Perioperative Management of Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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Abstract Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedure have demonstrated their efficacy in treating patients with diffused peritoneal carcinomatosis. As a counterpart patients face major and life threatening derangements of their hemodynamic, respiratory and metabolic physiologic balance during the surgery and in the immediate postoperative period. All these derangements demonstrated to be mild and short-lived in the majority of patients when timely addressed. Anesthesiologists, intensive care physicians and surgeons are involved in providing surveillance and organ support till the patient is effectively weaned after the operation. Moreover they are involved in pain control, metabolic and nutritional support. A malnourished state is common due to wasting syndrome from the tumor, difficult feeding and massive ascites. Lastly physicians need to be aware of the quality of life impact of this procedure.

Keywords Peritoneal Carcinosis, Perioperative, HIPEC, Hyperthermia, Cancer, Management

1. Introduction

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are extensive, life and quality of Life (QoL) threatening procedure. All the available studies covered an extremely selected population of patients usually young (less than 70 years-old), without relevant comorbidity (mainly ASA 1 or 2) and with a near to normal performance status scale (Karnofsky performance status >80%) [1, 2, 3, 4, 5]. Despite this highly selected population, morbidity and mortality are as high as 65% [1] and 12% [6], respectively. Patients face major hemodynamic,

respiratory and metabolic derangements during the procedure that need to be timely addressed; moreover anesthesiologists, as perioperative physicians and surgeons, are committed to providing surveillance and organ/metabolic support in the first period after the procedure itself. The present study aims to resume the main physiologic and metabolic changelings which can be observed in patients who undergone CRS + HIPEC procedures, added to the main indication to manage the patients pre-, intra- and post-operatively. In fact patients who undergo such an aggressive treatment have to deal with a multisystemic derangement often starting from a baseline situation which is could be non-optimal. In fact patients undergoing CRS and HIPEC could be pre-operatively hypoxic because of ascites, pleural effusion and atelectasias. HIPEC phase promotes an increasing in airway pressure and a reduction in functional residual capacity because of the diaphragm cranial shift [7, 8]. The increase of PaCO₂ and the concomitant decrease in A-a gradient and arterial pH confirm the gas exchanges deterioration [9]. During CRS the maintaining of a normovolemia can be difficult and fluid turnover exceeding the well-established 6-8 mL•kg⁻¹•h⁻¹ for major abdominal surgery [10]. 12 mL/kg-1/h-1 is the most frequent fluid requirement [3, 4, 11, 12]. HIPEC phase is characterized by an increase in heart rate [3, 12], mean central venous pressure (CVP), pulmonary artery pressure, wedge pressure [7, 12], intrathoracic blood volume index [11] and cardiac index [13, 12, 14]; on the contrary mean arterial pressure and systemic vascular resistance showed a reduction [9, 11]. The hypermetabolic state that is due to the hyperthermia is clearly demonstrated by the increase in end tidal CO₂ and in oxygen extraction and consumption [3, 15]. The use of open abdomen perfusion technique ("Coliseum Technique") and the keeping of core temperature as close to normal as possible can drastically reduce all these hemodynamic

effects of HIPEC [13]. The earliest report by Shime et al in 1994 on the effect of the hyperthermia (mean core temperature 40°C) on the hemodynamic balance showed a significant reduction in mean arterial pressure and systemic vascular resistance [15]. However in recent studies is showed as the core temperature never outreaches 38°C [3, 9].

Coagulation abnormalities are always reported. The elongation of Prothrombin Time (PT), activated Partial Thromboplastin Time (PTT) and/or pathological reduction of platelets count over the baseline are demonstrated by different studies [3, 4, 8, 9]. This dysfunction is reported to peak around 24/48 hours post-surgery [3, 8], with a restoration of a normal coagulation profile in 72 hours [3], even if baseline values are reached in almost 5 days [9]. These abnormalities could be probably explained only considering a multifactorial genesis. The two main causes seem to be the dilutional dysfunction [16] secondary to massive fluid shift and bleeding and the impairment of coagulation factors profiles due to massive ascites [17] and malnourishment. The need for transfusion (Fresh frozen plasma (FFP) or Packed red blood cells (PRBC)) is reported by Schmidt et al as high as 50% of the patients intra-operatively and 28% post-operatively [3]. Renal dysfunction, electrolyte disorder and hyperglycemia are frequently observed in the intraoperative and postoperative course [3, 7, 9, 18]. Lastly the most used pain control modality is thoracic epidural analgesia [3, 4, 8, 9, 11, 15, 19] which is reported to last longer than in major abdominal surgery (7 vs 4 days) [3].

2. Preoperative Patient Study and Management

2.1. Respiratory Status

The standard evaluation with chest X-ray and careful medical history record is enough in the majority of patients. If increased bronchial reactivity is reported pulmonary function test should be considered. Moreover due to the high incidence of hydrothorax preoperative pleural effusion evacuation and Continuous Positive Airway Pressure (CPAP) periods could be selectively considered to optimize pulmonary reserve.

2.2. Hemodynamic Balance

Many of the published trials excluded patients with an uncontrolled cardiac disease and ASA higher than 3 [3, 20]. The evaluation of the patient by a cardiologist and risk stratification is mandatory. If a history of previous heart failure is reported, cardiac evaluation (echocardiogram, stress test if there's suspected reduced coronary reserve) can be suggested. Moreover it has to be considered the possible cardiotoxicity from previous chemotherapy.

2.3. Coagulation

Standard coagulation evaluation (PT, aPTT, platelets count, list of antithrombotic drugs) is enough and no author advocates for more expensive tests. Special care is required in patients with massive ascites. Vorgias et al calculated as patients optimally debulked from ovarian cancer would need 2 units of FFP and human albumin per day for up to 3 days to theoretically replace the lost proteins [17]. In fact ascitic fluid is rich in proteins with a varying concentration of 0.5-4.2 g•100mL⁻¹ (50%-70% albumin, 30%-45% globulins, 0.3%-4.5% fibrinogen). The evacuation of up to 2-3 liters of this fluid could impair the coagulation asset.

2.4. Renal Status, Electrolyte Balance, Glycemic Control

Standard evaluation: The preoperative positioning of ureteral stents reduces the risk of urological complication [21].

2.5. Pain Control

No study specifically addresses this issue as chronic pain facilities are extremely heterogeneous around the world. However a consult with the palliative care/chronic pain physician can be useful in order to plan a follow-up of the patients. Thoracic epidural is probably the best option to perioperatively control pain. It is associated with a shorter mechanical ventilation period, from 10 to 3 hours [3], and a better patient satisfaction [22]. Anyway these patients seem to be efficiently and safely managed perioperatively even with high level of intravenous opioids. Different studies reported a percentage of patients ranging from 21% to 38% [9, 3] with no epidural catheter showing an average longer period on mechanical ventilation and ICU admission but no increase in perioperative complications. The common coagulation unbalances in these patients don't seem to affect the safe placement of a thoracic epidural catheter [23].

3. Intraoperative Management

3.1. Respiratory Status

Due to the cranial shift of the diaphragm an impaired tissue oxygenation and an increase in peak airway pressures up to 30 mmHg are reported during the HIPEC [4]. A lung protective strategy similar to those observed during long laparoscopic procedures, consisting of low tidal volume, positive end expiratory pressure and recurrent recruitment maneuvers should be considered [24]. Whenever the patient's history is suggestive for severe reduction of functional residual capacity an open abdomen perfusion technique should be considered [13].

3.2. Hemodynamic Balance

Even if all the hemodynamic changes are constantly

reported to be short lived after surgery, major fluid shift and amine support are constantly reported in literature. The possibility to evaluate dynamic parameters of cardiac preload and fluid responsiveness is of utmost importance. All the available case series used at least as hemodynamic monitor: hourly urinary output, CVP and an invasive arterial line [3, 9]. Others used invasive, or advanced, monitoring such as pulmonary artery catheter [7, 12, 15], continuous esophageal echo-Doppler monitoring [8, 13, 14] or transthoracic thermodilution technique (Picco; Pulsion Medical System, Munich, Germany) [11]. Several authors argued that CVP is unreliable due to the increased intra abdominal pressure (IAP) and table tilting during the HIPEC phase [13, 14, 19]. Moreover the urinary output can be reduced secondary to toxicity of chemotherapeutic agent or to the increased IAP itself. No standardized protocol to face cardiac failure is reported and the amine use is related to the local policies. Low doses dopamine were employed by Cafiero et al and by Miao et al to prevent renal dysfunction as suggested by some authors during laparoscopic procedures [14, 9, 25]. As a counterpart none of the studies where dopamine was not employed showed an increased rate of renal failure.

3.3. Coagulation

During CRS and HIPEC the maintaining of a normal coagulation asset faces with different coexisting challenges: dilution coagulopathy due to large amount of crystalloids and/or colloids infusion; transfusion coagulopathy due to PRBC transfusion, if needed; and long-standing coagulation abnormalities due to dysproteinemia secondary to malnourishment and ascites evacuation. This scenario complicates the understanding of normal coagulation tests such as PT, aPTT and platelet counts. Thromboelastography would allow a better evaluation of the coagulation profile reducing bleedings and blood-products requirements [26, 27].

3.4. Renal Status, Electrolyte Balance, Glycemic and Temperature Control

Calcium, potassium, sodium are routinely checked. Minor electrolyte (magnesium) unbalance is reported [9]. The use of furosemide is frequently reported [9, 11, 14]. Forced diuresis by the use of high dose loop-diuretics is still considered “standard of care” during chemotherapy with platinum compound. Despite this “standard practice” there is no definitive evidence of renal protection by the use of high dose of loop-diuretics, as stated by the Special Interest Group on Cancer Care of the European Society of Clinical Pharmacology [28]. They recommended a “brisk diuresis” during the platinum compound infusion and in the immediate days after, by a prolonged saline infusion. Drug clearance is mainly linked to renal blood flow and not to plain urine output. De Somer et al reported hyperglycemia and hyponatremia when a perfusate of 5% dextrose was used as a

carrier for oxaliplatin [18]. This paper points out the need for the anesthesiologist to know the composition of the perfusate and to prevent possible electrolyte unbalances due to the abdominal perfusion itself. [27]. Temperature control devices and strategies need to match the different requirements during the CRS and HIPEC phases. During CRS there is an intense warm loss and hypothermia must be prevented using all the warming devices available (i.e., forced air warming, warmed infusions, arm blankets). On the contrary patients must be cooled down during the HIPEC phase. Cold fluids, ice packs, cooling mattress have been used to cool the patients during the HIPEC procedure [11, 14, 15]. Sometimes those devices were used to lower the core temperature before the abdominal cavity filling [7, 9].

3.5. Pain Control

A continuous infusion of local anesthetic and/or opioids through the epidural route is defined as unsafe by several authors [9, 29, 30, 31] because of its high potential to worsen hypotensive episodes due to its synergic effect with hyperthermia in reducing the systemic vascular resistances and because of the sympathetic blockade epidural analgesia produces [27]. Schmidt et al found no detrimental effect using epidural analgesia [3]. Some data suggest the favorable effect of epidural analgesia in improving patients survival rate by decreasing the recurrence rate or at least elongating the disease free survival. De Oliveira et al in a cohort of patients affected by ovarian cancer found a significantly longer time to cancer recurrence in the patients with thoracic epidural working during the procedure of CRS, but not HIPEC, (73 months vs 38 months in the control group) [32]. On the contrary, the time to recurrence was not different between the patients that never had thoracic epidural or had it just as postoperative pain relief technique [32]. This possible positive effect can be secondary to the increased function of Natural Killer Cells when the surgical stress response is reduced [33, 34] and high level of intravenous opioids is avoided [35].

4. Postoperative Management

4.1. Respiratory Status

Postoperative respiratory support is not always necessary even if CPAP periods can be useful [20]. Cooksley et al reported to have extubated all the patients in the OR, whereas Miao et al extubated 62% before PACU admission [8, 9]. Interestingly Schmidt et al. reported that the presence of epidural analgesia was significantly associated with a reduction in the mechanical ventilation period (3.1 hours vs 10.3 hours, respectively) and in an higher proportion of patients extubated in the OR (41% vs 14%, respectively) [3]. Arakelian et al reported as the use of early postoperative CPAP can be helpful to speed up the recovery [20].

4.2. Hemodynamic Balance

The hemodynamic setting in these patients is rarely complicated. No study specifically addresses the right place to be discharged after the OR or the right period of critical care monitoring. Cooksley et al reported that a 26% of the patients still need vasopressor at the end of the procedure and at the arrival in ICU. However no patients developed renal failure or had a difficult weaning from hemodynamic support [8]. Patients would need fluid requirement because of the fluid loss through the drainages can reach up to 4 liters a day [4]. This needing of a careful fluid turn-over substitution and timely vasopressor weaning suggests for an intensive, or at least sub-intensive, care to provide adequate post-operative surveillance. Cooksley suggested that a shorter hospital length of stay is probably due to admission, and prolonged observation period, in a critical care unit [8].

4.3. Coagulation Considerations

The coagulation profile takes at least 5 days to get back to baseline. Surveillance and eventual transfusions are needed [9].

4.4. Renal Status, Electrolyte Balance, Glycemic Control

Impairment to these functions is reported to not be long lasting. Standard care is needed.

4.5. Pain Control

Postoperatively all the usual precautions and the usual surveillance should be taken. In case of the development of chronic pain the patients should be referred to a palliative care center or to a chronic pain clinic [27].

5. Postoperative Patient Care

5.1. Nutritional Support

No author addressed the specific topics of the nutritional and metabolic support. The percentage of patients with a poor nutritional baseline is reported to be as high as 67% in ovarian cancer and 54% and 83% in colorectal and gastric cancer, respectively [36, 37, 38]. Moreover the massive resections needed are likely to cause a deep catabolic and pro-inflammatory state. All malnourished patients before surgery should have a nutritional consultation and should start a nutritional support [39]. The effect on small bowel physiology of HIPEC are quite unknown, however patients should be treated basing on the guidelines for perioperative nutritional support after major surgery [40]. Enteral feeding should be started as soon as possible. A naso-jejunal catheter can be a valuable option to start early enteral feeding in selected patients [8]. This issue should be correctly evaluated because of malnourishment, has been identified as a major

determinant of surgery success and quality of life recovery.

5.2. Quality of Life

CRS and HIPEC represent a radical treatment in patients that have little possibility to be definitively cured. Literature showed that patients that understand their “terminal state” are likely not to wish to submit themselves to extensive, life and quality of life threatening procedures [41]. In this scenario a careful counseling between physician and patient is mandatory. McQuellon reported that no patient in the cohort of long-term survivor regretted having undergone the procedure [42]. Even in presence of an high perioperative mortality and morbidity rate, median survival improves significantly [1, 6]. In colorectal cancer survival rates up to 30% at 5-years have been reported [43, 44]. In evaluating risk-benefit balance the QoL of patients undergoing such an aggressive surgical intervention has been evaluated in several papers [42, 45, 46, 47 48]. Regardless of the cohort of patients analyzed, or the scores used to describe the QoL, all the papers reported – after a drop in quality and physical functioning in the first few months following the procedure – a steady increase that reached baseline or overcome it as in the case of patients with ovarian cancer and massive ascites [4, 5, 47, 44].

6. Conclusion

Respiratory, hemodynamic and coagulation derangements were the first ones to be extensively monitored. As the hyperthermia plays a pivotal role, the improvement in understanding the effect of hyperthermia on these systems failure will lead to an improvement in the capacity to reduce complications. In planning the diagnostic-therapeutic algorithm the resulting QoL of the patients must be kept in mind.

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