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A clinical case

Anesthetic management for extended pleurectomy with intrapleural hyperthermic chemoperfusion (HITOC) for pleural mesothelioma: The first experience

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Abstract

Hyperthermic intrapleural chemoperfusion (HITOC) is a type of adjuvant treatment performed immediately after surgery in the operating room. HITOC is a challenging procedure not only for the surgical team but also for the anesthesiologists.

This publication is devoted to the first anesthesiological manual in Kazakhstan for HITOC. During the entire operation, such changes as acute changes in body temperature associated with increased intrathoracic pressure during the administration of chemotherapeutic fluid (from 3 to 5 liters of solution at 42 C) were expected, and they could contribute to severe hemodynamic disturbances, with an increase in cardiac output, a decrease in systemic vascular resistance and an increase in cardiac index and end-tidal carbon dioxide concentration (EtCO2). It is also important to consider the nephrotoxicity of the chemotherapeutic agents used and the need to prevent kidney

damage. Increased body temperature also led to metabolic acidosis and an increase in serum lactate levels. For pain management, intraoperative epidural analgesia was performed using local anesthetics to reduce intraoperative systemic opioid requirements and reduce the need for prolonged mechanical ventilation. Severe complications associated with HITOC are rare, and renal complications can be reduced by fluid balancing and cytoprotection. Cytoreductive surgery combined with HITOC can be performed with acceptable morbidity and mortality rates in selected patients. Patients should be evaluated by a multidisciplinary team to determine their eligibility for this therapeutic alternative. A team of trained anesthesiologists and intensivists who are leaders in the preoperative, operative, and postoperative care of HITOC candidates is critical to the success of the procedure. Early clinical results may support the use of this surgical option to provide better local tumor control in a multimodal treatment setting.

Keywords: pleural mesothelioma, pleurectomy, epidural block, hyperthermic intrapleural chemotherapy, anesthesiological assistance.

1. Introduction

The effect of hyperthermia on human neoplastic cells in neoplasms was established in the 1970s. Subsequently, hyperthermic intrathoracic chemotherapy (HITHOC), also called HIOC or HITOC, was developed. HITOC is a type of adjuvant treatment performed immediately after the surgical stage in the operating room [1,2]. HITOC is an analogue of HIPEC. It is used in the treatment of malignant mesothelioma, a primary malignant neoplasm of the pleura. And recently, this method has been evaluated in the treatment of secondary malignant neoplasms of the pleura (e.g., thymus tumors, secondary pleural carcinoma) [3,4].

Table 1 - Countries and the number of clinics performing HITOC worldwide

Region / Country	Number of clinics / centres	Comments and examples
Germany	~17 centres (university hospitals)	Since 2008, 343 HITHOC procedures have been carried out in 17 thoracic-surgery departments; centres include Regensburg, Munich, Heidelberg, Freiburg and Cologne (pubmed.ncbi.nlm.nih.gov, en.wikipedia.org)
Czech Republic	~2 clinics	Offered in leading university hospitals; Doctor.Global lists two centres
Belarus	1 clinic	N.N. Alexandrov National Cancer Centre in Liasny — one of nine HITHOC-performing clinics worldwide
France	1 clinic	Included among the nine global centres providing HITHOC services
Netherlands	1 clinic	Doctor.Global reports one centre.
Japan	>1 investigation (Nara)	"Nagada Medical University" has published a small series involving 19 patients
the USA	≥5 specialized centres	Baylor St. Luke's (Houston), AdventHealth (Orlando), Brigham & Women's (Boston), UPMC (Pittsburgh), Moffitt (Tampa)

HITOC is a complex procedure not only for the surgical team but also for anesthesiologists. Numerous changes in hemodynamics (hypotension, tachycardia, cardiac arrhythmias), respiratory parameters, temperature, metabolic, and coagulation parameters are possible during the perioperative period [5]. Adverse events in the perioperative period are a result of hypothermia and fluid redistribution during cytoreductive surgery, while in the second phase – during perfusion – they are a result of a rapid increase in intrathoracic pressure, regional and systemic hyperthermia, and the toxicity of cytostatics [6,7].

Consequently, the main goals of anesthesia are to monitor and maintain the patient's hemodynamic stability with targeted fluid control in accordance with the enhanced recovery after surgery (ERAS or Fast track) protocol, as well as to prevent acidosis by maintaining normothermia and normal gas exchange [8,9,10].

Since HITOC has only recently come into use, there are few described studies, clinical cases, and publications worldwide focusing on the anesthesia, intensive care, and postoperative period aspects of this method. This circumstance creates difficulties in finding information regarding not only the procedure itself but also perioperative measures such as anesthetic management and the early postoperative period. There is no precise methodology, protocol, or guideline that would help anesthesiologists and intensivists be prepared for all complications and outcomes of the operation.

The purpose of this publication was to demonstrate our own experience in providing anesthetic management during HITHOC in patients with malignant pleural mesothelioma.

This publication describes a clinical case of anesthetic management during HITOC for a patient with pleural mesothelioma. The patient underwent 4 courses of chemoradiotherapy, followed by surgical intervention – extended pleurectomy + HITOC.

2. Case presentation

A 35-year-old male patient was diagnosed with pleural mesothelioma. Relevant comorbidities included Stage 1 hypertension with a risk of 3 and Grade 2-3 exogenous-constitutional obesity (Body Mass Index [BMI] of 42.9 kg/m^2). His estimated glomerular filtration rate (eGFR), calculated using the CKD-EPI formula, was 89 mL/min/1.73m^2. His medical history indicated a nasal septum deviation surgery in 2021. On December 21, 2022, the patient underwent right thoracoscopy with pleural mass biopsy, which confirmed the diagnosis of Stage II (T2N0M0) pleural mesothelioma. Prior to the current surgical intervention, he had completed six courses of chemotherapy. The planned surgical procedure comprised an extended pleurectomy (EP) with HITOC, performed under general anesthesia in conjunction with epidural analgesia.

Following a thorough preoperative anesthetic consultation and the acquisition of written informed consent, the patient was approved for surgery. Given that this specific surgical procedure had not been previously performed in the Republic of Kazakhstan, a specialized approach was adopted. This involved extensive discussion of the patient's medical history and the collaborative development of a comprehensive management strategy by the anesthesia team. A detailed, staged anesthetic plan was formulated for this patient, and potential intraoperative and postoperative complications were anticipated.

Preoperative assessment included evaluation of the patient's cardiopulmonary reserve through comprehensive clinical examination, echocardiography, and a six-minute walk test. Additionally, the dynamic and functional reserve of the respiratory system was assessed via spirometry and arterial blood gas analysis.

Upon arrival in the operating room, the patient was conscious, oriented, and hemodynamically stable. Continuous monitoring included electrocardiography (ECG), non-invasive blood pressure (NIBP), and pulse

oximetry. Premedication consisted of diazepam 10 mg intramuscularly and dexamethasone 8 mg (for airway edema prophylaxis), administered 30 minutes prior to surgical incision. Venous access was secured with two 18 G catheters in the upper extremities. An epidural catheter was inserted at the Th7-Th8 thoracic vertebral level to facilitate both intraoperative and postoperative analgesia. Combined general anesthesia was induced with fentanyl 100 mcg, propofol 200 mg, ketamine 100 mg, and rocuronium 50 mg. Endotracheal intubation was successfully performed without complications using a left-sided 41 Fr double-lumen tube. The Volume Control mode was selected with a tidal volume of 4-6 mL/kg, FiO2 of 50%, respiratory rate of 14 breaths/min, inspiratory-to-expiratory (I:E) ratio of 1:2, and a positive end-expiratory pressure (PEEP) of 5 cm H2O. Monitoring was further augmented with a temperature probe and central venous access. Anesthesia was maintained with sevoflurane (MAC 1) and a continuous epidural infusion of ropivacaine titrated via a perfusor at a rate of 2-3 mL/hour. The patient was positioned in a lateral decubitus position on a warming/cooling blanket.

This required adjustments to the mechanical ventilation parameters, including a tidal volume of 2-3 mL/kg, an FiO2 of 60%, a respiratory rate of 20 breaths/min, (I:E) ratio of 1:1.5, and a PEEP of 8 cm H2O.

The primary surgical phase, an extended pleurectomy, was protracted and presented significant surgical challenges, including considerable blood loss. Volume resuscitation was managed using crystalloids and colloids in accordance with the Enhanced Recovery After Surgery (ERAS) protocol, addressing an estimated blood loss of 1300 mL.

Throughout the intraoperative period, serial acid-base status (ABS) analyses (Figure 1) were performed to guide the correction of acute anemia, metabolic disturbances, and electrolyte imbalances. To maintain appropriate glycemic control, blood glucose levels were monitored at regular intervals. All warming devices were activated approximately 45 minutes prior to the initiation of HITOC.

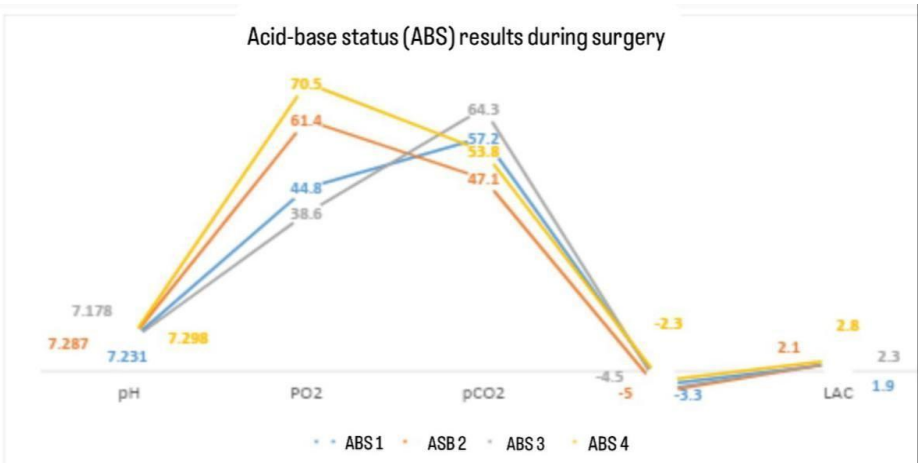

Figure 1 - illustrates the acid-base status (ABS) data for the patient during the HITOC. The time points for the ABS analyses are: ABS 1 at the start of surgery, ABS 2 during the cytoreduction phase, ABS 3 during the HITOC phase, and ABS 4 upon transfer to the Anesthesia and Resuscitation Intensive Care Unit (ARICU)

Throughout the intraoperative period, the patient maintained a subcompensated mixed acidosis with pH values ranging from 7.2-7.3, PCO2 between 47-57 mmHg, base excess (BE) from 3.2-5.4 mmol/L, and HCO3- between 18-23 mmol/L. Elevated metabolite levels were also observed, including hyperglycemia up to 8 mmol/L and lactatemia up to 3 mmol/L.

Intrapleural chemoperfusion was initiated with a Cisplatin solution at 75 mg/m^2 (total 206.25 mg), diluted in 6.5 liters of 0.9% sodium chloride solution, heated to 42°C. The total duration of the HITOC phase was 40 minutes.

Optimal body temperature was maintained by infusing balanced cold solutions (solution temperature

24-26°C), applying a cooling mattress, and using head cooling. Temperature monitoring was performed at two sites: an esophageal temperature probe and a skin temperature probe positioned over the right scapula. The patient's core body temperature, as measured by the esophageal probe, ranged from 37°C to 38.2°C (Figure 2).

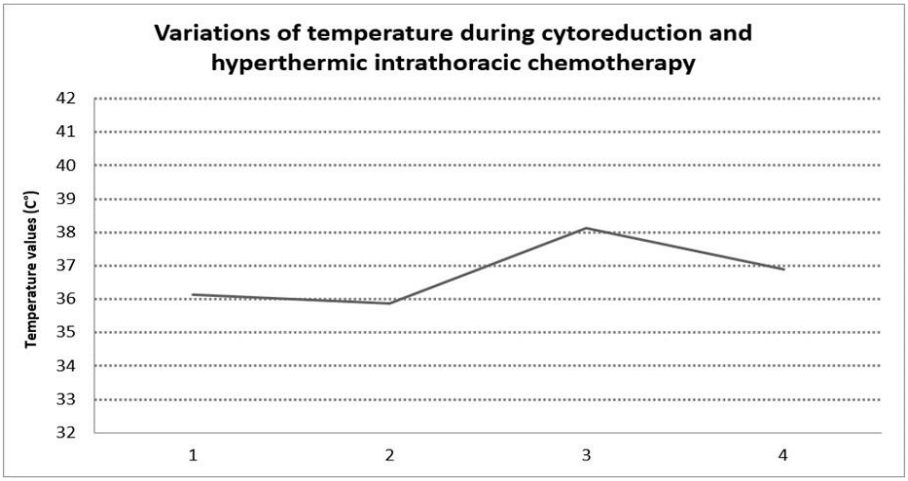

Figure 2 illustrates the fluctuations in body temperature observed during both the cytoreduction phase and the HITOC) phase. Interval 1-2 represents the cytoreduction phase. Interval 2-3 indicates the period of cytostatic perfusion. Interval 3-4 marks the conclusion of HITOC

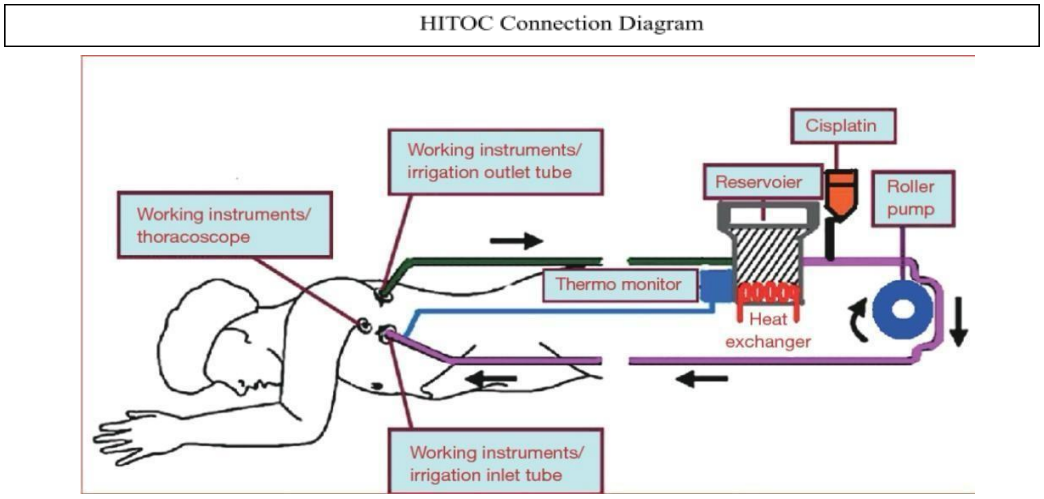

Figure 3 illustrates the HITOC circuit connection for the patient

The patient was subsequently connected to the HITOC device (Figure 3). Approximately 15 minutes into the HITOC procedure, a notable decrease in oxygen saturation (SpO2) was observed, dropping to 88-90% on the monitor. Concurrently, arterial blood pressure (BP) decreased to 70/48 mmHg. A norepinephrine infusion was initiated at a maintenance dose, and ventilatory parameters were adjusted. The mechanical ventilation mode was switched to Pressure Control, with an FiO2 of 60%, a Ppeak of 35 cm H2O, an Pinsp of 18 cm H2O, a respiratory rate with an I:E ratio of 1:2, and PEEP set to 0 cmH2O. Despite these interventions, the patient's blood pressure remained low (90/60 mmHg), and SpO2 stayed at 88% until the conclusion of the HITOC session (Figure 4). Following the completion of the HITOC session, the patient's SpO2 improved, ranging from 92-96%, and hemodynamic stability was maintained with norepinephrine until the end of the operation.

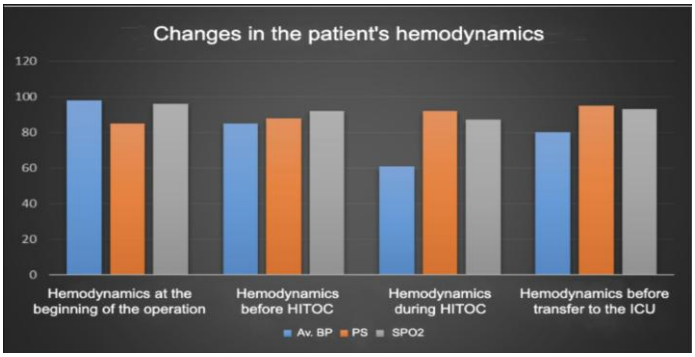

Figure 4 illustrates the hemodynamic fluctuations observed during the procedure

Following the completion of HITOC, a thorough revision of the surgical wound and hemostasis were performed. Subsequently, in consultation with the surgical team, two-lung ventilation (TLV) was re-established with adjusted mechanical ventilation parameters: FiO2 of 60%, inspiratory pressure (Pins) of 20, respiratory rate of 18 breaths/min, I:E ratio of 1:1.5, and PEEP of 8 cmH2O.

At the conclusion of the operation, the patient's vital signs were as follows: arterial blood pressure (BP) of 101/65 mmHg with continuous vasopressor support from norepinephrine at 0.002 mcg/kg/min, a body temperature of 36.8°C, a pulse rate (PR) of 101 beats/min, and an SpO2 of 91%. The total volume of intravenous infusion administered was 6690 mL.

The overall duration of anesthesia was 7 hours and 18 minutes. The total rocuronium consumption throughout the anesthetic period was 200 mg. Urine output was 1250 mL and concentrated. The patient was re-intubated with an 8.0 endotracheal tube on the operating table without complications. Subsequently, the patient was transferred to the intensive care unit.

In the postoperative period, persistent hypotension necessitated vasopressor support for two days. Transfusion of red blood cell suspension was administered due to hemoglobin levels of 70 g/L. Norepinephrine was discontinued on the third postoperative day following stabilization of the patient's hemodynamics. A single episode of elevated body temperature, reaching 38°C, was noted 24 hours post-surgery. Lung function, as assessed by spirometry and arterial blood gas analysis (ABS), remained within normal limits. The patient remained in the intensive care unit for 3 days before being transferred to a general ward.

Beginning on postoperative day 5, the patient experienced recurrent evening fevers. Consequently, antimicrobial therapy was adjusted in collaboration with a clinical pharmacologist, based on wound culture results and blood sterility analyses. Follow-up computed tomography (CT) scans of the chest did not reveal evidence of pneumonia; however, infiltrative changes were observed in the soft tissues surrounding the post-thoracotomy wound.

Additionally, a period of drug-induced acute kidney injury (AKI) was noted, characterized by a decrease in eGFR (EPI formula) to 68 mL/min/1.73m^2. Renal function recovered within 5-7 days following targeted treatment. In the ward, the patient received comprehensive therapy, including antibacterial, antifungal, anticoagulant, hepatoprotective, gastroprotective, intravenous fluid, and analgesic regimens.

3. Discussion

Extended pleurectomy combined with intrathoracic hyperthermic chemoperfusion is a highly infrequent procedure globally. Our experience represents the first reported case in Kazakhstan. Anticipated physiological alterations included acute body temperature changes, which can be attributed to increased intrathoracic pressure following the instillation of the chemotherapeutic solution (typically 3 to 5 L at 42°C). These changes can contribute to severe hemodynamic disturbances, manifesting as increased cardiac output, reduced systemic vascular resistance, elevated cardiac index, and an increase in EtCO2 [1,4,8].

HITHOC, when integrated with cytoreductive surgery for patients with malignant pleural neoplasms, including mesothelioma and recurrent thymoma, is a method with confirmed clinical efficacy in enhancing both recurrence-free and overall survival [2,6,11,14]. However, the execution of this procedure is associated with a spectrum of pronounced physiological and metabolic changes that demand meticulous attention from the anesthesiology service.

A critical determinant of the perioperative course and outcome is the systemic absorption of cytostatics, particularly cisplatin, when administered under hyperthermic conditions. Several studies have demonstrated that despite regional drug administration, a significant quantity of the active substance is absorbed into the systemic circulation, potentially reaching nephrotoxic concentrations [1,3,13]. This necessitates mandatory patient hydration, implementation of forced diuresis, and hourly urine output monitoring to prevent acute kidney injury.

The hyperthermic solution (typically 42°C) exerts a complex influence on patient physiology, encompassing vasodilation, increased cardiac output, elevated oxygen consumption, and augmented carbon dioxide production. Consequently, temperature management mandates stringent control of core body temperature (via esophageal, urinary, or other invasive monitoring) and the application of active external cooling methods. In instances where hyperthermia exceeds 39–39.5°C, a reduction in solution temperature and metabolic correction may be required [7,8,15].

Fluid losses during the procedure can be substantial, resulting from both exudation through the pleural surface and evacuation of the perfusate. This underscores the necessity for goal-directed fluid therapy (GDFT), guided by comprehensive hemodynamic monitoring. The utilization of advanced monitoring modalities (e.g., PiCCO, FloTrac) and titrated vasopressor support enables optimization of perfusion pressure, reduction of infusion volumes, and mitigation of hypervolemia risk. The judicious use of albumin-containing solutions may be warranted in cases of reduced oncotic pressure, particularly in patients presenting with preoperative hypoalbuminemia.

Anesthetic management during HITHOC mandates an individualized approach, considering the high metabolic load, potential drug toxicity, and the extent of surgical intervention. Studies by Ried et al. (2021) and specialized anesthesiology reviews [8] emphasize the advisability of employing total intravenous anesthesia (TIVA) to enhance temperature and metabolic control, while avoiding adverse effects of inhaled anesthetics under hyperthermic conditions. Protective ventilation (tidal volume ≤6 mL/kg ideal body weight, PEEP ≥5 cm H_2O), blood gas and lactate monitoring, and early extubation in the context of stable gas exchange are indispensable components of the protocol.

Coagulopathies, frequently encountered in the late intraoperative or early postoperative period, necessitate real-time hemostasis assessment methods, specifically thromboelastography (TEG) or rotational thromboelastometry (ROTEM). This allows for targeted correction of hemostatic disturbances and minimizes the volume of transfusion therapy.

In conclusion, the successful execution of HITHOC requires interdisciplinary collaboration and strict adherence to standards of perioperative monitoring and support. Standardization of anesthetic approaches, encompassing algorithms for fluid, vasoactive, and

temperature management, is paramount to reducing the incidence of complications and enhancing procedure safety.

4. Conclusions

It is crucial to consider the nephrotoxicity of the chemotherapeutic agents utilized and the imperative to prevent renal injury. Elevated body temperature also contributed to metabolic acidosis and increased serum lactate levels.

For pain management, intraoperative epidural analgesia with local anesthetics was employed to reduce systemic opioid requirements and diminish the need for prolonged mechanical ventilation. Severe complications associated with HITOC are rare, and renal complications can be mitigated through meticulous fluid balance and cytoprotection.

Cytoreductive surgery combined with HITHOC can be performed with acceptable morbidity and mortality rates in selected patients. Patients must be evaluated by a multidisciplinary team to determine their eligibility for this therapeutic alternative. The most critical role in the success of the operation is played by a team of well-prepared anesthesiologists and intensivists, who are leading specialists in the preoperative, intraoperative, and postoperative management of HITHOC candidates. Early clinical outcomes can foster the expanded use of this surgical option to provide superior local tumor control within a multimodal treatment framework.

Conflict of Interests. None declared.

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Плевра мезотелиомасы кезіндегі плевраішілік гипертермиялық химоперфузия (HITOC) мен кеңейтілген плеврэктомия үшін анестезиялық нұсқама: Алғашқы тәжірибе

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Түйіндеме

Гипертермиялық плевра ішілік химиоперфузия (HITOC) – операция бөлмесінде отадан кейін бірден орындалатын адъювантты емнің бір түрі. HITOC хирургиялық топ үшін ғана емес, анестезиологтар үшін де күрделі процедура.

Бұл қолжазба Қазақстандағы алғашқы анестезиологиялық тәжірибеге және HITOC бойынша нұсқауларға арналған. Операция кезінде химиотерапевтік сұйықтықты енгізу кезінде кеуде ішілік қысымның жоғарылауымен байланысты дене температурасының күрт өзгеруі (42°C температурада 3-5 литр ерітінді) сияқты өзгерістер күтілді және жүректің шығарылуының жоғарылауымен, жүйелі тамырлар төзімділігінің төмендеуімен және кардиококсидтік индекстің жоғарылауымен жүретін ауыр гемодинамикалық бұзылыстар дамуына ықпал етуі мүмкін (EtCO2). Сондай-ақ қолданылатын химиотерапевтік заттардың бүйрекке улы әсерін ескере отырып, бүйрек зақымдануының алдын алу қажеттігін ескеру қажет. Дене температурасының жоғарылауы метаболикалық ацидозға және қан сарысуындағы лактат деңгейінің жоғарылауына әкелді. Ауырсынуды басқару үшін отаішілік жүйелі опиоидтық қажеттіліктерді азайту және ұзақ механикалық желдету қажеттілігін азайту үшін жергілікті анестетиктерді қолдану арқылы интраоперациялық эпидуральды анальгезия жасалды. HITOC-пен байланысты ауыр асқынулар сирек кездеседі. Ал бүйректік асқынуларды сұйықтықты теңестіру және цитопротекция арқылы азайтуға болады. HITOC-пен біріктірілген циторедуктивті хирургия таңдалған науқастарда сырқаттанушылық пен өлім-жітім көрсеткіштеріне сәйкес таңдалып орындалуы мүмкін. Науқастарды олардың осы терапевтік баламаға жарамдылығын анықтау үшін мультидисциплинарлық топ бағалауы керек. HITOC кандидаттарының операцияға дейінгі, операциялық және операциядан кейінгі күтімінде арнайы дайындалған анестезиолог-реаниматологтардың командасы болуы процедураның сәтті болуы үшін өте маңызды. Ерте клиникалық нәтижелер мультимодальды емдеу жағдайында жақсы жергілікті ісік бақылауын қамтамасыз ету үшін осы хирургиялық опцияны пайдалануды қолдауы мүмкін.

Түйін сөздер: плевралық мезотелиома, плеврэктомия, эпидуральды блокада, гипертермиялық плевраішілік химиотерапия, анестезияны жүргізу.

Анестезиологическое обеспечение расширенной плеврэктомии с внутриплевральной гипертермической химиоперфузией (HITOC) плевральной мезотелиоме: Первый опыт

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Резюме

Гипертермическая интраплевральная химиоперфузия (HITOC) — это вид адъювантного лечения, который проводится сразу после операции в операционной. HITOC — сложная процедура не только для хирургической бригады, но и для анестезиологов.

Данная публикация посвящена первому в Казахстане анестезиологическому опыту и руководству по HITOC. В течение всей операции ожидались такие изменения, как острые изменения температуры тела, связанные с повышением внутригрудного давления при введении химиотерапевтической жидкости (от 3 до 5 литров раствора при 42°C), и они могли способствовать тяжелым гемодинамическим нарушениям, с увеличением сердечного выброса, снижением системного сосудистого сопротивления и увеличением сердечного индекса и концентрации углекислого газа в конце выдоха (EtCO2). Также важно учитывать нефротоксичность используемых химиотерапевтических агентов и необходимость предотвращения повреждения почек. Повышение температуры тела также приводило к метаболическому ацидозу и повышению уровня лактата в сыворотке. Для лечения боли интраоперационная эпидуральная анальгезия проводилась с использованием местных анестетиков для снижения интраоперационной системной потребности в опиоидах и снижения необходимости в длительной искусственной вентиляции легких. Тяжелые осложнения, связанные с HITOC, редки, а почечные осложнения можно уменьшить за счет балансировки жидкости и цитопротекции. Циторедуктивная хирургия в сочетании с HITOC может быть выполнена с приемлемыми показателями заболеваемости и смертности у отдельных пациентов. Пациенты должны быть оценены многопрофильной командой для определения их соответствия этой терапевтической альтернативе. Команда обученных анестезиологов и реаниматологов, которые являются лидерами в предоперационном, оперативном и послеоперационном уходе за кандидатами на HITOC, имеет решающее значение для успеха процедуры. Ранние клинические результаты могут подтвердить использование этого хирургического варианта для обеспечения лучшего локального контроля опухоли в условиях мультимодального лечения.

Ключевые слова: мезотелиома плевры, плеврэктомия, эпидуральная блокада, гипертермическая интраплевральная химиотерапия, анестезиологическое обеспечение.