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Postoperative early laboratory changes and follow-up process of patients underwent hyperthermic intrathoracic chemotherapy

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Abstract

Background The aim of combining hyperthermic intrathoracic chemotherapy (HITHOC) with surgery is to achieve local control in patients with pleural malignancies. Liver and kidney dysfunction resulting from this procedure have been reported in the literature. The objective of the study is to examine whether the laboratory abnormalities observed during the initial period persist until day 30.

Methods The study conducted a retrospective analysis of the blood glucose levels, renal function markers, and hepatic function markers of 30 patients who underwent pleurectomy-decortication and HITHOC for pleural mesothelioma from January 2010 to April 2022. The measurements were taken in the postoperative period on the first four and 30th days. The study analyzed the initial and final laboratory results caused by the procedure.

Results Out of the total of 30 patients, 29, 28, 14, and 12 patients had elevated glucose levels on the first four days after the surgery, respectively. There was no association between glucose abnormalities and preoperative-postoperative diabetes mellitus. A minority of patients experienced atypical alterations in kidney and liver functions during the initial postoperative period. There was no apparent relationship between the renal and hepatic functions in the early and late periods after the surgery.

Conclusion Although there were fluctuations in glucose levels and renal and hepatic functions in the early period after surgery, there were no persistent alterations in these parameters by day 30. Elevated glucose levels during the early period were not associated with the development of newly diagnosed diabetes mellitus after surgery. The findings of our study provide evidence that HITHOC is a favorable and well-tolerated treatment option for mesothelioma.

Keywords Chemotherapy, Diabetes, Intracavitary, Mesothelioma, Nephrotoxicity, Pleurectomy

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Introduction

Hyperthermic intrathoracic chemotherapy (HITHOC) is a treatment approach that provides regional tumor control for individuals with pleural malignancies. The procedure involves the intrapleural administration of a chemotherapeutic drug [1]. HITHOC is used in combination with cytoreductive surgery to improve the effectiveness of the surgery through the anti-tumor properties of high-temperature chemotherapeutic drugs [2, 3].

The typical dosage range for cisplatin in HITHOC is 50–250 mg/m^2. Circulating heated cisplatin is used within the thorax to eliminate any residual tumor cells, penetrating tissues to a depth of approximately 3–4 mm [4]. While not as efficacious as intravascular treatment, the absorption of cisplatin through the pleural and peritoneal surfaces is recognized. The pleural and peritoneal absorption of this substance has been demonstrated to have adverse effects on the kidneys, nervous system, gonads, and gastrointestinal system [5]. Moreover, investigations have identified the presence of hyperglycemia in patients receiving cisplatin therapy, and it is advised to closely monitor glucose levels during the course of treatment [6].

Given the adverse effects and pleural absorption of cisplatin, we examined the early postoperative changes associated with the HITHOC. The primary objective of this study was to report our discoveries regarding the harmful effects on the kidneys and liver, as well as the levels of glucose, and to examine the long-term consequences of initial alterations caused by the HITHOC procedure.

Methods

A retrospective analysis was conducted between January 2010 and April 2022 on the clinical data of patients who underwent pleurectomy-decortication (PD), and HITHOC for malignant pleural mesothelioma (MPM). The study commenced upon the approval of the Hospital Ethics Committee on 06.07.2022, with the reference number 2022/07–88.

Study population

The study comprised patients who had previously received a diagnosis of MPM by any diagnostic technique and had undergone PD and HITHOC procedures at our clinic. All patients presented with tumors that were either operable or had the potential to be operable, falling into Stage 1, 2, or 3.

Exclusion criteria

Four patients were excluded due to an abnormal laboratory test result on day −1. Out of the total number of patients, six had neoadjuvant treatment. Three patients did not have complete early postoperative measurements. Four patients were unable to finish the HITHOC operation for various reasons. The individuals who underwent anatomical resection (four patients) were excluded in order to minimize the impact of the inherent issues associated with anatomical resection on the study. Five individuals were excluded from the study due to their initiation of adjuvant treatment prior to one month after the surgery.

Surgical procedure

We did not make any changes in the treatment method during the study period. Before the procedure, a thorough examination was performed on all individuals, which included blood count, renal and hepatic function tests, coagulation testing, and blood glucose level assessment. 100 cc/h saline infusion was administered for 10 h prior to the procedure. Prior to the surgery, saline solutions containing cisplatin with a concentration of 100 mg/m^2 were created. The dosage was uniform for all patients. PD was performed through thoracotomy in all cases. Following PD, chest tubes were inserted in both the apical and basal regions of the thorax. Additionally, two thermal probes were placed via the thoracotomy incision. Cisplatin solutions prepared before the surgical procedure were heated up to 43°C and then circulated in the thorax for 60 min. A 100 cc/h intravenous saline solution was administered for hydration during the first 10–12 h after the surgery. We did not employ any renal protection protocols, with the exception of administering fluids before and after the surgery.

Standardization of laboratory parameters and groups

All patients received assessment of blood tests, blood glucose levels, urea, creatinine, as well as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. These evaluations were conducted one day before to the surgery (Day −1), immediately after the surgery (Day 0), and on the first, second, and third days following the operation. The patient groups were categorized based on laboratory values and dates of measurement. The groups were designated with names such as glucose 0 (representing the glucose levels on day 0), glucose 1, glucose 2, glucose 3, AST 1, AST 2… Our references were 50–110 mg/dL for glucose, 10–50 mg/dL for urea, 0.7–1.3 mg/dL for creatinine, 35 U/L and below for AST, 45 U/L and below for ALT. Blood samples were taken from all patients at 06:00 am, except on the day of their operation. On the day of the operation, a blood sample was taken two hours following the surgery. Since the change of blood count parameters such as neutrophils, lymphocytes, etc. considered a natural process they were not included in this study. No adjuvant treatment was administered to any of the patients within the first 30 days following surgery to promote optimal wound healing. As a result of this condition, the laboratory data of

our patients were not affected by chemotherapy. None of the participants included in the study were obese or had a history of steroid treatment. The patients' nutritional regimens were selected based on their pre-existing comorbidities both before and after the surgery. They did not receive any treatment expected to cause hyperglycemia (such as dextrose-containing fluids or medicines with the side effect of hyperglycemia) in the preoperative or postoperative period.

On day 30, the levels of urea, creatinine, AST, and ALT were documented. On day 30, individuals were categorized based on their diagnosis of diabetes mellitus (DM): those who did not develop DM, those who were diagnosed with DM after surgery, and those who already had DM before the surgery. An investigation was conducted to examine the correlation between initial laboratory abnormalities and complications occurring on the 30th day after surgery.

The patients were staged by the tumor-lymph node-metastasis staging of the International Mesothelioma Interest Group (IMIG). The correlation between the stage of a medical condition and the occurrence of postoperative complications has been investigated as well.

Statistical analysis

The data was analyzed using descriptive statistics, which include measures such as the mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The Shapiro-Wilk test was used to assess the normality assumption of the quantitative data. The Mann-Whitney U test was employed to analyze variables that did not adhere to the assumption of normality. The evaluation of the correlation between quantitative data was conducted using Spearman's Rho correlation coefficient, while the analysis of the associations between categorical variables was conducted using the Pearson Chi-square test and Fisher's Exact probability test. The statistical analyses were conducted using IBM SPSS Statistics 25.0, a software package developed by IBM Corp. (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY). All analyses were conducted using a significance threshold of 0.05.

Results

Out of the sample population, 63.3% were male, which amounts to nineteen individuals. The mean age was 59.97±8.87 (44–75) years. When analyzing the data by geographic regions, it was found that nine patients (30%) were admitted from the Aegean region, followed by six patients (20%) from the Central Anatolia region, and five patients (16.7%) from the Southeastern Anatolia region. Out of the total number of patients, ten individuals (33.3%) had at least one additional medical condition. Specifically, six patients (20%) had hypertension, three patients (10%) had diabetes mellitus, two patients (6.7%) had hyperthyroidism, and one patient (3.3%) had rheumatoid arthritis.

A total of 30 patients underwent PD and HITHOC for MPM. Sixteen (53.3%) of the patients were operated from the right hemithorax. In postoperative period, at least one hyperglycemic value was seen in 29 patients. Hyperglycemia wasn't considered as a complication. Therefore, there were 27 patients (90%) with at least one complication. Patient characteristics, early and late complications are presented in Table 1.

During the preoperative period, all patients had normal blood glucose levels. However, on postoperative day 0, 29 of them exhibited hyperglycemia. The number of patients with hyperglycemia decreased progressively, with 28 on day 1, 14 on day 2, and 12 on day 3. The glycose levels exhibited a consistent downward trend on a daily basis. Simultaneously, the average glucose levels of all patients exhibited a declining trend, as shown in the figure. The alterations in glycose patterns were documented and classified. Hence, the glucose levels demonstrated a progressive decrease over a period of time in a collective of 18 patients. The all glycose levels of 9 cases were elevated. The glucose levels of two patients exhibited fluctuation, whereas the glucose level of one patient demonstrated an increase.

The presence of DM during the preoperative period did not show any significant relationship with early postoperative glucose measurements (p-values: 0.735, 0.626, 0.464, 0.320 for glucose measurements at 0, 1, 2, and 3 days respectively) or with the patterns of glucose levels observed on a daily basis (p-value: 0.528). Three patients had preoperative DM. On the 30th day after surgery, four patients were newly diagnosed with diabetes mellitus (DM), while twenty-three patients remained without a DM diagnosis. High glycose values on day 0, 1, 2, 3 weren't prognostic factors for the development of new DM after surgery (respectively p: 0.854, 0.722, 0.536, 0.523). There was no statistically significant correlation between the course of glucose and the development of DM (p:0.579) (Table 2).

During the initial 4 days following the surgery, 26 patients (86.7%) exhibited normal urea levels, while 28 patients (93.3%) maintained normal creatinine values throughout all measurements. There were no patients with high levels of urea or creatinine who needed dialysis within the initial four-day period. On the 30th day, urea levels of 26 patients (86.7%) and creatinine levels of 29 patients (96.7%) were within the normal range. There was no correlation observed between early and late abnormality in urea and creatinine levels (urea p-value: 0.071, creatinine p-value: 0.964). The incidence of renal failure was remarkably low.

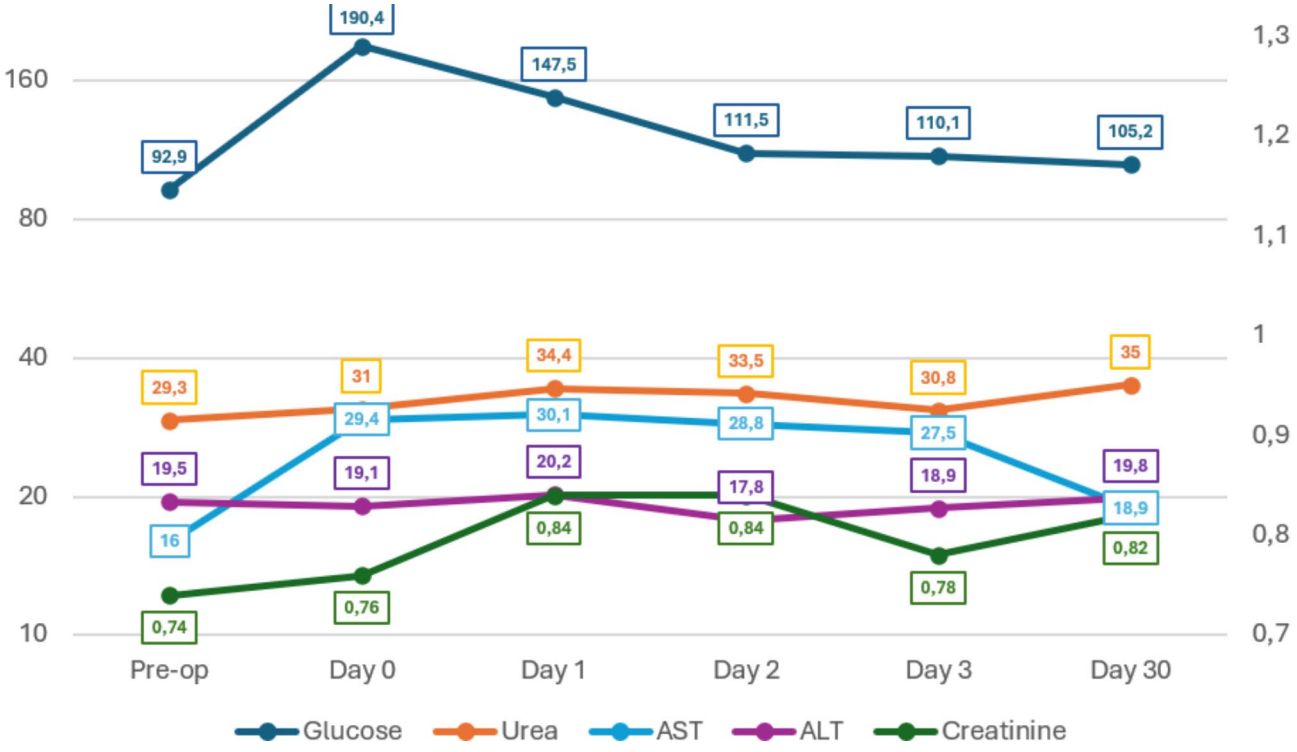

Fig. 1 Mean values of glucose, urea, creatinine, AST and ALT measured on pre-op, post-op 0,1,2 and post-op 30th days

Table 1 Patient characteristics and complications

Characteristics		Frequency (*n*)	(%)
Count		30	100
Mean age		59.97 (44–75)	
Gender	Male	19	63.3
	Female	11	36.7
Subtype of mesothelioma	Epithelial	26	86.7
	Biphasic	4	13.3
Stage	I	3	10
	II	18	60
	III	9	30
Postoperative complications and abnormalities (Day 0,1,2,3)	Hyperglycemia	29	96.7
	Urea	4	13.3
	Creatinine	2	6.7
	AST	12	40
	ALT	4	13.3
	Blood transfusion	14	46.7
	Prolonged air leak	7	23.3
	Fever	3	10
	Arrhythmia	3	10
	Chylothorax	1	3.33
Abnormalities on day 30	Urea	4	13.3
	Creatinine	1	3.33
	AST	1	3.33
	ALT	3	10
	New diagnosis DM	4	13.3
Mean hospital stay (day)		8.40 (4–18)	

During the initial 4 days after surgery, 18 patients (60%) had normal AST values, while 26 patients (86.7%) had normal ALT values. On day 30, AST values of 29 patients (96.7%), and ALT values of 27 patients (90%) were normal. There was no correlation between elevated levels of AST and ALT in the early period and the occurrence of liver function abnormalities on postoperative day 30 (p-values: 0.953 and 0.774, respectively). It is noteworthy that abnormal values in the early period returned to normal in the majority of patients by day 30. The figure displays the distribution of the mean values of urea, creatinine, AST, and ALT measurements based on each of the days.

Increased incidence of abnormal values in all parameters was observed among older patients and males, although no statistically significant differences were found. Mesothelioma subtype, preoperative comorbidities and stage weren't associated with the early (including glucose) or late postoperative measurements of any parameter. The mean hospital stay was 8.40±3.73 [4–18] days. When factors such as age, gender, comorbidities and disease stage were investigated, no significant relationship was found between these factors and hospital stay.

Table 2 The relationship of early glucose measurements with preoperative and postoperative DM status

		Presence of DM (Day 30th)				
		Preoperative DM	New diagnosis DM after surgery	Never diagnosed DM	**Total**	**p**
Postoperative day	Glucose level					
Day 0	High	3	4	22	29	0.854
	Normal	0	0	1	1	
Day 1	High	3	4	21	28	0.722
	Normal	0	0	2	2	
Day 2	High	2	1	11	14	0.536
	Normal	1	3	12	16	
Day 3	High	2	2	8	12	0.518
	Normal	1	2	15	18	
Glucose course for 4 days	High	2	1	6	9	0.579
	Fluctuating	0	1	1	2	
	Decreasing	1	2	15	18	
	Increasing	0	0	1	1	
Total		3	4	23	30	

Discussion

Due to biological and anatomical characteristics, there is currently no definitive treatment approach for MPM. However, various treatment strategies are currently under investigation [7]. HITHOC is a known procedure in the treatment of primary and secondary pleural malignancies (such as thymic carcinoma). It is a method to prevent recurrences, provide local control of the disease, and a longer survival period [8]. Sugarbaker et al. analyzed 103 MPM patients. 72 of patients underwent HITHOC combined with PD, while 31 underwent PD alone. HITHOC group exhibited longer disease-free survival [9]. The meta-analysis conducted by Zhao et al. indicates that HITHOC is a secure and efficient treatment for enhancing both the overall and disease-free survival rates of patients [10].

Recent literature frequently reports that patients with MPM tolerate the HITHOC procedure well. Aprile et al. performed a study including the data of 27 patients who underwent HITHOC for pleural metastasis of thymoma, and reported low rates of complications related to the HITHOC and this procedure was particularly effective in terms of local disease-free survival [11]. Patel et al. observed no intraoperative complications in their study of 7 patients who underwent HITHOC for various pleural malignancies, including MPM, thymic carcinoma, and solitary fibrous tumor of the pleura [12]. Nevertheless, Ried et al. conducted an analysis of patients who underwent HITHOC and documented a 2.6% incidence of intraoperative complications and 11.7% incidence of postoperative complications related to HITHOC. The sole postoperative complication observed was renal failure. According to the study, the rate of postoperative complications related to surgery was 50.9% [3]. We excluded the patients who were unable to tolerate the procedure during the surgery. The postoperative complications we encountered were not specifically classified as being either related to the surgical procedure or solely to the HITHOC treatment. The overall rates of complications were high, but the incidence of renal-hepatic failure was low, consistent with the findings in the literature.

A study involving 71 patients found that 31 of them (43.7%) experienced surgery-related complications, including prolonged air drainage, pneumonia, cardiac complications, chylothorax, and postoperative hemorrhage [13]. In their study of 49 patients who underwent PD and HITHOC, Ambrogi et al. observed no complications during the surgery and no deaths after the surgery. The study found that the rate of postoperative morbidity was 46.9%, and the mean length of postoperative hospitalization was 8 (5–45) days [14]. Out of the 30 patients included in our study, 27 (90%) of them experienced at least one complication that could be attributed to both the surgical procedure and HITHOC. Our complications differed significantly from the literature data due to our categorization strategy. The mean hospital stay was 8.40±3.73 [4–18] days in accordance with the literature.

The meta-analysis conducted by Jarvinen et al. examined both the overall complication rates and the complication rates specifically related to the HITHOC procedure [15]. The overall complication rates varied between 16.7% and 62.9% across the 11 studies. The incidence of renal failure resulting from HITHOC varies significantly across different studies. Zellos et al. [16] reported the highest incidence rate at 75.7%, while Tilleman et al. [17] reported the lowest incidence rate at 3.3%.

The nephrotoxic effect of intravenous administration of cisplatin is well-established, however, there is limited data on the nephrotoxicity caused by intrathoracic administration. Markowiak et al. conducted a study on 84 patients to examine renal complications following

HITHOC. They discovered that 29 patients, which accounts for 34.5% of the sample, experienced abnormal renal function [18]. Every patient was given preoperative hydration, with an average volume of 2 liters. The control group specifically received amifostine and sodium thiosulfate. They reported the prevention of renal dysfunction. Hofmann et al. suggested a cisplatin dosage of 150–175 mg/m^2 for HITHOC. They also found that effective perioperative management can help reduce the occurrence of postoperative renal failure [19]. All 30 patients in our study received preoperative and perioperative hydration. Only two cases exhibited elevated levels of creatinine during the early postoperative period. Additionally, one patient had a high creatinine value on day 30. While there was no statistically significant correlation, our rates of postoperative renal failure were low. Currently, we do not apply any additional protective treatment apart from daily hydration.

There is no comprehensive data in the literature about hyperglycemia due to intrathoracic administration of cisplatin. Although our routine postoperative treatments didn't include any factors that may cause hyperglycemia, early glucose values were high in most of the patients. The relationship between postoperative glucose measurements and the development of diabetes weren't statistically proven. However, high glycose levels in the early follow-up of most patients and four new DM cases in postoperative late period were a crucial finding. This finding supports the need for caution in terms of DM development due to HITHOC and careful monitoring of blood glycose levels.

The main limitation of the study was the small population. The high glucose variability of the cases and the presence of new postoperative diabetes cases emphasize that these studies should be multicentered and performed with a higher number of patients. We think that our study may provide appropriate data for future meta-analyses. We have experienced significant data loss as a result of laboratory measurements that were not recorded and the initiation of oncological treatment within the first month. Consequently, we had to exclude these patients from the analysis, leaving us with a sample size of only 30 patients for analysis. It is important to standardize follow-up in the postoperative period.

Conclusion

Our study investigating the complications of HITHOC procedure found that early biochemical changes may occur following PD and HITHOC and glucose balance gets severely impaired. No statistically significant relationship was found between preoperative or early postoperative changes. However, our findings, which indicate that a significant number of patients experienced high glucose abnormalities during the early period and that four patients developed new diabetes, require further investigation. In addition, the low occurrence of renal-hepatic failure during the initial period after surgery and the absence of the need for dialysis or long-term liver damage one month after surgery indicate that the procedure can be safely performed, and our hydration procedure is also safe.

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Author contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by S.A., S.K.A, H.Y. The first draft was written by S.A. S.K.A., A.G.E., T.I.A., K.T., A.Ç., U.C. supervised for the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
The data supporting the findings of this study are available from the corresponding author, S.A., upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of İzmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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