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TOPIC HIGHLIGHT

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Anesthetic management of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedures

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Abstract

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy procedure are performed with increasing frequency to treat patients with diffused peritoneal carcinomatosis. These procedures have showed to increase life expectancy in what was previously considered a "terminal condition". Anyway patients face major and life threatening derangements of their hemodynamic, respiratory and metabolic physiologic balance during the surgery and in the immediate postoperative period. Despite the need of an advanced organ monitoring and support all these derangements seem to be mild and short-lived when timely addressed, at least in the majority of patients. Intensive care physicians are involved in providing surveillance and organ support till the patient is effectively weaned after the operation. Moreover, the anesthesiologist as perioperative physician is involved in pain control, metabolic and nutritional support of this cohort of patients. This task can be challenging considering that part of the patients are already on a long list of pain control medication after previous surgery or chemotherapy. A malnourished state is common too and it is secondary to difficult feeding, wasting syndrome from the tumor and massive ascites. The last issue the anesthesiologists need to be aware of is the impact over the quality of life (QoL) of this procedure. The patient's underlying pathology is unlikely to be definitively cured so no treatment is an acceptable choice. The possibility to withhold the treatments must be part of the consultation process like the discussion about the QoL in the immediate, as well as in the long-term, after the operation. Careful monitoring and treatment of every aspect that can impact the QoL must be taken and the efforts to be poured into an effective preservation of the QoL must be doubled when compared with a patient scheduled for major abdominal surgery.

Key words: Peritoneal carcinomatosis; Anesthesia; Hyperthermic intraperitoneal chemotherapy; Morbidity; Mortality

Core tip: The strenght of this review is to be part of an editorial project that addresses all the aspects of hyperthermic intraperitoneal chemotherapy and cytoreductive surgery procedure. As last article of this special number it gives a comprehensive overview of the anestesiologic issues and an in-depth view of the perio-

perative problems and how they affect life and quality of of the patients that undergone this type of surgery. Moreover for every topic preoperative, intraoperative and postoperative considerations are provided in order to give a clear guide to the physician that approchese these patients.

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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 American Standards Association (ASA) 1 or 2] and with a near to normal performance status scale (Karnofsky performance status > 80%)[1-5]. 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, are committed to providing surveillance and organ/metabolic support in the first period after the procedure itself.

We will provide an overview of the challenges the anesthesiologist has to face; for every issue we will provide preoperative, intraoperative and postoperative considerations, when appropriate.

RESPIRATORY STATUS

These patients could be pre-operatively hypoxic because of ascites, pleural effusion and atelectasis. During the HIPEC phase of the procedure there is an increase in airway pressure and a reduction in functional residual capacity. As the abdominal cavity is filled-up with the chemotherapeutic agent we observe an elevation of the diaphragm and an increase in the intra-abdominal pressure (IAP)[7,8]. An increased $PaCO_2$ and a decrease in the A-a gradient and arterial pH is the hallmark of the gas exchanges deterioration. All these changes are short-lived after the HIPEC phase is terminated apart from the pH reduction, due to a persistence of the metabolic acidosis[9].

Preoperative consideration

Standard evaluation with Chest X-ray and careful medical history record is probably enough. However, pulmonary function test should be considered if a history of increased bronchial reactivity is reported. Moreover due to the high incidence of hydrothorax preoperative pleural effusion evacuation and Continuous Positive Airway Pressure (CPAP) periods should be considered in order to optimize pulmonary reserve before surgery.

Intraoperative considerations

An impaired tissue oxygenation and an increase in peak airway pressures up to 30 mmHg are reported during the HIPEC phase secondary to the cranial shift of the diaphragm[4]. A lung protective strategy consisting of low tidal volume, positive end expiratory pressure and recurrent recruitment maneuvers should be considered as the respiratory derangements are similar to those observed during long laparoscopic procedures and should be treated accordingly[10]. Whenever a previous history suggestive of severe reduction of Functional Residual Capacity is reported an open abdomen technique, as the coliseum one, should be employed for its smoother impact on hemodynamic and respiratory systems[11].

Postoperative considerations

The vast majority of patients can be extubated in the operating room at the end of surgery. Anyway, beside patients still on mechanical ventilation at the end of the procedure all the patients should be monitored postoperatively for respiratory complications. Postoperative CPAP can be extremely useful to speed up the recovery as reported by Arakelian *et al*[12] and should be discussed pre-operatively with the patients and planned for the first postoperative period.

HEMODYNAMIC BALANCE

CRS and HIPEC phase of the procedure show different hemodynamic features. During the CRS we face an extreme surface exposure, often severe bleeding, massive ascites evacuation, as in the case of ovarian tumors, and extensive tumor and peritoneal resection. Keeping normovolemia can be difficult and fluid turnover exceeding the well-established 6-8 mL/kg per hour for major abdominal surgery[13] is often reported. About 12 mL/kg per hour is the most frequent fluid requirement observed during this procedure to keep an adequate end-organ perfusion as detected by urinary output or appropriate advanced hemodynamic monitoring[3,4,14,15]. HIPEC phase is characterized by two conflicting features. If hyperthermia induces a hyperdynamic state the increased IAP, when the abdominal cavity is filled up with chemotherapeutic agent, creates a hypovolemic state due to the reduction of the venous return. A plain description of the hemodynamic parameters during the HIPEC phase is: an increase in heart rate[3,15], mean central venous pressure (CVP), pulmonary artery pressure, wedge pressure[7,15], intrathoracic blood volume index[14] and cardiac index[11,15,16]; on the contrary mean arterial pressure and systemic vascular resistance showed a trend, if not a statistically significant, reduction over the baseline[9,14]. An increase in end tidal CO_2[3] and an increase

in oxygen extraction and consumption rate are the signs of the hypermetabolic state that is due to the hyperthermia[17]. All these changes are constantly reported to be short-lived after the completion of the HIPEC phase and the vast majority of patients, if not all, were weaned off from hemodynamic support at discharge from the operating room, if ever supported with an amine infusion. Moreover the hemodynamic derangements can be reduced if: an open abdomen technique is employed and the core temperature is kept as close to normal as possible. Esquivel *et al*[11] reported only a statistically significant increase in cardiac output during the HIPEC phase when the "Coliseum Technique" was used while the increase in heart rate, mean CVP and the decrease in systemic vascular and mean arterial pressure were not a statistically, and clinically, significant trend. The earliest report from Shime *et al*[17] in 1994 on the effect of the hyperthermia on the hemodynamic balance showed remarkable changes with a reduction in mean arterial pressure and systemic vascular resistance from 93.8 to 75.5 mmHg and from 2214 to 1239 dynes × s/min^{5} × m^{2}, respectively, and an increase in cardiac index and wedge pressure from 3.4 to 4.6 mL/min per square meter and from 7.5 to 9.6 mmHg, respectively. Those changes were paired with a core temperature that approached 40 ℃ at the end of the perfusion whereas in more recent studies the core temperature never outreached 38 ℃[3,9]. This proportionally direct effect of temperature over the hyperdynamic state of the patient is well known. Several studies conducted during the procedures of whole-body hyperthermia showed how when the core temperature gets warmer the hyperdynamic state gets worst[18].

Preoperative considerations

No study specifically targets the cohort of patients with heart failure. To this day, in the large RCTs published patients with an uncontrolled cardiac disease were excluded as no patient with ASA higher than 3 was considered eligible[3,12]. A thorough cardiac evaluation (echocardiogram, stress test if there's suspected reduced coronary reserve) can be a prudent approach if a history of previous heart failure or reduced physical activity is reported. In this case the patients should be referred to the cardiologist for evaluation and risk stratification. Beside this we consider it sensible to refer every patients to a cardiologist if he/she had a possible cardiotoxicity from previous chemotherapy and/or he/she developed a fast malnourishment state. Indication for HIPEC should be questioned whenever an uncontrolled cardiac disease is detected and eventually the patients should be considered for palliative care only.

Intraoperative considerations

All the hemodynamic changes are constantly reported to be short lived after surgery. Despite this, major fluid shift and amine support are constantly reported too. All the available case series used at least as hemodynamic monitor: hourly urinary output, CVP and an invasive arterial line[3,9] whereas others used invasive, or advanced, monitoring such as pulmonary artery catheter[7,15,17], continuous esophageal echo-Doppler monitoring[8,11,16] or transthoracic thermodilution technique[14] (Picco; Pulsion Medical System, Munich, Germany). In our institution invasive monitoring is usually considered mandatory just for patients with a known reduced cardiac performance. Anyway some minimally invasive devices as Vigileo/flo-Trac, Pulsion Picco, trans-esophageal echocardiography can be extremely helpful in guiding transfusion and fluid turn-over therapy. Several authors[11,16,19] argued that CVP is unreliable due to the increased IAP and table tilting during the HIPEC phase. Moreover the urinary output can be reduced secondary to toxicity of chemotherapeutic agent or to the increased IAP itself. In this scenario the possibility to evaluate in a real time manner dynamic parameters of cardiac preload and fluid responsiveness is of utmost importance in order to reduce the risk "flood or dry" the patient and to ensure an appropriate end-organ perfusion. Beside fluid therapy amine support is an open issue during the procedure. No standardized protocol to face cardiac failure is reported and the amine used is related to the local policies of the different institutions. Low doses dopamine were employed by Cafiero *et al*[16] and by Miao *et al*[9] to prevent renal dysfunction as a "renal dose" of dopamine is reported to increase renal perfusion during laparoscopic procedures[20]. Anyway dopamine seems to have little effect, if at all, because none of the studies where it was not employed showed an increased rate of renal failure.

Postoperative considerations

Hemodynamic unbalances are usually short lived. Anyway Cooksley *et al*[8] reported that a 26% of the patients were still on vasopressor at the end of the procedure and at the arrival in intensive care unit (ICU), even if no patients developed renal failure or had a difficult weaning from hemodynamic support. Moreover fluid requirement can be difficult to anticipate as massive fluid loss through the drainages, up to 4 L a day[4], are reported. Careful fluid turn-over substitution and timely weaning from vasopressor support advocate for an intensive, or at least intermediate, care to deliver adequate post-operative surveillance so to prevent renal dysfunction and decreased end-organ perfusion.

PAIN CONTROL

The elective pain control modality in the vast majority of the centers is thoracic epidural[3,4,8,9,14,17,19]. Massive surface scarring is enough to justify the high level of pain reported and the longer use of advanced and invasive modality of pain control. For example, the cohort of patients from Schmidt *et al*[3] had a median of 7 d of continuous infusion of local anesthetic and opioids *via* the epidural route, which is much longer than the usual 3/4 d after major abdominal surgery.

Preoperative considerations

It is important to notice that the patients scheduled

for CRS and HIPEC procedure had a long, and often troubled, medical history. Some of them are already on a long list of analgesic medications and some others show features of chronic and neuropathic pain after the chemotherapy. No study specifically addresses this issue as chronic pain facilities are extremely heterogeneous around the world and the patients themselves undergo surgery with a different diagnosis of disease and had more or less invasive procedures and different chemotherapeutic regimen. However a consult with the palliative care/chronic pain physician can be useful in order to plan a follow-up of the patients when they're discharged from the hospital. Thoracic epidural is probably the best option to control pain perioperatively. It is associated with a shorter mechanical ventilation period, from 10 to 3 h[3], and a better patient satisfaction[21]. Anyway these patients seem to be efficiently and safely managed perioperatively even with high level of intravenous opioids. A percentage of patients ranging from 38%[3] and 21%[9] had no epidural catheter and they did not show a significant increase in perioperative complications, if we exclude a longer period on mechanical ventilation and ICU admission. Coagulation unbalances are common in these patients as they develop massive ascites or have a long-standing history of bleeding or malnourishment. However, it does not seem to affect the safety of the placement of a thoracic epidural catheter as no epidural hematoma is reported[22]. Risk benefit ratio is probably in favor of thoracic epidural considering the difficulty to control pain and wean from mechanical ventilation that these patients have.

Intraoperative considerations

A continuous infusion of local anesthetic and/or opioids through the epidural route is felt unsafe by several authors[9,23-25] 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. Anyway Schmidt *et al*[3] found no detrimental effect using epidural analgesia during the procedure. We can speculate whether there's any potential advantage in using epidural analgesia in the prevention of the development of chronic postoperative pain in a similar manner to its use during thoracic surgery[26]. Beside this there's an increasing amount of data that suggest how the use of epidural analgesia may improve patients survival rate by decreasing the incidence of tumor relapse or at least elongating the time to relapse of the tumor. de Oliveira *et al*[27] found a significantly longer time to cancer recurrence in the patients that had thoracic epidural working during the procedure of CRS, but not HIPEC, (73 mo *vs* 38 mo in the control group) in a cohort of patients affected by ovarian cancer. On the contrary, time for cancer recurrence was not different between the patients that never had thoracic epidural or had it just as postoperative pain relief technique. This possible positive effect can be secondary to the increased function of nartural killer cells when the surgical stress response is reduced[28,29] and high level of intravenous opioids is avoided[30].

Postoperative considerations

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.

COAGULATION CONSIDERATIONS

Coagulation abnormalities are always reported in this cohort of patients. They are defined as an abnormal elongation of prothrombin time - international normalised ratio (INR), activated partial thromboplastin time (aPTT) and/or pathological reduction of platelets count over the baseline[3,4,8,9]. This dysfunction is reported to peak around 24/48 h post-surgery[3,8], with a restoration of a normal coagulation profile in 72 h[3], even if baseline values are reached in almost 5 d[9]. Schmidt *et al*[3] reported that Fresh Frozen Plasma (FFP) and packed red blood cells (PRBC) were transfused in 50% of the patients intra-operatively and 28% post-operatively. Coagulation abnormality is, probably, multifactorial in its genesis. The two sides of the problems seem to be a dilutional dysfunction[31] secondary to massive fluid shift and bleeding and an impairment of coagulation factors profiles due to massive ascites[32] and malnourishment.

Preoperative considerations

Standard coagulation evaluation (INR, aPTT, platelets count, list of antithrombotic drugs) is enough and no author advocates for more expensive tests. The fear of intraoperative bleeding should not prevent us from considering the high thrombotic risk that some patients may have. Some of them are women, in their fifties, with an ovarian cancer, that are going to keep for 8-10 h a gynecological position on the operating table. All of these are well known prothrombotic risk factors. Special care is required by patients with massive ascites. Ascitic fluid is rich in proteins with a varying concentration of 0.5-4.2 g/100 mL of proteins. Of this amount 50%-70% is albumin, 30%-45% are globulins and 0.3%-4.5% is fibrinogen. The evacuation of up to 2-3 L of this fluid changes something more than the oncotic pressure of the patient. Vorgias *et al*[32] calculated the theoretical substitution requirement of patients optimally debulked from ovarian cancer and found out that infusions for up to 3 d of 2 units of FFP and human albumin were required.

Intraoperative considerations

Coagulation during CRS and HIPEC procedure means to deal in a short period of time with: dilution coagulopathy due to large amount of crystalloids and/or colloids infusion; transfusion coagulopathy due to PRBC transfusion to keep an adequate oxygen delivery, in the scenario of massive bleeding; 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 INR, aPTT and platelet counts. Thromboelastography (TEG) gives the possibility of a thorough evaluation of

the coagulation profile and it is probably more useful in this type of surgery than in others. Even if no paper specifically addresses this question TEG-guided transfusion of blood products may substantially reduce bleeding and eventually blood-products requirements similarly to what happens in other major surgeries[33].

Postoperative considerations

The coagulation profile takes at least 5 d[9] to get back to baseline values so surveillance and timely transfusion is needed. Renal status, electrolyte balance, glycemic and temperature control: renal dysfunction, electrolyte disorder and hyperglycemia are frequently observed[3,7,9,34]. They are related to the fluids infused, end-organ perfusion achieved and quality and quantity of perfusate used to deliver the chemotherapeutic agent in the abdominal cavity. Temperature control is of utmost importance as it is directly related to the gravity of deregulation in the hemodynamic and coagulation balance.

RENAL STATUS, TEMPERATURE AND METABOLISM

Standard evaluation: If ureteral stents are positioned preoperatively to be used as landmark during CRS phase it should be advisable to check for their bilateral patency.

Intraoperative considerations

Calcium, potassium, sodium are routinely checked. Minor electrolyte such as magnesium should be tested too as their unbalance is reported[9]. The use of furosemide to enhance urine output to clear as much chemotherapeutic agent as possible is frequently reported[9,14,16]. Forced diuresis by the use of high dose loop-diuretics is still considered "standard of care" during chemotherapy with compound derived from platinum. 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[35]. They recommended a "brisk diuresis" during the platinum compound infusion and in the immediate days after by a prolonged saline infusion. In our case series of CRS and HIPEC we had three renal insufficiencies in 70 cases during the last year, two of them were obstructive, none of them required dialysis (unpublished data). This small incidence of renal impairment was probably related to the invasive monitoring of euvolemia during the procedure despite a diuretic use (20 mg of furosemide before HIPEC induction). In our opinion diuretics use has still a place in the "standard of care" of these patients as hypovolemia can be easily detected and corrected if invasive monitoring is ensued and there is no clear evidence "against" the use of loop-diretics. Drug clearance is mainly linked to renal blood flow and not to plain urine output. the prolonged use of diuretics can be misleading as we can face a good urinary output in the presence of an unnoticed end-organ perfusion decrease therefore euvolemia must be pursued with any effort. De Somer *et al*[34] reported hyperglycemia and hyponatremia when a perfusate of 5% dextrose was used as a carrier for oxplatin. 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. Even if the peritoneal surface is reduced the exposed area is still enough to give a statistically, and clinically, relevant impact over the electrolytes and fluid balance. Temperature control devices and strategies need to match the different requirements during the CRS and HIPEC phase of the procedure. During the cytoreduction when the abdominal cavity is open 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 when the warm infusate is delivered into the abdominal cavity. Cold fluids, ice packs, cooling mattress[14,16,17] have been used to cool the patients during the HIPEC procedure. Sometimes those devices were used to lower the core temperature before the abdominal cavity filling[7,9].

Postoperative consideration

None of these disturbances is reported to be long lasting after the completion of the procedure so just standard care is needed.

QoL

CRS and HIPEC represent a radical treatment in a patient that has little possibility, if any, to be definitively cured. Data from the literature suggest that patients that understand their "terminal state" are likely not to wish to submit themselves to extensive, life and QoL threatening procedures[36]. In this scenario no treatment, obviously excluding palliative and supportive care, is an acceptable choice and a careful counseling between physician and patient is mandatory. Anyway patients that are referred to a center that performs CRS and HIPEC are usually aware that the procedure will gain time for them, or at least for the majority of them. Moreover McQuellon *et al*[37] eported that no patient in the cohort of long-term survivor regretted having undergone the procedure. Although perioperative mortality and morbidity can be high[1,6], median survival improves significantly and for colorectal cancer a survival rate of 30% at 5-year is reported[38,39]. The quality of the life gained with this procedure has been evaluated in several papers[37,40-44]. 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[4,5,42] or overshot it as in the case of patients with ovarian cancer and massive ascites[39]. McQuellon *et al*[37] published the only report on long-term survivors after HIPEC and CRS. They showed as 87% of the patients that survived longer than 3 years rated their health as good or excellent and none of them regretted having undergone the procedure. To interpret data from QoL studies on HIPEC patients mean to deal with at least three main problems. The first one is the non

standardized use of score across the studies as already reported by Piso *et al*[43]. Secondarily it is extremely complicated to interpret data from QoL studies as, especially in a cohort of patients with a terminal disease, factors as adaptation to disease, response shift, dispositional optimism can deeply change some of the scoring and maybe have little effect over the life of the patients[41,45]. The typical effect is that little improvement in QoL may be not significant at a population level but, at the patient level, it can be important enough to enter or not a rehabilitation or supportive care program. Thirdly a significant proportion of the patients do not reply to the follow-up since some of them die or their conditions are so deteriorated that they cannot reply to the questionnaires. McQuellon *et al*[40] evaluated the QoL data of patients starting with a cohort of 64 patients at baseline but only 23 patients replied to the 1-year follow-up questionnaire. Another study[42] evaluated 96 patients at baseline but only 24 were able to complete the 1-year follow-up, similarly Schmidt *et al*[4], with a baseline cohort of 67 patients and a 25 patients at the time of the follow-up. Even though it is possible to consider and weigh during the analysis the effect of missing data and of the non-random distribution of the results we need to focus keep in mind that probably the data just reflect the best possible outcome of this surgery and that a real "average effect" it does not exist.

POSTOPERATIVE CARE

The procedure is long and complex and even though the physiological derangements are predominately short-lived these patients deserve an intense postoperative monitoring. Postoperative respiratory support is not always necessary even if CPAP periods can be useful to get back to baseline respiratory function levels[12]. Cooksley *et al*[8] reported to have extubated all the patients in the OR before discharging them to the Critical Care Unit, whereas Miao *et al*[9] extubated 62% before PACU admission. Interestingly Schmidt *et al*[3] observed how the presence of a working epidural analgesia was significantly associated with a reduction in the mechanical ventilation period (3.1 h *vs* 10.3 h, respectively) and in an higher proportion of patients extubated in the operating room (41% *vs* 14%, respectively). From an hemodynamic point of view these patients are rarely on amine support but suffer from high volume of fluids loss from the drains, up to 4 L a day[3], secondary to the huge wounded surface. Even if the postoperative period is less troubled than the surgery one these patients needs to be monitored for a while and all the derangements eventually corrected in a timely manner. No study specifically addresses the right place to be discharged after the OR or the right period of critical care monitoring. Anyway we agree with the statement by Cooksley *et al*[8], that a shorter hospital length of stay is probably due to admission, and prolonged observation period, in a critical care unit.

NUTRITIONAL SUPPORT

No author addressed the specific topics of the nutritional and metabolic support in the patients undergoing CRS and HIPEC. This category of patient is known to have a poor nutritional baseline as malnutrition prevalence is reported to be as high as 67%[46] in ovarian cancer patients and 54%[47] and 83%[48] in colorectal and gastric cancer, respectively. Moreover the debulking phase of the surgery involves massive resections that are likely to cause a deep catabolic and pro-inflammatory state. All malnourished patients should have a nutritional consultation before surgery and should start a nutritional support to reach a better metabolic profile[49] before surgery. Although little is known about the effect on small bowel physiology of the hyperthermic intrabdominal chemotherapy, it is advisable that these patients should be treated according to the guidelines about perioperative nutritional support after major surgery[50]. So nutritional states must be assessed preoperatively and enteral feeding started as soon as possible after the resolution of mechanical bowel obstruction. Positioning a nasojejunal catheter can be a valuable option to start early enteral feeding as already reported in this group of patients[8]. This area of research is of increasing interest due to the fact that starvation, or better malnourishment, has been identified as a major determinant of surgery success and QoL recovery.

CONCLUSION

CRS and HIEPC are complex procedures. High morbidity and mortality rates are reported, nonetheless it has showed its power to gain life in a relevant part of the patients and its safety in high volume centers. Respiratory and hemodynamic derangements were the first ones to be extensively evaluated. Morbidity related to these two systems failure is decreasing since pathophysiology of hyperthermia is better understood and better temperature, hemodynamic and respiratory control is achieved through new devices or technique. The research agenda of this procedure is an open challenge and the issue to be addressed in the next future are how to increase QoL of the patients through a better understanding of the coagulation derangement, and issues concerning pain patterns, nutritional support and social rehabilitation.

REFERENCES

1 **Verwaal VJ**, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, Zoetmulder FA. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; **21**: 3737-3743 [PMID: 14551293 DOI: 10.1200/JCO.2003.04.187]

2 **Yan TD**, Links M, Xu ZY, Kam PC, Glenn D, Morris DL. Cytoreductive surgery and perioperative intraperitoneal chemotherapy for pseudomyxoma peritonei from appendiceal mucinous neoplasms. *Br J Surg* 2006; **93**: 1270-1276 [PMID: 16838392 DOI: 10.1002/bjs.5427]

3 **Schmidt C**, Creutzenberg M, Piso P, Hobbhahn J, Bucher M. Peri-operative anaesthetic management of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. *Anaesthesia* 2008; **63**: 389-395 [PMID: 18336490 DOI: 10.1111/j.1365-2044.2007.05380.x]

4 **Schmidt U**, Dahlke MH, Klempnauer J, Schlitt HJ, Piso P. Perioperative morbidity and quality of life in long-term survivors following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 2005; **31**: 53-58 [PMID: 15642426]

5 **Tuttle TM**, Zhang Y, Greeno E, Knutsen A. Toxicity and quality of life after cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2006; **13**: 1627-1632 [PMID: 17013686 DOI: 10.1245/s10434-006-9186-6]

6 **Shen P**, Hawksworth J, Lovato J, Loggie BW, Geisinger KR, Fleming RA, Levine EA. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma. *Ann Surg Oncol* 2004; **11**: 178-186 [PMID: 14761921]

7 **Kanakoudis F**, Petrou A, Michaloudis D, Chortaria G, Konstantinidou A. Anaesthesia for intra-peritoneal perfusion of hyperthermic chemotherapy. Haemodynamic changes, oxygen consumption and delivery. *Anaesthesia* 1996; **51**: 1033-1036 [PMID: 8943594 DOI: 10.1111/j.1365-2044.1996.tb14998.x]

8 **Cooksley TJ**, Haji-Michael P. Post-operative critical care management of patients undergoing cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC). *World J Surg Oncol* 2011; **9**: 169 [PMID: 22182345 DOI: 10.1186/1477-7819-9-169]

9 **Miao N**, Pingpank JF, Alexander HR, Royal R, Steinberg SM, Quezado MM, Beresnev T, Quezado ZM. Cytoreductive surgery and continuous hyperthermic peritoneal perfusion in patients with mesothelioma and peritoneal carcinomatosis: hemodynamic, metabolic, and anesthetic considerations. *Ann Surg Oncol* 2009; **16**: 334-344 [PMID: 19050961 DOI: 10.1245/s10434-008-0253-z]

10 **Valenza F**, Chevallard G, Fossali T, Salice V, Pizzocri M, Gattinoni L. Management of mechanical ventilation during laparoscopic surgery. *Best Pract Res Clin Anaesthesiol* 2010; **24**: 227-241 [PMID: 20608559]

11 **Esquivel J**, Angulo F, Bland RK, Stephens AD, Sugarbaker PH. Hemodynamic and cardiac function parameters during heated intraoperative intraperitoneal chemotherapy using the open "coliseum technique". *Ann Surg Oncol* 2000; **7**: 296-300 [PMID: 10819370]

12 **Arakelian E**, Gunningberg L, Larsson J, Norlén K, Mahteme H. Factors influencing early postoperative recovery after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Eur J Surg Oncol* 2011; **37**: 897-903 [PMID: 21783337]

13 **Joshi GP**. Intraoperative fluid restriction improves outcome after major elective gastrointestinal surgery. *Anesth Analg* 2005; **101**: 601-605 [PMID: 16037184 DOI: 10.1213/01.ANE.0000159171.26521.31]

14 **Raue W**, Tsilimparis N, Bloch A, Menenakos C, Hartmann J. Volume therapy and cardiocircular function during hyperthermic intraperitoneal chemotherapy. *Eur Surg Res* 2009; **43**: 365-372 [PMID: 19844110 DOI: 10.1159/000248164]

15 **Tsiftsis D**, de Bree E, Romanos J, Petrou A, Sanidas E, Askoxylakis J, Zervos K, Michaloudis D. Peritoneal expansion by artificially produced ascites during perfusion chemotherapy. *Arch Surg* 1999; **134**: 545-549; discussion 550 [PMID: 10323428]

16 **Cafiero T**, Di Iorio C, Di Minno RM, Sivolella G, Confuorto G. Non-invasive cardiac monitoring by aortic blood flow determination in patients undergoing hyperthermic intraperitoneal intraoperative chemotherapy. *Minerva Anestesiol* 2006; **72**: 207-215 [PMID: 16570032]

17 **Shime N**, Lee M, Hatanaka T. Cardiovascular changes during continuous hyperthermic peritoneal perfusion. *Anesth Analg* 1994; **78**: 938-942 [PMID: 8160994]

18 **Deja M**, Hildebrandt B, Ahlers O, Riess H, Wust P, Gerlach H, Kerner T. Goal-directed therapy of cardiac preload in induced whole-body hyperthermia. *Chest* 2005; **128**: 580-586 [PMID: 16100141 DOI: 10.1378/chest.128.2.580]

19 **Raspe C**, Piso P, Wiesenack C, Bucher M. Anesthetic management in patients undergoing hyperthermic chemotherapy. *Curr Opin Anaesthesiol* 2012; **25**: 348-355 [PMID: 22517311 DOI: 10.1097/ACO.0b013e32835347b2]

20 **Pérez J**, Taurá P, Rueda J, Balust J, Anglada T, Beltran J, Lacy AM, Garcia-Valdecasas JC. Role of dopamine in renal dysfunction during laparoscopic surgery. *Surg Endosc* 2002; **16**: 1297-1301 [PMID: 12000983 DOI: 10.1007/s00464-001-9201-8]

21 **Ali M**, Winter DC, Hanly AM, O'Hagan C, Keaveny J, Broe P. Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. *Br J Anaesth* 2010; **104**: 292-297 [PMID: 20124282 DOI: 10.1093/bja/aeq006]

22 **Schmidt C**, Steinke T, Moritz S, Bucher M. Thoracic epidural anesthesia in patients with cytoreductive surgery and HIPEC. *J Surg Oncol* 2010; **102**: 545-546 [PMID: 20607760 DOI: 10.1002/jso.21660]

23 **de la Chapelle A**, Pérus O, Soubielle J, Raucoules-Aimé M, Bernard JL, Bereder JM. High potential for epidural analgesia neuraxial block-associated hypotension in conjunction with heated intraoperative intraperitoneal chemotherapy. *Reg Anesth Pain Med* 2005; **30**: 313-314 [PMID: 15898044]

24 **Desgranges FP**, Steghens A, Rosay H, Méeus P, Stoian A, Daunizeau AL, Pouderoux-Martin S, Piriou V. [Epidural analgesia for surgical treatment of peritoneal carcinomatosis: a risky technique?]. *Ann Fr Anesth Reanim* 2012; **31**: 53-59 [PMID: 22154448 DOI: 10.1016/j.annfar.2011.08.020]

25 **Desgranges FP**, Steghens A, Mithieux F, Rosay H. Potential risks of thoracic epidural analgesia in hyperthermic intraperitoneal chemotherapy. *J Surg Oncol* 2010; **101**: 442 [PMID: 20213731 DOI: 10.1002/jso.21485]

26 **Sentürk M**, Ozcan PE, Talu GK, Kiyan E, Camci E, Ozyalçin S, Dilege S, Pembeci K. The effects of three different analgesia techniques on long-term postthoracotomy pain. *Anesth Analg* 2002; **94**: 11-15, table of contents [PMID: 11772793]

27 **de Oliveira GS**, Ahmad S, Schink JC, Singh DK, Fitzgerald PC, McCarthy RJ. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. *Reg Anesth Pain Med* 2011; **36**: 271-277 [PMID: 21519312 DOI: 10.1097/AAP.0b013e318217aada]

28 **Pollock RE**, Babcock GF, Romsdahl MM, Nishioka K. Surgical stress-mediated suppression of murine natural killer cell cytotoxicity. *Cancer Res* 1984; **44**: 3888-3891 [PMID: 6744305]

29 **Pollock RE**, Lotzová E, Stanford SD. Surgical stress impairs natural killer cell programming of tumor for lysis in patients with sarcomas and other solid tumors. *Cancer* 1992; **70**: 2192-2202 [PMID: 1394051]

30 **Yeager MP**, Colacchio TA, Yu CT, Hildebrandt L, Howell AL, Weiss J, Guyre PM. Morphine inhibits spontaneous and cytokine-enhanced natural killer cell cytotoxicity in volunteers. *Anesthesiology* 1995; **83**: 500-508 [PMID: 7661350]

31 **Schols SE**, Lancé MD, Feijge MA, Damoiseaux J, Marcus MA, Hamulyák K, Ten Cate H, Heemskerk JW, van Pampus EC. Impaired thrombin generation and fibrin clot formation in patients with dilutional coagulopathy during major surgery. *Thromb Haemost* 2010; **103**: 318-328 [PMID: 20024495 DOI: 10.1160/TH09-06-0396]

32 **Vorgias G**, Iavazzo C, Mavromatis J, Leontara J, Katsoulis M, Kalinoglou N, Akrivos T. Determination of the necessary total protein substitution requirements in patients with advanced stage ovarian cancer and ascites, undergoing debulking surgery. Correlation with plasma proteins. *Ann Surg Oncol* 2007; **14**: 1919-1923 [PMID: 17406944 DOI: 10.1245/s10434-007-9404-x]

33 **Ronald A**, Dunning J. Can the use of thromboelastography predict and decrease bleeding and blood and blood product requirements in adult patients undergoing cardiac surgery? *Interact Cardiovasc Thorac Surg* 2005; **4**: 456-463 [PMID:

17670456 DOI: 10.1510/icvts.2005.115154]
34 **De Somer F**, Ceelen W, Delanghe J, De Smet D, Vanackere M, Pattyn P, Mortier E. Severe hyponatremia, hyperglycemia, and hyperlactatemia are associated with intraoperative hyperthermic intraperitoneal chemoperfusion with oxaliplatin. *Perit Dial Int* 2008; **28**: 61-66 [PMID: 18178949]
35 **Faerch K**, Vaag A, Holst JJ, Glümer C, Pedersen O, Borch-Johnsen K. Impaired fasting glycaemia vs impaired glucose tolerance: similar impairment of pancreatic alpha and beta cell function but differential roles of incretin hormones and insulin action. *Diabetologia* 2008; **51**: 853-861 [PMID: 18317726 DOI: 10.1007/s00280-008-0711-0]
36 **Weeks JC**, Cook EF, O'Day SJ, Peterson LM, Wenger N, Reding D, Harrell FE, Kussin P, Dawson NV, Connors AF, Lynn J, Phillips RS. Relationship between cancer patients' predictions of prognosis and their treatment preferences. *JAMA* 1998; **279**: 1709-1714 [PMID: 9624023]
37 **McQuellon RP**, Loggie BW, Lehman AB, Russell GB, Fleming RA, Shen P, Levine EA. Long-term survivorship and quality of life after cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol* 2003; **10**: 155-162 [PMID: 12620911]
38 **Rossi CR**, Deraco M, De Simone M, Mocellin S, Pilati P, Foletto M, Cavaliere F, Kusamura S, Gronchi A, Lise M. Hyperthermic intraperitoneal intraoperative chemotherapy after cytoreductive surgery for the treatment of abdominal sarcomatosis: clinical outcome and prognostic factors in 60 consecutive patients. *Cancer* 2004; **100**: 1943-1950 [PMID: 15112276 DOI: 10.1002/cncr.20192]
39 **Cotte E**, Passot G, Mohamed F, Vaudoyer D, Gilly FN, Glehen O. Management of peritoneal carcinomatosis from colorectal cancer: current state of practice. *Cancer J* 2009; **15**: 243-248 [PMID: 19556911 DOI: 10.1097/PPO.0b013e3181a58d67]
40 **McQuellon RP**, Loggie BW, Fleming RA, Russell GB, Lehman AB, Rambo TD. Quality of life after intraperitoneal hyperthermic chemotherapy (IPHC) for peritoneal carcinomatosis. *Eur J Surg Oncol* 2001; **27**: 65-73 [PMID: 11237495]
41 **McQuellon R**, Gavazzi C, Piso P, Swain D, Levine E. Quality of life and nutritional assessment in peritoneal surface malignancy (PSM): recommendations for care. *J Surg Oncol* 2008; **98**: 300-305 [PMID: 18726903 DOI: 10.1002/jso.21050]
42 **McQuellon RP**, Danhauer SC, Russell GB, Shen P, Fenstermaker J, Stewart JH, Levine EA. Monitoring health outcomes following cytoreductive surgery plus intraperitoneal hyperthermic chemotherapy for peritoneal carcinomatosis. *Ann Surg Oncol* 2007; **14**: 1105-1113 [PMID: 17206478 DOI: 10.1245/s10434-006-9304-5]
43 **Piso P**, Glockzin G, von Breitenbuch P, Popp FC, Dahlke MH, Schlitt HJ, Nissan A. Quality of life after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancies. *J Surg Oncol* 2009; **100**: 317-320 [PMID: 19697438 DOI: 10.1002/jso.21327]
44 **Schmidt C**, Moritz S, Rath S, Grossmann E, Wiesenack C, Piso P, Graf BM, Bucher M. Perioperative management of patients with cytoreductive surgery for peritoneal carcinomatosis. *J Surg Oncol* 2009; **100**: 297-301 [PMID: 19697426 DOI: 10.1002/jso.21322]
45 **Sloan JA**, Frost MH, Berzon R, Dueck A, Guyatt G, Moinpour C, Sprangers M, Ferrans C, Cella D. The clinical significance of quality of life assessments in oncology: a summary for clinicians. *Support Care Cancer* 2006; **14**: 988-998 [PMID: 16794811 DOI: 10.1007/s00520-006-0085-y]
46 **Laky B**, Janda M, Bauer J, Vavra C, Cleghorn G, Obermair A. Malnutrition among gynaecological cancer patients. *Eur J Clin Nutr* 2007; **61**: 642-646 [PMID: 17021596 DOI: 10.1038/sj.ejcn.1602540]
47 **Laviano A**, Meguid MM. Nutritional issues in cancer management. *Nutrition* 1996; **12**: 358-371 [PMID: 8875522]
48 **Andreyev HJ**, Norman AR, Oates J, Cunningham D. Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? *Eur J Cancer* 1998; **34**: 503-509 [PMID: 9713300]
49 **Martindale RG**, Maerz LL. Management of perioperative nutrition support. *Curr Opin Crit Care* 2006; **12**: 290-294 [PMID: 16810037 DOI: 10.1097/01.ccx.0000235204.54579.14]
50 **Weimann A**, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. *Clin Nutr* 2006; **25**: 224-244 [PMID: 16698152 DOI: 10.1016/j.clnu.2006.01.015]

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