Original Article

Anesthesia Clinical Outcome and Management in Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy: A Retrospective Analysis

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Background: Anesthetic technique and outcome of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is not well established.

Objective: To evaluate the anesthetic management of CRS with HIPEC and to analyze whether supplement epidural anesthesia will provide any benefit on the outcomes.

Materials and Methods: All patients that underwent CRS with HIPEC between January 2008 and December 2017 at King Chulalongkorn Memorial Hospital were retrospective reviewed. Patients were divided into two groups, 1) received a combination of epidural and general anesthesia (EGA), and 2) received general anesthesia (GA) to compare intraoperative hemodynamic stability, postoperative pain control, time to tracheal extubation, and postoperative complications between groups.

Results: Twenty patients had EGA, and 14 patients had GA. EGA group had significant more incidences of intraoperative hypotension at 70% versus 21.4%, which required more use of vasopressor at 65% versus 21.4% ($p<0.05$). There was no statistical difference between groups in total blood loss, time to extubation, and ICU length of stay. There were no significant differences in the pain score at 12 and 24 hours postoperative. Epidural complications were not detected. There was no mortality within 30 days.

Conclusion: Adding epidural analgesia to GA in CRS with HIPEC increased the incidence of hypotension and did not reduce the pain or duration of extubation.

Keywords: Anesthesia; Epidural; HIPEC; Outcome

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In the past, intraperitoneal malignancy with peritoneal carcinomatosis was a sign of end-stage cancer disease and an incurable condition. The cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) have been developed to be a therapeutic option for selected patients with evidence of peritoneal carcinomatosis from the gastrointestinal tract, ovary, and the disease of pseudomyxoma peritonei. The CRS with HIPEC can increase life expectancy and reduce the rate of cancer recurrence[1-6]. CRS is a technique that peritoneally resect the macroscopic tumor from the abdominal organs. Next, HIPEC is performed by perfusing the abdominal cavity with 42°C to 43°C of chemotherapeutic agents to remove the microscopic tumor load. Currently, the evidence in the literature regarding the anesthetic management for CRS with HIPEC in Thailand is limited.

The CRS with HIPEC is a long and complex procedure. There are significant blood and fluid loss during tumor debulking in CRS phase. Before and during the HIPEC phase, there are hemodynamic, hematological, and metabolic alterations. Even in the early postoperative period, these changes can be detected and can significantly result in morbidity and mortality. Therefore, it is important that anesthesiologists understand these effects so they can achieve a better outcome post CRS with HIPEC.

The use of epidural anesthesia and analgesia are a part of an enhanced recovery program, mostly because it blunts the neuroendocrine response during surgery

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and have a better postoperative pain control as well as promote faster mobilization. Epidural analgesia has been widely used in surgery for the upper abdomen and has a very positive result in reducing the pain score. However, the sympathetic blockade produced by an epidural block, can result in hypoperfusion and organ dysfunction of which the latter can be detected after surgery[2,3].

A decade ago, CRS with HIPEC technique was developed at the King Chulalongkorn Memorial Hospital. As a result of this, the intraoperative hemodynamic stability, postoperative pain control, time to tracheal extubation, and postoperative complications of CRS with HIPEC procedures were retrospectively reviewed. The objective of the present study was to evaluate the effect of adding epidural analgesia to general anesthesia (GA) during CRS with HIPEC.

Materials and Methods

After obtaining the approval from the King Chulalongkorn Memorial Hospital's ethics Committee (IRB number 644/60) approval, the authors performed a retrospective medical chart review of all patients who had CRS with HIPEC at the present study institution between January 2008 and December 2017. The inclusion criteria were age 18 to 80 years and histologically proven to have peritoneal carcinomatosis. The exclusion criteria were incomplete medical record or missing data. The patients were divided into two groups, 1) patients who received a combination of epidural anesthesia and general anesthesia (EGA), and 2) patients who received GA.

The anesthetic monitoring for CRS with HIPEC at the authors' unit were as follows, arterial line, central venous pressure line, electrocardiogram (EKG), capnography, esophageal temperature, urine output, and pulse oximetry. Fluid infusions during surgery follow target central venous pressure 6 to 10 cm H_2O. Red blood cell was transfused when hematocrit was less than 28%. The occurrence of hypothermia was prevented by infusion of warm fluids into the patient, the use of warm water underbody mattress, the use of forced-air warming blanket, and the use of warm water irrigation in the surgical field. At the end of the surgery, all the patients were admitted to the intensive care unit (ICU). It was a routine procedure that the patient stayed overnight at the ICU after the surgery as per the hospital's protocol.

The patient's characteristics and underlying surgical pathology prior to surgery were extracted from the medical record of the patient. Intraoperative data included fluid infusions, transfusion of blood products, blood loss, urine output, temperature, number of hypotension events, and use of vasopressor were also retrieved from the medical record of the patient. Intraoperative hypotension was defined as mean arterial pressure (MAP) from direct intra-arterial pressure measurement (IBP) of less than 55 mmHg for more than 10 minutes. Postoperative data such as time to extubation, length of stay in the ICU, pain score, opioids consumption, prothrombin time international normalized ratio (PT-INR), platelet count, white cell count, creatinine, and major complications were also extracted from the patient's medical record. Descriptive statistics presented the patient's data. The incidence of intraoperative hypotension, the use of a vasopressor, intravenous fluid, blood products, blood loss, time to extubation, length of stay in the ICU, postoperative pain score at 24 and 48 hours, and opioids consumption were compared between the two groups.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics, version 21.0 (IBM Corp., Armonk, NY, USA). Categorical data were expressed as numbers or percentages and continuous variables were presented as mean and standard deviation if the data was normally distributed. If the data was not normally distributed, then the data was presented as median, minimum, and maximum. When the data were different between two groups, t-test was used for continuous variables, chi-square (χ^2) test, or Fisher's exact test was used for nominal variables, and Mann-Whitney test was used for postoperative pain score.

Results

Between January 2008 and December 2017, 34 patients underwent CRS with HIPEC in the present study institute. Twenty patients received a combination of EGA while 14 patients received GA. The diagnoses were appendiceal, colorectal, and ovarian cancer. The median age was 58 years with a range of 37 to 78 years old, and 73.8% were women. The demographic data between the two groups were comparable (Table 1).

In the EGA group, all epidural catheters were inserted in the thoracic region from T8 to T12 and the anesthesiologist selected the precise anatomic level to match the planned incision. Epidural anesthesia was induced with an initial bolus of 0.25% bupivacaine 8 to 10 ml, followed by a continuous infusion of 0.25%

Table 1. Patients' demographic data

Data	EGA (n=20); mean±SD	GA (n=14); mean±SD	p-value
Age (year)	55±11	62±8.8	0.069
Sex (male:female)	4:16	5:9	0.307
BMI	24.1±3.4	27.9±11.2	0.056
Anesthetic time (hour)	11.3±1.6	10.6±1.4	0.261
ASA physical status (I:II:III)	6:10:4	2:6:6	0.299

SD=standard deviation; EGA=epidural and general anesthesia; GA=general anesthesia; BMI=body mass index; ASA=American Society of Anesthesiologists

Table 2. Intraoperative data

Data	EGA (n=20); median (min-max)	GA (n=14); median (min-max)	p-value
Hypotension; n (%)	14 (70.0)*	3 (21.4)	0.005
Vasopressor used; n (%)	13 (65.0)*	3 (21.4)	0.012
Blood loss (mL)	900 (200 to 5,000)	1,000 (500 to 1,300)	0.284
Crystalloid (L)	3.85 (1 to 9)	3.45 (2 to 6)	0.264
Synthetic colloid (L)	1.0 (0.5 to 2)	1.0 (0.5 to 2.5)	0.264
FFP (mL)	524 (180 to 1,846)	822 (200 to 1,158)	0.841
PRC (mL)	459 (196 to 1,719)	350 (209 to 1,176)	0.181
Urine output (mL/kg/hour)	1.9 (0.8 to 7.0)	2.1 (0.6 to 4.5)	0.624

EGA=epidural and general anesthesia; GA=general anesthesia; FFP=fresh frozen plasma; PRC=packed red cell

* p<0.05

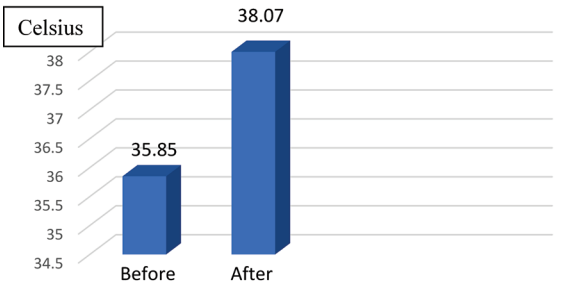

Figure 1. Core temperature before infusion and after removal of HIPEC.

bupivacaine with fentanyl of 2 mcg/ml at the rate of 4 to 5 ml/hour until the end of surgery. Then 4 mg of morphine in normal saline 10 ml was administered epidurally. GA was induced in both groups with propofol, cisatracurium or rocuronium, while sevoflurane or desflurane 0.8 to 1.2 MAC, oxygen 40% in air, and cisatracurium or rocuronium were used for maintenance. For the patient without epidural anesthesia, increment of 2 to 3 mg of morphine was administered intravenously.

Intraoperative data showed that there was a significant higher incidence of hypotension and more vasopressor use in the EGA group (Table 2). There were no significant differences between the two groups for the following variables, blood loss, infusion of crystalloid and colloid, amount of blood, and fresh frozen plasma transfused. The median blood loss was 1,000 ml and the range was 200 to 5,000 depending on the type of surgery performed and more than half of the patients required blood component transfusion. In 70% of the patients from EGA group, intraoperative hypotension occurred significantly much more than in the GA group at 70% versus 21.4% ($p<0.05$). About 65% of all patients from EGA group required more use of vasopressor compared to those from the GA group at 65% versus 21.4% ($p<0.05$). The mean core temperature after the CRS phase was 35.85°C and when heat chemotherapeutic infusion was performed in the HIPEC phase, there was a significant increase in the temperature. After hyperthermic intraabdominal chemotherapeutic was removed, the temperature increased incrementally by a mean difference of 2.2°C from 35.85°C to 38.07°C (Figure 1). The mean temperature before and after HIPEC were comparable between the two groups. One patient from the EGA group and one patient from the GA group had an increase in core temperature greater than 39°C.

Postoperative analgesia was maintained with intermittent epidural injection of 4 mg of morphine every 12 hours for at least 48 hours, or combination of 0.1% bupivacaine with fentanyl 2 mcg/mL were continuously infusion epidurally at a rate of 4 mL/hour with epidural catheter. However, after 72 hours, all epidural catheters were removed from the patients. In the patients without epidural, the patient-controlled analgesia PCA system was with intravenous morphine, which was continuously infused at a rate of 1 mg/hour, bolus 1 mg, lockout 5 minutes with a maximum dose in four hours was 30 mg, or intravenous fentanyl at 20 to 60 mcg/hour by infusion pump for at least 48 hours after the operation. The rescue analgesics in both groups were intravenous tramadol.

The course of postoperative data is shown in Table 3. All patients intubated with ventilator support except one patient from the EGA group who was extubated in the operating room. The rest of the patients in the EGA group were extubated within two days after surgery, whereas 7% of the patient from the GA group had to delay extubation to the third day after postoperation. There was no significant

Table 3. Postoperative data

Data	EGA (n=20); median (min-max)	GA (n=14); median (min-max)	p-value
VAS pain score at 12th hour	2 (0 to 6)	3 (0 to 8)	0.845
VAS pain score at 24th hour	1.5 (0 to 4)	2 (0 to 4)	0.732
First 24 hours IV tramadol used (mg/kg)	0.1 (0 to 3.9)*	3.1 (0.9 to 3.9)	<0.001
Time to stay in ICU (hour)	24 (12 to 62)	34 (13 to 60)	0.430
Time to extubation (hour)	11.5 (0 to 3.8)	12.5 (9 to 52)	0.091

EGA=epidural and general anesthesia; GA=general anesthesia; VAS=visual analog scale; IV=intravenous; ICU=intensive care unit

* p<0.05

Table 4. Postoperative complications

Complications	EGA (n=20)	GA (n=14)
Acute kidney injury	1	1
UTI sepsis	1	1
Delirium	1	-
Subdural hematoma	1	-
Surgical anastomosis leakage	-	2
Arrhythmia	-	1

EGA=epidural and general anesthesia; GA=general anesthesia; UTI=urinary tract infection

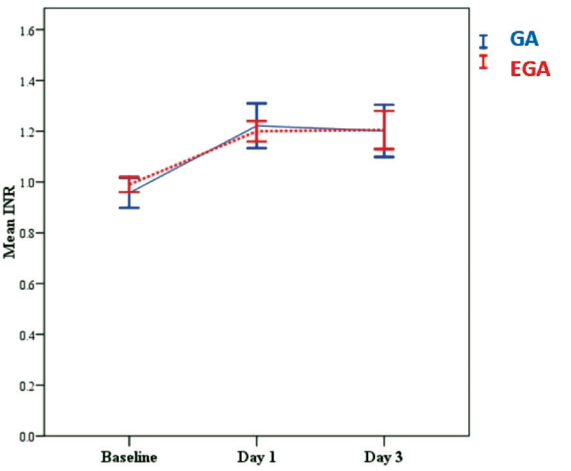

Figure 2. PT-INR at baseline, day 1 and day 3.

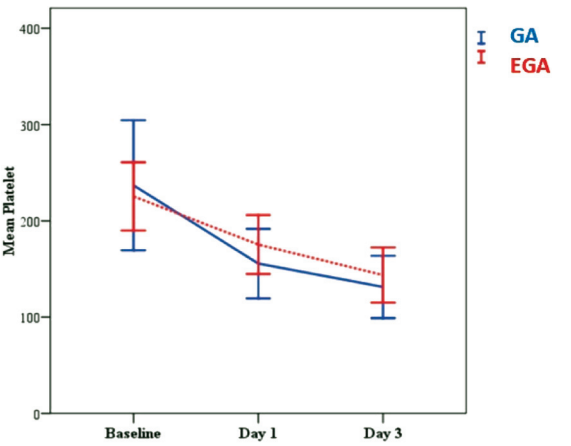

Figure 3. Platelet count at baseline, day 1 and day 3.

difference in the median time to extubation between the two groups at 11.5 hours in the EGA group and 12.5 hours in the GA group. Patients in the EGA group were discharged from the ICU earlier than in the GA group, but this was not statistically significant at 24 hours in the EGA group versus 34 hours in the GA group. The visual analog scale (VAS) pain score at 12 and 24 hours postoperation were also not statistically different between the two groups with scores of 2 and 1.5 in the EGA group, and 3 and 2 in the GA group. Tramadol was intravenously administered for 24 hours, which was lower in the EGA group ($p<0.05$).

Postoperative complications were not significantly different between the two groups (Table 4) and there was no mortality 30 days postoperation. There was an insignificant rising of creatinine and white blood cell count on day 1 and day 3 in both groups. Two patients (5.8%) developed acute kidney injury according to RIFLE criteria, two (5.8%) had UTI sepsis, two (5.8%) had surgical anastomosis leakage, one (2.9%) had post-operative subdural hematoma, one (2.9%) had delirium, and one (2.9%) developed arrhythmia. There was no statistical difference in PT-INR and platelet count between the two groups. All patients in both groups had significantly elevated PT-INR and decreased platelet count compared to the baseline levels. PT-INR elevation from baseline with a mean difference on day 1 and on day 3 were statistically significant at 0.21 and 0.22 in the EGA group, and 0.26 and 0.24 in the GA group, respectively (Figure 2). There was a significant reduction in the platelet count compared to the baseline level at –5,000 and –8,170 in the EGA group, and –8,136 and –10,564 in the GA

group, respectively) (Figure 3). In the EGA group, there were no complications related to placement of the epidural catheter or its removal such as abscess or hematoma.

Discussion

Thirty-four patients underwent CRS with HIPEC procedures in the present study institution. The results suggest that use of epidural anesthesia and analgesia did not improve the outcome.

A combination use of EGA showed a significant intraoperative hemodynamic effect. There was a higher incidence of hypotension that required more use of vasopressor. Epidural analgesia did not show any superiority in pain scores compare to intravenous PCA morphine or fentanyl. For both groups, there was no reduction of time stayed in the ICU and did not shorten the extubation time. However, one patient from the EGA group was extubated immediately after surgery while the rest of the patients in the EGA group were extubated within two days after surgery whereas, 7% of the patient from the GA group had to delay extubation to the third day after postoperation. The present study result was different from the previous studies that reported that patient who received epidural analgesia had higher rate of immediate postoperative extubation in about 40% to 78%[2-4].

The decision to use epidural must be done case by case. In the present study, the authors did not have any serious complication, but in a previous study[4], one of their patients developed epidural abscess. The cause of epidural abscess may be postoperative infection or sepsis. Postoperative coagulopathy is considered a risk when CRS with HIPEC is performed, thereby, limiting the use and safe management of epidural anesthesia. Hence laboratory values included PT-INR and platelet count should be checked and coagulopathy should be corrected before removal of the epidural catheter. Moreover, neutropenia or another systemic toxicity of chemotherapeutic must be considered in epidural catheter infection.

An elevated level of PT-INR and decreased platelet count are statistically significant at day 1 and day 3 postoperation. Another major concern is postoperative coagulopathy because there was a massive blood loss and blood transfusion, dilutional coagulopathy, hypothermia, and HIPEC. These factors are known to occur after surgery. From the previous studies, PT-INR were normalized gradually within three to five days[7]. Therefore, it is important to monitor the epidural catheter to ensure that there is no epidural hematoma. In the present study, one patient from the EGA group developed a thin subdural hematoma during post operative period, this patient had an elevated PT-INR that increased to 1.4 and platelet count dropped to 104,000.

CRS with HIPEC is a long, complex, abdominal surgical procedure with additional hyperthermia and intraoperative chemotherapy. It is expected that there will be extensive bleeding and shifts of fluid. In the present study, a variety of surgeries were performed so the blood loss ranged from 200 to 5,000 mL. The blood loss in the present study was lower compared to the previous studies, which can be explained by the present study surgical technique and the surgeries performed were less extensive[1,7]. It is crucial to prepare the blood component, intravenous access, and vasopressor in advance so when it is needed, it will be available for use immediately. Administration of normal fluid is guided by the estimates of blood loss, urine output, hemodynamics, and hemoglobin and acid-base measurements, because there will be a large fluid shift so it may be useful to also monitor the cardiac output non-invasively.

Temperature changes such as hypothermia during CRS phase and hyperthermia during the HIPEC phase are of concern when administering anesthesia. The authors found that temperature can rise incrementally by 2.2°C during the HIPEC phase. In our study, 5.8% of the patients had a higher temperature than 39°C compared to the previous study[8], which had a temperature higher than 39°C in 18% of their patients. This may be due to the use of an effective cooling method. Thus, it is important to monitor intraoperative temperature and prepare the cooling device that is optimized to achieve normal range of temperature throughout the surgery process.

A combination use of EGA showed a significant intraoperative hemodynamic effect. There was higher incidence of hypotension that required more use of vasopressor at 70% in EGA group versus 21.4% in GA group ($p<0.05$). Epidural analgesia did not show any superiority in pain scores at 12 and 24 hours postoperative compared to the intravenous PCA regimen. However, the EGA group had lesser tramadol consumption for rescued pain compared to the GA group at 0.1 mg/kg in EGA group versus 3.1 mg/kg in the GA group ($p<0.05$). These results did not show any benefit of epidural anesthesia pertaining to the function of the respiratory system or postoperative respiratory complications. There was no reduction of neither the ICU length of stay nor the extubation time. However, one patient from the EGA group was

extubated immediately after surgery, while the rest of the patients in the EGA group were extubated within two days after surgery, whereas 7% of the patient from the GA group had delayed extubation to the third day postoperation. The present study results were different from the previous studies that reported that patient who received epidural analgesia had higher rate of immediate postoperative extubation in about 40% to 78%[2-4]. The reasons that intubation continued in the present study were the concerns about the long duration of surgery, the extensive blood loss, and the hemodynamic derangement.

The decision to use epidural anesthesia in CRS with HIPEC should be done case by case. In the present study, there was no serious complication, but in a previous study[4], one of their patients developed epidural abscess. Neutropenia or another systemic toxicity of chemotherapy must be considered regarding to epidural catheter infection. Postoperative coagulopathy is considered another risk when CRS with HIPEC is performed. There was a massive blood loss, dilutional coagulopathy, and chemotherapy, which affected coagulation. The present study revealed statistically significant elevated level of PT-INR and decreased platelet count at day 1 and day 3 postoperation. From the previous studies[7], PT-INR were normalized gradually within three to five days. Hence laboratory values including PT-INR and platelet count should be checked and coagulopathy should be corrected before removal of the epidural catheter. Therefore, it is important to monitor the epidural catheter to ensure that there is no epidural hematoma. In the present study, one patient from the EGA group developed a thin subdural hematoma during post-operative period; this patient had an elevated PT-INR that increased to 1.4 and platelet count dropped to 104,000.

Postoperative complications were not significantly different between the two groups. In the present study, 5.8% of the patients had acute kidney injuries, which indicated that hemodynamic optimization, including optimizing cardiac output, tissue perfusion, and oxygenation is recommended to prevent renal injury.

The present study has some limitations due to small number of patients and that all the patients were from a single center. Furthermore, data were collected retrospectively, and anesthetic management protocol was not strict.

Conclusion

The CRS with HIPEC is a high-risk procedure with extensive fluid shift and hemodynamic and metabolic derangement, so it is important to prepare things in advance for any situation that may arise and communicating constantly with the team is essential. Adding EGA increased the incidence of hypotension and the use of vasopressor. Moreover, it did not reduce the pain better than in the GA group, nor had faster extubation. The risks of postoperative coagulopathy and infection are of concern when selecting an epidural technique.

What is already known on this topic?

The CRS with HIPEC is a complex, large-extent, and long-duration surgical procedure. There are many concerns for anesthesiologists including significant blood and fluid loss, hemodynamic, hematological, and metabolic alterations during intraoperative and early postoperative period. Adequate pain control is one of the keys to enhance recovery after surgery. Epidural analgesia has been widely used as effective pain control in upper abdominal surgery.

What this study adds?

Addition of continuous epidural anesthesia to GA in cytoreductive surgery with HIPEC did not show significant benefit on acute postoperative pain control, ICU length of stay, and time to extubation. This study revealed the higher incidence of intraoperative hypotension and vasopressor need in patients that received epidural anesthesia.

Conflicts of interest

The authors declare no conflict of interest.

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