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AIM: *The aim of this study is to determine the incidence of intraoperative hyperlactatemia and its risk factors in patients undergoing laparoscopic colorectal surgery.*
MATERIAL AND METHODS: *We retrospectively enrolled 75 patients who underwent laparoscopic resection for colorectal cancer. Initial lactate levels were determined from blood gas analysis before the incision. The end lactate values were recorded after the termination of the pneumoperitoneum. Hyperlactatemia defined as lactate levels between 2 mmol/L and 5 mmol/L without evidence of acidosis. The patients were divided into two groups as normolactatemia and hyperlactatemia according to lactate values at the end of the surgery.*
RESULTS: *Of the 75 patients, 45 (60.0%) had higher lactate levels than normal at the end of the surgery. The median age of the study population was 62 (24-84) years. Forty (53.3%) of the patients were male. Most of the patients in the study had colon cancer origin [56 cases (74.7%)]. Univariate logistic regression analysis for a possible independent risk factor in terms of hyperlactatemia showed that Charlson comorbidity index (CCI) ≥ 3, body mass index (BMI) ≥ 30 kg/m^2, the operative time, and the tumor size were significant ($p < 0.05$). Multivariate analysis found that only BMI ≥ 30 kg/m^2 and the operative time were significant ($p = 0.004$, and $p < 0.001$, respectively).*
CONCLUSION: *According to our work, obesity (BMI ≥ 30 kg/m^2) and the operative time in laparoscopic colorectal surgery were independent risk factors for intraoperative hyperlactatemia at the end of the operation. Therefore, clinicians should be vigilant about the inevitable consequences of surgery by making appropriate preparation.*

KEY WORDS: Colorectal cancer, Lactate, Hyperlactatemia, Laparoscopy

Introduction

Hyperlactatemia is a term used for situations where the blood lactate level exceeds 2 mm/L and is also an independent predictor of mortality [1]. Therefore, intraoperative blood lactate monitoring is critical for cancer patients. Elevated lactate is an indicator of tissue hypoxia, and its concentrations depend on the balance between production and elimination. The main organ in which lactate is eliminated is the liver (60%) and kidney (30%) [2,3].

Laparoscopic surgery provides an advantage of faster recovery, less pain, and shorter hospital stays. Due to these advantages, the laparoscopy is preferred in many abdominal surgeries, especially colorectal cancer surgery [4]. On the other hand, decreased hepatic and renal perfusion secondary to increased intraabdominal pressure (IAP) during laparoscopy (pneumoperitoneum with CO_2) causes hyperlactatemia. IAP causes lactate increase by disrupting splanchnic microcirculation and causing tissue hypoxia. This effect becomes more pronounced as the duration of the surgery is extended [5].

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Some studies showing that intraoperative hyperlactatemia is associated with poor outcomes [6, 7], there are also studies reporting that it has no effect [8]. The aim of this study was to determine the incidence of intraoperative hyperlactatemia and its risk factors in patients undergoing laparoscopic colorectal surgery.

Materials and Methods

Ethical approval (Ethical Committee No. 2019.4/23-200) was provided by the Institutional Research and Ethics Committee of our hospital. This committee waived the need for informed consent from all eligible patients.

We retrospectively enrolled 75 patients who underwent laparoscopic resection for colorectal cancer in our center between January 2013 and June 2019. In this study, exclusion criteria were emergency surgery or palliative surgery, under 18 years of age, and conversion to open surgery. The blood lactate levels of all patients were measured intra-arterially. Initial lactate levels were determined from blood gas analysis before the incision. The end lactate values were recorded after the termination of the pneumoperitoneum. Patients, those who had an initial intra-arterial blood lactate level greater than 2 mmol/L, were excluded from the analysis. Patients with chronic kidney, liver, and heart disease with impaired organ function were also excluded from the study.

Hyperlactatemia defined as lactate levels between 2 mmol/L and 5 mmol/L without evidence of acidosis [9]. Patients with a value of above 5 mmol/L were excluded from the study. The patients were divided into two groups as normolactatemia and hyperlactatemia according to lactate values at the end of the surgery.

Standard anesthesia induction was applied to all patients with 1-2 mcg/kg fentanyl, 2 mg/kg propofol, and 0.1 mg/kg rocuronium. After orotracheal intubation, mechanical ventilation was performed with 8 ml/kg tidal volume and 12 breaths/minute. Anesthesia was maintained with sevoflurane. We performed rectal cancer surgery in the trendelenburg position (15° right).

The demographic, clinical, and surgical characteristics of the patients were noted as variables. Demographic data included age, sex, Charlson comorbidity index (CCI) [10], American Society of Anesthesiologists (ASA) score, BMI. As clinical data, neoadjuvant therapy, tumor localization, tumor size, pT stage, and TNM stage were taken into account. Operative details included total volume of fluids administered, the volume of urine output, the volume of blood loss, and operative duration. In the assessment of the Charlson Comorbidity Index, type 2 diabetic patients using metformin were also noted. The patients' pneumoperitoneum pressure was 12-14 mmHg.

Statistical Analysis

The SPSS (Statistical Product and Service Solutions) software version 22 for Windows (SPSS Inc. Chicago, IL, USA) was used for statistical analyses of the study. The normality of the distribution of the data was carried out using the Kolmogorov-Smirnov test. Qualitative data were presented as frequency and percentage. Quantitative data were given as mean ± S.D if the data were normally distributed, and median (min-max) if not normally distributed. The association of hyperlactatemia with categorical variables were analyzed using Chi-square and Fisher's exact tests. The Mann-Whitney-U test was used to examine whether hyperlactatemia was related to blood loss, administered fluid volume, and urine output. The effect of operative time on hyperlactatemia was investigated with the student's t-test. Variables that were significant with hyperlactatemia were subjected to univariate and multivariate logistic regression analysis. A p-value lower than 0.05 was accepted as statistically significant.

Results

Of the 75 patients, 45 (60.0%) had higher lactate levels than normal at the end of the surgery. Table I shows the demographic, clinical, and surgical characteristics of patients with hyperlactatemia and normolactatemia. The median age of the study population was 62 (24 - 84) years. Forty (53.3%) of the patients were male. Most of the patients in the study had colon cancer origin [56 cases (74.7%)]. A statistically significant relationship was found between increased BMI and elevated lactate levels (p = 0.029)(Table I)

The median arterial lactate levels of patients with hyperlactatemia at the beginning and end of the operation were 1.0 (0.3 - 2.0) mmol/L and 3.0 (2.1 - 4.9) mmol/L, respectively (Table II). Twelve (26.7%) of those with elevated lactate levels had a CCI of 3 and more (p = 0.039). Thirteen of 27 patients with CCI ≥ 3 were diabetes mellitus (DM) patients (p = 0.001) (Table III). All significant parameters in Table I were reevaluated in univariate logistic regression analysis for a possible independent risk factor in terms of hyperlactatemia. It was seen that all of them remained significant. However, according to the multivariate analysis, the BMI continued their significance (p = 0.004, the odds ratio of 10.461 [95% confidence interval], 2.095 - 52.230). Thus, obese patients (BMI ≥ 30 kg/m2) were found to have an increased risk of hyperlactatemia 10.4 times compared to non-obese patients. The operative time was also significant for increased lactate levels (p < 0.001) (Table IV).

TABLE I - *Patient demographic, clinical, and surgical characteristics.*

	Variables n (%)	**Normal lactatemia n=30 n (%)**	**Hyperlactatemia n=45**	**p**
[a]Age, years	<65	20 (66.7%)	31 (68.9%)	0.840
	65	10 (33.3%)	14 (31.1%)	
[a]Sex	Male	14 (46.7%)	26 (57.8%)	0.345
	Female	16 (53.3%)	19 (42.2%)	
[a]CCI	0-2	15 (50.0%)	33 (73.3%)	**0.039**
	3	15 (50.0%)	12 (26.7%)	
[a]Diabetes mellitus	No	27 (90.0%)	35 (77.8%)	0.171
	Yes	3 (10.0%)	10 (22.2%)	
[b]Metformin	No	27 (90.0%)	39 (86.7%)	0.733
	Yes	3 (10.0%)	6 (13.3%)	
[a]ASA score	I-II	13 (43.3%)	18 (40.0%)	0.774
	III-IV	17 (56.7%)	27 (60.0%)	
[a]Neoadjuvant	Yes	2 (6.7%)	9 (20.0%)	0.182
	No	28 (93.3%)	36 (80.0%)	
[b]BMI kg/m^2	<30	24 (80.0%)	25 (55.6%)	**0.029**
	30	6 (20.0%)	20 (44.4%)	
[a]Localization	Colon	25 (83.3%)	31 (68.9%)	0.159
	Rectum	5 (16.7%)	14 (31.1%)	
[a]Tumor size	<5cm	28 (93.3%)	32 (71.1%)	**0.018**
	5cm	2 (6.7%)	13 (28.9%)	
[ap]T stage	pT1-pT2	3 (10.0%)	12 (26.7%)	0.077
	pT3-pT4	27 (90.0%)	33 (73.3%)	
[a]TNM stage	I-II	21 (70.0%)	27 (60.0%)	0.377
	III-IV	9 (30.0%)	18 (40.0%)	
		Mean ± SD or Median (Min-Max)		
[c]Operative time/min		168.1 ± 36.5	237.5 ± 52.8	**<0.001**
[d]Blood loss/mL		80 (15-700)	50 (25-225)	0.631
[d]Administered Crystalloid /mL		2010 (1000-4590)	2000 (1000-5500)	0.663
[d]Urine output/mL-h		50 (35-80)	50 (30-80)	0.723

[a]Chi-Square test; [b]Fisher's exact test; cStudent t test; [d]Mann-Whitney U test; SD: Standart Deviation;
CCI: Charlson Comorbidity Index; ASA: American Society of Anesthesiologists; BMI: Body Mass Index
Another significant variable was tumor size (p = 0.018). The only significant intraoperative parameter related to hyperlactatemia was the duration of surgery (p <0.001).

Discussion

In this study, which included a retrospective analysis of 75 patients who underwent laparoscopic colorectal cancer surgery, the incidence of hyperlactatemia and its risk factors were investigated. The peculiarity of this study is that according to our research, there was no clinical study that directly addresses the risk factors of

TABLE II - *Lactate measurements at the start and end of the operation.*

Lactate measurements	Hyperlactatemia No (n =30) Median (Min-Max)	Yes (n =45) Median (Min-Max)
Start of the operation	0.9 (0.5-1.6)	1.0 (0.3-2.0)
End of the operation	1.4 (0.7-1.9)	3.0 (2.1-4.9)

TABLE III - *Hyperlactatemia relationship with DM in patients with CCI ≥3.*

	Charlson Comorbidity Index (CCI) ≥3n =27		Hyperlactatemia No	Yes	p
DM	no	n =14 (51.9%)	12 (85.7%)	2 (14.3%)	0.001
	yes	n =13 (48.1%)	3 (23.1%)	10 (76.9%)	

TABLE IV - *The risk factors for intraoperative hyperlactatemia by univariate and multivariate regression analyses.*

Variables	Hyperlactatemia Univariate OR (95.0% CI)	p	Multivariate OR (95.0% CI)	p
CCI, ≥3	0.364(0.137-0.963)	0.042	0.627 (0.153-2.561)	0.516
BMI, ≥30 kg/m^2	3.200 (1.097-9.334)	0.033	10.461 (2.095-52.230)	0.004
Tumor size, ≥5cm	5.687 (1.180-27.412)	0.030	4.375 (0.520-36.782)	0.174
Operative time/min	1.032 (1.018-1.047)	<0.001	1.036 (1.018-1.054)	<0.001

OR: Odds Ratio; CI: Confidence Interval; CCI: Charlson Comorbidity Index; BMI: Body Mass Index

hyperlactatemia during laparoscopic colorectal surgery. Our findings revealed some risk factors affecting lactate metabolism, such as BMI and operative time, as a result of multivariate analysis. Also, the incidence of hyperlactatemia at the end of the operation was 60% of this study.

Changes in the blood lactate level can be explained by the disruption of the balance between its production and utilization. Lactate sources under normal conditions are the skin (27%), red blood cells (23%), brain (18%), and skeletal muscle (17%) [11]. Lactate, contrary to what is most known, should not be seen only as an indicator of tissue hypoxia and anaerobic metabolism. Lactate plays a role in intercellular and interorgan cooperation so that hyperlactatemia cannot be a marker of tissue hypoxia alone. Lactate is created by the enzyme lactate dehydrogenase (LDH), which reduces pyruvate. LDH keeps the lactate pyruvate ratio in an equilibrium of 10:1. The primary source of pyruvate is anaerobic glycolysis. Thus, the leading cause of hyperlactatemia is anaerobic glycolysis. In other words, glucose as an essential function in lactate production [8,12].

Individuals with Type 2 DM are more exposed to hyperlactatemia due to limited lactate transfer and decreased aerobic-oxidative capability [13]. The number of patients with DM in this study was 13 (17.3%), all but one had type 2 DM. In our study, no relationship was found between DM and hyperlactatemia (p = 0.171). In contrast, Wu et al. [12] found this relationship significant (p = 0.010). In the study of Duval et al. [7], consisting of cardiac surgery patients, they found the lactate change of 433 patients > 2 mmol/L differences between the baseline value and the end of the surgery, 98 of them had DM. However, they reported that there was no significant association between hyperlactatemia and DM (p = 0.360). Metformin, which mainly inhibits mitochondrial respiration in the liver, by this means, causes lactic acidosis [14], but it does not influence on anaerobic lactate production [15]. The metformin usage rate in this study was 12%, and there was no significant relationship with elevated lactate concentration (p = 0.733). This result was similar to Lee et al.'s [16] study. In their study of 1954 patients with Type-2-DM, metformin consumption was 61.4%. Aharaz and his coworkers [17] also showed that metformin was not related to the risk of lactic acidosis.

In our study, which included a population of malignant patients, there were 27 patients with a CCI score of 3 and above, and 13 of them had DM. According to these results, the hyperlactatemia group had higher comorbidity rates than the normolactatemia group (p = 0.039). Aharaz et al. [17] presented a similar result for lactic acidosis. In their study, while the CCI was ≥ 63.8%, this rate was quite low, with 24.7% in the control group.
According to this study, another independent risk factor predicts hyperlactatemia was BMI ≥ 30 kg/m^2. Increased circulating fatty acids released by adipocytes in obesity patients disrupt muscle glucose uptake and use, leading to metabolic changes such as hyperlactatemia [18]. In the hypoxic conditions of solid tumors, where oxygen concentration is insufficient due to intense cancer cells, lactate is produced by anaerobic glycolysis (Pasteur effect). In addition, thanks to the "Warburg effect", the need for oxidative phosphorylation of the tumor is eliminated even if there is oxygen in the environment, and lactate is produced in cancer by glycolysis [19]. This explanation reveals the correlation between increased tumor size and high lactate levels, which is an additional important finding in our study. The predictive role of both BMI and tumor diameter for high lactate levels in our study was consistent with the literature [17].
Operative time has the potential to affect intraoperative lactate levels. It is possible to explain this effect via IAP. That is, with increased IAP, hepatic and renal blood flow, which are the main organs of lactate clearance, decreases. Besides, hypoxic conditions occur with reduced blood flow in the splanchnic area, and thereby lactate production increases. If IAP is under 12 mmHg, it can be tolerated, and the condition can be overcome with minimal organ dysfunction [4,20]. While the mean operative time of the normolactatemia group in our study was 168.1 ± 36.5 minutes, this time was 237.5 ± 52.8 min in the hyperlactatemia group (p < 0.001). In other words, after a laparoscopic operation of about 3 hours, lactate levels did not reach 2 mmol/L, but at 4 hours, it was associated with lactate elevation. In contrast to our study, in another study, blood lactate levels at the 3rd hour of the operation were 1.8 ± 1.2 mmol/L. However, this situation was not significant (p > 0.005) [8].
This present study revealed two independent risk factors for intraoperative hyperlactatemia by multivariate regression analysis. These were operative time and BMI. These findings suggested that prolonged operative times and obese patients constitute a risky group for intraoperative lactate increase.
The limitations of the study were the retrospective design and the lack of details of the used anesthetics and vasopressors agents.

Conclusion

Obesity (BMI ≥ 30 kg/m^2) and prolonged operation time in laparoscopic colorectal surgery were independent risk factors for intraoperative hyperlactatemia at the end of the operation. Therefore, clinicians should be vigilant about the inevitable consequences of surgery by making appropriate preparation.

Riassunto

Scopo: di questo studio è determinare l'incidenza dell'iperlattatemia intraoperatoria e i suoi fattori di rischio nei pazienti sottoposti a chirurgia laparoscopica del colon-retto.
Materiali e Metodi: Abbiamo arruolato retrospettivamente 75 pazienti sottoposti a resezione laparoscopica per carcinoma del colon-retto. I livelli iniziali di lattato sono stati determinati dall'analisi dei gas nel sangue prima dell'incisione. I valori di lattato finale sono stati registrati dopo la fine dello pneumoperitoneo. La iperlattatemia è definita come livelli di lattato tra 2 mmol / L e 5 mmol / L senza evidenza di acidosi. I pazienti sono stati divisi in due gruppi con normolattatemia e iperlattatemia in base ai valori di lattato alla fine dell'intervento.
Risultati: Dei 75 pazienti, 45 (60,0%) presentavano livelli di lattato più alti del normale alla fine dell'intervento. L'età media della popolazione in studio era di 62 (24-84) anni. Quaranta (53,3%) dei pazienti erano maschi. La maggior parte dei pazienti nello studio aveva origine di cancro al colon [56 casi (74,7%)]. L'analisi di regressione logistica univariata per un possibile fattore di rischio indipendente in termini di iperlattatemia ha mostrato che l'indice di comorbidità di Charlson (CCI) ≥ 3, l'indice di massa corporea (BMI) ≥ 30 kg / m^2, il tempo operativo e la dimensione del tumore erano significativi (p < 0.05). L'analisi multivariata ha rilevato che solo un BMI ≥ 30 kg / m^2 e la durata dell'intervento rappresentano dati significativi (p = 0,004 e p <0,001, rispettivamente).
Conclusione: Secondo il nostro studio l'obesità (BMI ≥ 30 kg / m^2) e la durata dell'intervento laparoscopico per cancro del colon-retto sono fattori di rischio indipendenti per l'iperlattatemia intraoperatoria al termine dell'intervento. Pertanto, i medici dovrebbero essere vigili sulle inevitabili conseguenze dell'intervento chirurgico effettuando una preparazione adeguata.

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