Clinical Study

Intensive Care Unit Admission after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Is It Necessary?

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Introduction. Cytoreductive surgery (CS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is a novel approach for peritoneal carcinomatosis. However, high rates of complications are associated with CS and HIPEC due to treatment complexity; that is why some patients need stabilization and surveillance for complications in the intensive care unit. Objective. This study analyzed that ICU stay is necessary after HIPEC. Methods. 39 patients with peritoneal carcinomatosis were treated according to strict selection criteria with CS and HIPEC, with closed technique, and the chemotherapy administered were cisplatin 25 mg/m²/L and mitomycin C 3.3 mg/m²/L for 90-minutes at 40.5°C. Results. 26 (67%) of the 39 patients were transferred to the ICU. Major postoperative complications were seen in 14/26 patients (53%). The mean time on surgical procedures was 7.06 hours (range 5–9 hours). The mean blood loss was 939 ml (range 100–3700 ml). The mean time stay in the ICU was 2.7 days. Conclusion. CS with HIPEC for the treatment of PC results in low mortality and high morbidity. Therefore, ICU stay directly following HIPEC should not be standardized, but should preferably be based on the extent or resections performed and individual patient characteristics and risk factors. Late complications were comparable to those reported after large abdominal surgery without HIPEC.

1. Introduction

Cytoreductive surgery (CRS) with intraperitoneal (i.p.) chemotherapy and hyperthermia (HIPEC) has emerged as a novel approach for peritoneal carcinomatosis. This is a complex procedure that implies extensive resection of the peritoneal surface, sometimes multiple visceral resections, high rates of i.p. chemotherapy with hyperthermia, and prolonged operative time (in general, from 10–14 hours). High rates of potential fatal complications associated with HIPEC have been reported in the literature [1, 2]; that is why some patients need to be admitted to intensive care unit for stabilization, detection, and early resolution of complications associated with the extension of the surgical procedure, the toxicity of the drugs administered, or both. Particular emphasis should be placed on the dose of cisplatin.
administered i.p., because in a multivariate analysis it has been reported that doses >240 mg correlate with the appearance of postoperative complications [3–5]. Post-HIPEC morbidity rates range from 30 to 74% and mortality ranges from 0 to 19% [1, 2, 6, 7]. It is difficult to compare clinical results with others centers in terms of patient selection, surgical technique, time, duration, and degree of hyperthermia, as well as the dosages of the drugs. All factors have been compiled in complication classification systems of morbidity, toxicity, and mortality such as the Clavien-Dindo classification, the Elias classification, the National Cancer Institute (NCI), and the Common Terminology Criteria for Adverse Events (CTCAE). These systems are different and there is correlation among the degrees of complication; thus, the seriousness of a clinical condition does not refer to the clinical severity in another classification [8, 9]. Despite the limitations, taking into account the serious complications that merit a reintervention, admittance to the intensive care unit (ICU), or the utilization of invasive procedures, complication rates range between 12 and 54% [1, 2, 6, 7, 10]. However, it is not clear whether a stay in the ICU is necessary for strict surveillance after CS + HIPEC.

The objective of this work was to analyze whether postoperative management after CS + HIPEC requires postsurgical care in the ICU as a mandatory measure in our Institution.

2. Materials and Methods

We review retrospectively the charts of 39 patients with peritoneal carcinomatosis who were operated on from January, 2007, to January, 2012, after cytoreductive surgery (CRS) with HIPEC with 25 mg/m²/L of Cisplatin and 3.3 mg/m²/L of Mitomycin C (MMC) administered for 90 min at 40.5°C. The following data were procured: histology; age; gender; date and days of admittance to the ICU, the presence of bleeding, complications, time, and management of complications.

3. Results

Of the 39 patients treated with CS and HIPEC technique, 30 were females and 9 males, 14 patients with colorectal cancer, 6 with peritoneal pseudomixoma, 14 with carcinomatosis of the ovary, 2 with gastric cancer, and 3 with cancer of the appendix. The mean age of the patients was 55.4 years (range 30–72 years). The mean time of the surgical procedure was 7 (range 5–10 hours), the mean blood loss was 938.88 mL (range 100–3,700 mL) (Table 1), and 26 (67%) of cases were admitted to the ICU and the mean time in the ICU was 2.7 days (range 1–13 days).

The most frequent complication was diaphragmatic opening (see Table 2). The criteria to admission ICU were prolonged time during surgery and/or blood loss during surgery. There was no difference in complications or mortality between patients in the ICU or out of ICU (Tables 3 and 4). 23 (58%) patients were alive without evidence of disease, seven (18%) were alive with tumor activity, six (15%) died with tumor activity, and three (7.5%) are dead without tumor activity.

4. Discussion

Peritoneal carcinomatosis is considered the most common cause of death of intra-abdominal origin [6]. Despite the improvement of the treatment for this disease, CS with HIPEC need of an specialized team, adequate technology and infrastructure, and technological facilities to reduce morbidity and improve quality of life [7]. Likewise, identification
of risk factors that increase morbidity is also crucial for improving the results. In our study, morbidity was 48.6%, the most common complication was diaphragmatic opening (15%), and mortality was 5% (Table 2). It has been described that morbidity and mortality are directly proportional to the degree of cytoreduction, the learning curve, and the surgical technique [11, 12].

The complications were similar in severity in UCI and out UCI and during surgery (Table 3). The first two patients did not require admittance into the ICU, and the dehiscence developed 4 days after the patient’s admittance into the ICU. In addition one patient developed pneumonia and 3 acute kidney failures, both resolved with medical management (Table 4). Two cases (5%) die due to a postoperative bleeding, identified in the first 4 hours of the patient admittance to the ICU, and the other due to pulmonary thromboembolism, which presented at 48 h of the patient’s admittance into the ICU. The rates reported for morbidity and mortality range between 0% and 40% and 0 and 12.5%, respectively [13–19] (Table 5).

Smeenk et al. in 2006 [20] reported a toxicity of 54% and a mortality of 3% in 103 peritoneal pseudomixoma procedures, demonstrating the significant association between age and toxicity and intestinal perforation and tumor volume (Table 6).

The present work reports higher mortality when compared with previous studies [1, 2, 19, 20], which can be related to the fact that patients presented a more voluminous tumor disease at the time of surgery; thus, surgical time was longer than in those in whom there was more blood loss and frequency of diaphragmatic opening, which was the site where the greatest tumor burden was localized [19, 20].

Among the causes of death found in the literature were intestinal perforation, dehiscence of the anastomosis, intestinal fistula, bile duct leakage, postoperative bleeding, pancreatitis, and the habitual risks of surgery, such as deep vein thrombosis, pulmonary embolism, pneumonia, renal failure, diaphragmatic opening.

The gastrointestinal and respiratory tracts were most affected. After the gastrointestinal tract, the respiratory tract is probably the system that is most affected by postoperative complications. Pulmonary morbidity was found in six cases of our series and the majority of these were resolved without reintervention or invasive procedures, with the exception of a case of pulmonary embolism [25].

A study at Wake Forest University reports thoracic complications in a series of 42 patients treated with CS +...
HIPEC [26]. Thoracic complications were observed in 36 (86%) patients, atelectasia in 32 patients, and pleural effusion in 27 (64%) patients. The majority of the effusions (74%) occurred 1–3 days after CS + HIPEC. The incidence of thoracic complications in the HIPEC group was significantly higher than in the control group ($P < 0.05$). In our study, we uncovered common findings, including bibasilar atelectasia and pleural effusion after the use of MMC, but the majority did not merit any intervention. The prevention and management of these complications included careful inspection of the integrity of the diaphragmatic muscle and resection of its peritoneum. Early repair of eventual macroscopic perforations and prophylactic insertion of thoracic catheters after cytoreduction are practices performed by some authors. With regard to nephrotoxicity, our study reported two cases of alteration of serum creatinine, which after a mean period of 16 days (range 7–42 days) after surgery showed normal kidney function.

Studies reporting the systemic toxicity of CS + HIPEC are resumed up in Table 6. Verwaal reported kidney failure in 4.9% of cases. Glehen et al. observed a postoperative kidney failure rate of 1.3% [27].

The frequent complications found in the majority of series are digestive fistulae, whether in the form of anastomotic leakage or intestinal perforation outside of the anastomosis. Fistulae have been reported in between 3.9 and 34% of patients [17, 18, 28, 29] (Table 5). These numbers are higher than the rate reported for common elective surgery [30, 31].

5. Conclusions

Cytoreduction with intraperitoneal chemotherapy with hyperthermia is a treatment with high morbility. Therefore, adequate selection of patients is very important to diminish the complications that can be associated with the surgery, the hyperthermia, the chemotherapy, or altogether. The results of the present work suggest that the main factor associated with the development of complications is the extension of the CR process and not the application of chemotherapy and hyperthermia as principal factors, given that the delayed complications reported in our study were comparable with those reported in the literature after major abdominal surgery without HIPEC.

The results and mortality of the patients who went on to the ICU and those without the ICU are similar. Admittance to the ICU should be evaluated case by case considering the individual characteristics of the patients, their risk factors, and the extension of their surgical procedure.
Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. D. Stephens, R. Alderman, D. Chang et al., “Morbidity and mortality analysis of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the coliseum technique,” Annals of Surgical Oncology, vol. 6, no. 8, pp. 790–796, 1999.

[2] N. J. Gusani, S. W. Cho, C. Colovos et al., “Aggressive surgical management of peritoneal carcinomatosis with low mortality in a high-volume tertiary cancer center,” Annals of Surgical Oncology, vol. 15, no. 3, pp. 754–763, 2008.

[3] S. Kusamura, R. Younan, D. Baratti et al., “Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique,” Cancer, vol. 106, no. 5, pp. 1144–1153, 2006.

[4] L. Bijelic, T. D. Yan, and P. H. Sugarbaker, “Failure analysis of recurrent disease following complete cytoreduction and perioperative intraperitoneal chemotherapy in patients with peritoneal carcinomatosis from colorectal cancer,” Annals of Surgical Oncology, vol. 14, no. 8, pp. 2281–2288, 2007.

[5] D. Baratti, S. Kusamura, A. D. Cabras, P. Dileo, B. Laterza, and M. Deraco, “Diffuse malignant peritoneal mesothelioma: failure analysis following cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC),” Annals of Surgical Oncology, vol. 16, no. 2, pp. 463–472, 2009.

[6] P. Jacquet, A. D. Stephens, A. M. Averbach et al., “Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy,” Cancer, vol. 77, no. 12, pp. 2622–2629, 1996.

[7] J. H. Stewart IV, P. Shen, G. B. Russell et al., “Appendiceal neoplasms with peritoneal dissemination: outcomes after cytoreductive surgery and intraperitoneal hyperthermic chemotherapy,” Annals of Surgical Oncology, vol. 13, no. 5, pp. 624–634, 2006.

[8] R. Younan, S. Kusamura, D. Baratti, A.-S. Cloutier, and M. Deraco, “Morbidity, toxicity, and mortality classification systems in the local regional treatment of peritoneal surface malignancy,” Journal of Surgical Oncology, vol. 98, no. 4, pp. 253–257, 2008.

[9] E. de Bree, A. J. Witkamp, and F. A. N. Zoetmulder, “Intra peritoneal chemotherapy for colorectal cancer,” Journal of Surgical Oncology, vol. 79, no. 1, pp. 46–61, 2002.

[10] P. Pilati, C. R. Rossi, S. Mocellin et al., “Multimodal treatment of peritoneal carcinomatosis and sarcomatosis,” European Journal of Surgical Oncology, vol. 27, no. 2, pp. 125–134, 2001.

[11] L. G. Bayón, P. H. Sugarbaker, S. G. Moreno, V. L. Vazquez, S. Alves, and B. J. Moran, “Initiation of a program in peritoneal surface malignancy,” Surgical Oncology Clinics of North America, vol. 12, no. 3, pp. 741–753, 2003.

[12] D. Jayne, “Molecular biology of peritoneal carcinomatosis,” Cancer Treatment and Research, vol. 134, pp. 21–33, 2007.

[13] P. Jacquet, A. D. Stephens, A. M. Averbach et al., “Analysis of morbidity and mortality in 60 patients with peritoneal carcinomatosis treated by cytoreductive surgery and heated intraoperative intraperitoneal chemotherapy,” Cancer, vol. 77, no. 12, pp. 2622–2629, 1996.

[14] V. J. Verwaal, H. van Tinteren, S. V. Ruth, and F. A. Zoetmulder, “Toxicity of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy,” Journal of Surgical Oncology, vol. 85, no. 2, pp. 61–67, 2004.

[15] D. Elias, S. Antoun, B. Raynard et al., “Treatment of peritoneal carcinomatosis with complete cytoreductive surgery and intraperitoneal chemohyperthermia (IPCH). A phase I-II study in order to define the best procedure,” Chirurgie, vol. 124, no. 4, pp. 380–389, 1999.

[16] P. H. Sugarbaker, “It’s what the surgeon doesn’t see that kills the patient,” Journal of Nippon Medical School, vol. 67, no. 1, pp. 5–8, 2000.

[17] S. Rúfán, F. C. Muñoz-Casares, J. Briceño et al., “Radical surgery-peritoneectomy and intraoperative intraperitoneal chemotherapy for the treatment of peritoneal carcinomatosis in recurrent or primary ovarian cancer,” Journal of Surgical Oncology, vol. 94, no. 4, pp. 316–324, 2006.

[18] C. R. Rossi, M. Deraco, M. de Simone et al., “Hyperthermic intraperitoneal intraoperative chemotherapy after cytoreductive surgery for the treatment of abdominal sarcomatosis: clinical outcome and prognostic factors in 60 consecutive patients,” Cancer, vol. 100, no. 9, pp. 1943–1950, 2004.

[19] P. H. Sugarbaker, R. Alderman, G. Edwards et al., “Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy,” Annals of Surgical Oncology, vol. 13, no. 5, pp. 635–644, 2006.

[20] R. M. Smeenk, A. Bex, V. J. Verwaal, S. Horenblas, and F. A. N. Zoetmulder, “Pseudomyxoma peritonei and the urinary tract: involvement and treatment related complications,” Journal of Surgical Oncology, vol. 93, no. 1, pp. 20–23, 2006.

[21] R. E. Bristow, R. S. Tomacruz, D. K. Armstrong, E. L. Trimble, and F. J. Montz, “Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis,” Journal of Clinical Oncology, vol. 20, no. 5, pp. 1248–1259, 2002.

[22] F. A. N. Zoetmulder and P. H. Sugarbaker, “Patterns of failure following treatment of pseudomyxoma peritonei of appendiceal origin,” European Journal of Cancer A, vol. 32, no. 10, pp. 1727–1733, 1996.

[23] P. Sugarbaker, Peritoneal Carcinomatosis: Drugs and Diseases, Kluwer Academic, Boston, Mass, USA, 1996.

[24] P. H. Sugarbaker, F. J. Gionala, J. C. Speyer, R. Wesley, I. Barofsky, and C. E. Meyers, “Prospective, randomized trial of intravenous versus intraperitoneal 5-fluorouracil in patients with advanced primary colon or rectal cancer,” Surgery, vol. 98, no. 3, pp. 414–422, 1985.

[25] S. Kusamura, R. Younan, D. Baratti et al., “Cytoreductive surgery followed by intraperitoneal hyperthermic perfusion: analysis of morbidity and mortality in 209 peritoneal surface malignancies treated with closed abdomen technique,” Cancer, vol. 106, no. 5, pp. 1144–1153, 2006.

[26] M. Y. Chen, C. Chiles, B. W. Loggie, R. H. Chaplin, M. A. Perini, and R. A. Fleming, “Thoracic complications in patients undergoing intraperitoneal heated chemotherapy with mitomycin following cytoreductive surgery,” Journal of Surgical Oncology, vol. 66, no. 1, pp. 19–23, 1997.

[27] O. Glehen, D. Osinsky, E. Cotte et al., “Intra peritoneal chemotherapy using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis:
morbidity and mortality analysis of 216 consecutive procedures,” *Annals of Surgical Oncology*, vol. 10, no. 8, pp. 863–869, 2003.

[28] A. J. Witkamp, E. de Bree, M. M. Kaag, G. W. van Slooten, F. van Coevorden, and F. A. N. Zoetmulder, “Extensive surgical cytoreduction and intraoperative hyperthermic intraperitoneal chemotherapy in patients with pseudomyxoma peritonei,” *British Journal of Surgery*, vol. 88, no. 3, pp. 458–463, 2001.

[29] P. Shen, J. Hawksworth, J. Lovato et al., “Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy with mitomycin C for peritoneal carcinomatosis from nonappendiceal colorectal carcinoma,” *Annals of Surgical Oncology*, vol. 11, no. 2, pp. 178–186, 2004.

[30] C. Montesani, R. de Milito, S. Chiappalone, P. Narilli, A. D’Amato, and G. Ribotta, “Critical evaluation of the anastomoses in large bowel surgery: experience gained in 533 cases,” *Hepato-Gastroenterology*, vol. 39, no. 4, pp. 304–308, 1992.

[31] H. N. López-Basave, F. Morales-Vasquez, J. M. R. Molina et al., “Morbidity and mortality of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: National Cancer Institute, Mexico City, Mexico,” *ISRN Oncology*, vol. 2011, Article ID 526384, 6 pages, 2011.

[32] B. W. Loggie, R. A. Fleming, R. P. McQuellon et al., “Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for disseminated peritoneal cancer of gastrointestinal origin,” *The American Surgeon*, vol. 66, no. 6, pp. 561–568, 2000.

[33] B. J. Park, H. R. Alexander, S. K. Libbuti et al., “Treatment of primary peritoneal mesothelioma by continuous hyperthermic peritoneal perfusion (CHPP),” *Annals of Surgical Oncology*, vol. 6, no. 6, pp. 582–590, 1999.

[34] F. Cavaliere, P. Perri, F. di Filippo et al., “Treatment of peritoneal carcinomatosis with intent to cure,” *Journal of Surgical Oncology*, vol. 74, no. 1, pp. 41–44, 2000.

[35] A. A. Sarnaik, J. J. Sussman, S. A. Ahmad, and A. M. Lowy, “Technology of intraperitoneal chemotherapy administration: a survey of techniques with a review of morbidity and mortality,” *Surgical Oncology Clinics of North America*, vol. 12, no. 3, pp. 849–863, 2003.

[36] T. Fujimura, Y. Yonemura, H. Fujita et al., “Chemohyperthermic peritoneal perfusion for peritoneal dissemination in various intra-abdominal malignancies,” *International Surgery*, vol. 84, no. 1, pp. 60–66, 1999.

[37] E. A. Levine, J. H. Stewart IV, G. B. Russell, K. R. Geisinger, B. L. Loggie, and P. Shen, “Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy experience with 501 procedures,” *Journal of the American College of Surgeons*, vol. 204, no. 5, pp. 943–955, 2007.