent CRS-HIPEC, with 20 patients each in the low and high IAP groups. The baseline demographic and clinical characteristics of study participants are summarized in Table 1. There were 20 males and 20 females, with a mean age of 61.6 years. Primary tumor histologies include colorectal (67.5%), appendiceal (17.5%), as well as others (15.0%). 47.5% had primary disease. The two groups were not significantly different from each other with respect to demographic and clinical factors, apart from the primary tumor histology where colorectal cancer represented 50% of the low IAP group and 85% of the high IAP group.

Intra-operatively, there were no differences between the two groups in terms of extent of visceral resection, estimated blood loss, PCI, CC score, or fluid requirements; patients in the low IAP group had a longer average duration of surgery (Table 2). The average PCI was 5.6 ± 4.8, and 97.1% of patients underwent CC-0 cytoreduction. Median IAP achieved during HIPEC in both groups, but they were not significantly different from each other. RR remain unchanged (MD = 0.2 ± 1.5, p = 0.40), while ETCO2 (MD = 1.9 ± 2.1 mmHg, p < 0.01) and temperature (MD = 1.9 ± 0.8, p < 0.01) increased.

Across both groups, there was also a fall in in base excess (MD = −3.5 mmol/L ± 2.4, p < 0.01) and increase in serum glucose (MD = 3.4 mmol/L ± 1.4, p < 0.01) when comparing before and after HIPEC, which was again not significantly different between the groups. A decrease in hemoglobin was noted in the high IAP group (MD = −0.8 g/dL ± 0.7, p < 0.01) groups, which was not seen in the low IAP group (MD = −0.3 g/dL ± 1.2, p = 0.47). Slight changes in various other electrolytes were additionally noted in the high IAP group but were unlikely to be of clinical significance given the small magnitude of change. Post-operatively, high IAP did not result in increased rate of complications, time to full feeds, ICU or total hospital stay (Table 4).

### Discussion

CRS-HIPEC is a modality that has been used to good effect in PC of certain origins since the gradual adoption of locoregional therapies as a key pillar of treatment. While the technique of CRS has been standardized since the original description by Sugarbaker, there remains debate in how HIPEC should be optimally delivered, with variations in technique, drug regimen, duration, temperature, as well as IAP [13,14]. While early evidence suggests that increased IAP may be associated with increased local drug uptake and efficacy, how it affects critical intra- and post-operative parameters and outcomes remain unclear. The considerations of raised IAP in HIPEC mainly translate from existing knowledge in intra-abdominal hypertension and abdominal compartment syndrome, which are understood to pose significant risk of hypoperfusion and failure to various intra- and extra-abdominal organ systems secondary to their effects on arterial, venous, as well as microcirculatory blood flow [15]. In our current study, we report that an IAP of around 20 mmHg during HIPEC was well tolerated with intra- and post-operative outcomes that were not significantly different from normal-range IAP HIPEC of around 13 mmHg, apart from mild changes in hemoglobin level and serum chemistries.

Physiologically, an increased IAP can lead to cranial displacement of the diaphragm with compression of the heart, leading to reduced cardiac contractility [16]. Increased afterload and reduced venous return may also arise from compression of the descending aorta and inferior vena cava that further reduces cardiac output. Additionally, peripheral vasodilation from a rising body temperature during HIPEC results in a decrease in systemic vascular resistance, and a compensatory tachycardia occurs in order to maintain cardiac output [17]. Accordingly, an increase in HR with a concomitant decrease in MAP represent some of the most common physiologic changes reported during HIPEC in previous studies, which are well corroborated by our findings [18]. We echo the observations of Reis et al. (2020) that further changes in HR or MAP were not detected with increasing IAP, perhaps suggestive of a plateauing effect with good hemodynamic tolerance at least up to a level of 20 mmHg IAP [19]. While it has been demonstrated that it is possible to negate the drop in MAP using a greater volume of intra-
operative fluid resuscitation, more recent evidence suggests that a conservative approach to fluid management is associated with a lower rate of complications and liberal fluid therapy is therefore not usually recommended [7,20–22].

An upward displacement of the diaphragm also leads to the transmission of around 50% of IAP to the thoracic cavity. As a result, all measurements on intrathoracically measured pressures such as CVP are raised and lung volumes (specifically the functional residual capacity) are reduced [23]. Additionally, the rising body temperature during HIPEC triggers a hypermetabolic state with increased oxygen consumption and carbon dioxide generation and is reflected in a

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**Table 2. Operative details.**

| Surgical findings          | Low IAP (n = 20) | High IAP (n = 20) | p Value |
|----------------------------|-----------------|------------------|---------|
| Duration of surgery, minutes | 425.0 (84.9)    | 358.3 (79.3)     | 0.02    |
| Visceral resections (%)     |                 |                  |         |
| Diaphragmatic peritoneectomy| 6 (30.0)        | 2 (10.0)         | 0.11    |
| Gastrectomy                | 1 (5.0)         | 0 (0.0)          | 0.31    |
| Colectomy                  | 12 (60.0)       | 13 (65.0)        | 0.74    |
| Small bowel resection      | 4 (20.0)        | 8 (40.0)         | 0.17    |
| Cholecystectomy            | 1 (5.0)         | 2 (10.0)         | 0.55    |
| Splenectomy                | 0 (0.0)         | 2 (10.0)         | 0.15    |
| Bladder resection          | 1 (5.0)         | 0 (0.0)          | 0.31    |
| THBSO                      | 2 (10.0)        | 1 (5.0)          | 0.55    |
| Estimated blood loss, ml   | 488.9 (359.1)   | 514.7 (358.7)    | 0.83    |
| PCI                        | 5.8 (5.7)       | 5.4 (3.8)        | 0.80    |
| CC score (%)               |                 |                  | 0.32    |
| CC-0                      | 17 (100.0)      | 17 (94.4)        |         |
| CC-1                      | 0 (0.0)         | 0 (0.0)          |         |
| CC-2                      | 0 (0.0)         | 1 (5.6)          |         |
| Intra-operative fluids     |                 |                  |         |
| Crystalloids, ml           | 3608.6 (1848.8) | 3192.5 (946.8)   | 0.38    |
| Colloids, ml               | 25.0 (111.8)    | 0.0 (0.0)        | 0.32    |
| Albumin, ml                | 845.4 (455.4)   | 912.5 (521.1)    | 0.67    |
| HIPEC                      |                 |                  |         |
| Drug                       | 0.63            |                  |         |
| Mitomycin-c (%)            | 17 (85.0)       | 18 (90.0)        |         |
| Cisplatin (%)              | 3 (15.0)        | 2 (10.0)         |         |
| Temperature, °C            | 41.6 (0.9)      | 42.0 (0.3)       | 0.07    |
| Duration, minutes          | 60.0 (0.0)      | 60.0 (0.0)       | –       |
| Median IAP, mmHg (IQR)     | 12.0 (12.0—13.5)| 19.0 (18.0—20.8) | <0.01   |
| Perfusate volume, liters   | 3.4 (1.0)       | 4.9 (7.2)        | 0.52    |

CC: completeness of cytoreduction; FFP: fresh frozen plasma; HIPEC: hyperthermic intraperitoneal chemotherapy; IAP: intra-abdominal pressure; IQR: interquartile range; PCI: peritoneal cancer index; PCT: packed cell transfusion; THBSO: total hysterectomy and bilateral salpingo-oopherectomy.

Numbers in bold indicate p < 0.05.
Table 3. Intra-operative serum chemistry and blood gas analysis.

|                     | Low IAP (n = 20) | High IAP (n = 20) | p Value |
|---------------------|------------------|------------------|---------|
| Hemoglobin, g/dL    | 10.5 (2.1)       | 10.3 (1.4)       | 0.47    |
| Sodium, mmol/L      | 137.7 (2.3)      | 136.0 (2.8)      | 0.10    |
| Potassium, mmol/L   | 3.9 (0.5)        | 3.7 (0.4)        | 0.17    |
| Calcium, mmol/L     | 1.1 (0.1)        | 1.1 (0.0)        | 0.14    |
| Glucose, mmol/L     | 10.1 (1.8)       | 13.6 (2.0)       | <0.01   |
| pH                  | 7.35 (0.04)      | 7.31 (0.05)      | 0.02    |
| pCO2, mmHg          | 41.5 (2.0)       | 40.6 (5.7)       | 0.46    |
| pO2, mmHg           | 142.7 (80.7)     | 164.4 (59.8)     | 0.17    |
| Bicarbonate, mmol/L | 23.2 (1.6)       | 20.4 (2.0)       | <0.01   |
| Base excess, mmol/L | -2.8 (2.3)       | -5.8 (2.3)       | <0.01   |

HIPEC: hyperthermic intraperitoneal chemotherapy; IAP: intra-abdominal pressure.

Numbers in bold indicate p < 0.05.

Table 4. Post-operative outcomes.

|                     | Low IAP (n = 20) | High IAP (n = 20) | p Value |
|---------------------|------------------|------------------|---------|
| SICU stay, days     | 0.2 (0.5)        | 0.0 (0.0)        | 0.18    |
| Total hospital stay, days | 12.3 (3.9)   | 10.7 (4.3)       | 0.21    |
| Time to full feeds, days | 5.0 (2.8)    | 3.9 (1.3)        | 0.12    |
| Post-operative complications (%) | 8 (40.0)   | 3 (15.0)         | 0.08    |
| Grade I             | 3 (15.0)         | 0 (0.0)          |         |
| Grade II            | 4 (20.0)         | 2 (10.0)         |         |
| Grade III           | 1 (5.0)          | 1 (5.0)          |         |
| Grade IV            | 0 (0.0)          | 0 (0.0)          |         |
| Grade V             | 0 (0.0)          | 0 (0.0)          |         |

IAP: intra-abdominal pressure; SICU: surgical intensive care unit.

rising ETCO2 [24]. The same process also results in elevated lactate levels leading to metabolic acidosis, which is consistent with our current findings. Additionally, the risk of compromised blood flow to and from visceral organs with increasing IAP can further contribute to acidosis, although such an effect was not apparent at the IAP levels measured in our high IAP group.

Large intra-operative fluid shifts also occur during CRS-HIPEC, most commonly due to blood loss, ascites drainage, fluid replacement, as well as extensive cytoreduction and surface exposure following peritonectomy [25]. Furthermore, ascites drainage, existing malnutrition, as well as the peritonectomy procedure and HIPEC themselves causing exudative protein loss from capillary leak all contribute to hypoalbuminemia and the resultant third-spacing. These factors occur on the background of significant intra-operative fluid loss seen in CRS-HIPEC, averaging 10 to 12 ml/kg/h compared to only 6 to 8 ml/kg/h in other major abdominal surgeries. A goal-directed fluid regimen to maintain normovolemia that allows for adequate perfusion of major organs while avoiding overloading the patient is generally recommended. Nevertheless, dilutional anemia and coagulopathy is still a potential risk, particularly in situations of extensive blood loss common in patients with high disease load. Coagulopathy secondary to other contributory factors during HIPEC such as temperature fluctuations, protein loss, and volume shifts can exacerbate the situation, as can pre-operative factors such as neoadjuvant chemotherapy and nutritional deficiencies [18]. Serum electrolytes disturbances can also occur due to these massive fluid shifts, as well as from the systemic absorption of chemotherapy and carrier solution itself. Intra-operative hyperglycemia occurs typically with the use of dextrose-containing carrier solutions, but is also not uncommon with other carrier solutions as a normal stress response [26]. Other metabolic derangements common during HIPEC include hyponatremia, hypomagnesemia, hypokalemia, hypocalcemia, as well as hyperlactatemia from hyperglycemia-induced glycolysis. Intra-operative monitoring of serum chemistries and hemoglobin levels should therefore be routinely performed. An expected rise in blood glucose was noted in the current study which was not affected by increasing IAP. However, mild changes in the level of sodium, potassium, calcium, as well as hemoglobin were found in the high IAP group, perhaps as a consequence of the greater amount of perfusate used and resultant fluid shifts. While modest, such effects should nevertheless be closely monitored to preempt any complications that may arise.

Postoperatively after CRS-HIPEC, patients typically require monitoring in the high dependency or ICU for an average of 1 to 2 days [24]. Most common complications arising in the post-operative period include thrombosis, septic shock, multi-organ failure, hemodynamic and respiratory instability requiring vasopressor and ventilatory support, as well as surgical complications such as anastomotic leaks, abscesses, fistulas, and prolonged ileus [27]. Considerable fluid loss up to 10 liters per day can occur in the first 72 h after surgery and further monitoring of fluid and electrolyte balance as well as coagulation profile is essential. It should also be noted that there is a theoretical risk of impaired perfusion of intra-abdominal organs particularly during high IAP HIPEC that can manifest in the post-operative period, with complications such as acute kidney injury, liver failure, as well as mucosal injury [28]. An increased IAP of around 20 mmHg used in the current study was however not found to be associated with increased morbidity or intensive care requirement.

Previous works investigating the risks of high IAP HIPEC were mostly performed in animal models, with few studies conducted in humans. An IAP of 40 to 50 mmHg has been demonstrated to be well tolerated for 2 h in a porcine model with stable hemodynamic parameters, although IAP in excess of 50 mmHg was associated with decreased cardiac index and oxygen saturation [4]. In humans, Reis et al. and Goldenshluger et al. noted that increased IAP was not associated with increased hemodynamic instability and post-operative morbidity or mortality [19,29]. Our findings are largely consistent with these works, and further adds on to the existing literature by exploring how high IAP may impact on
serum chemistry and blood gas, so as to better guide future standardization and optimization of HIPEC.

Limitations of the current pilot study include a non-randomized design, a small sample size that may preclude the identification of subtle differences, as well as the exclusion of several parameters of potential interest, such as coagulation profile and airway pressures. These results may also not be generalizable to centers with differing HIPEC protocols, such as those that use a perfusion duration of 90 min instead of 60; there may be significant differences as fluid and electrolyte exchange across the peritoneum is likely time dependent, and may be affected with a longer duration of HIPEC. Additionally, variables such as abdominal compliance remain difficult to quantify, and the precise nature of how they affect downstream factors such as amount of carrier perfusate used and overall impact on various outcomes require further clarification.

In conclusion, the current study demonstrates that an increased IAP of around 20 mmHg during HIPEC is well tolerated, with minimal impact on intra-operative parameters and post-operative outcomes. Future research should aim to delineate the limits of tolerable IAP and factors predictive of tolerance, as well as the long-term efficacy of high IAP HIPEC in the management of peritoneal disease with large scale randomized controlled trials.

Disclosure statement
No potential conflict of interest was reported by the author(s).

Funding
This study is supported by the NCCS Cancer Fund (Research) and SingHealth Duke-NUS Academic Medicine Centre, facilitated by Joint Office of Academic Medicine (JOAM). CAJO is supported by the National Research Council Transition Award [NMRC/TA/0061/2017]. All the funding sources had no role in the study design, data interpretation or writing of the manuscript.

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