

Serum Lactate Dehydrogenase Levels May Predict Fentanyl Usage in Patients with Metastatic Cancers for The Treatment of Cancer Related Pain

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Abstract

Objective The increase in prescription opioid abuse has got attention from the medical societies, and politicians. On the other hand, pain is one of the most common symptoms in patients with cancer especially in advanced disease and pain usually decreased the quality of life in these population. In this study we aimed to investigate the possible correlation with any routine biochemical parameters and drugs dosage for cancer related pain to preventing the abuse.

Methods: A total of 75 local advanced or metastatic cancer patients who had treated and follow up in the oncology clinic. Our medical records were retrospectively evaluated.

Results: Seventy five patients with a mean age of 58(34-80) years and there were 54 man and 21 women. The most common metastatic sites were bone in 40 patients (53%), lymph nodes in 20 patients (26%), liver in 10 patients (13%) and brain in 7 patients (9%). All patient followed up with Comparative Pain Scale (CPS) and the median CPS score was 5 (3-9) before the pain treatment and significantly decreased during the follow up period, CPS was 2 (0-6), $P<0.001$. In the correlation analyses all baseline biochemical parameters and analgesics were analyzed. Serum lactate dehydrogenase levels were significantly correlated with fentanyl dosage (Pearson correlation was 0.33, $P=0.003$).

Conclusion: Regardless of the heterogeneity for cancer types, elevated serum LDH levels were significantly correlated the fentanyl dosage and baseline CPS score.

Keywords: Serum lactate dehydrogenase, pain, opioid, fentanyl,

Özet

Giriş: Opioid aşırı kullanımı sağlık sağlayıcıları ve denetleyicilerinin dikkatini çekmeye başlamıştır. Ancak diğer taraftan ise kanser hastalarında ağrı en sık semptom olmanın yanında ileri evre vakalarda ağrı sıklıkla hayat kalitesinin de düşürmektedir. Bu çalışmada rutin biyokimyasal parametreler ile opioid dozları arasındaki ilişkiyi aşırı kullanımı önlemek amacıyla araştırdık.

Metod: 75 ileri veya metastatik evrede kanser hastasını takip ettik. Medikal kayıtlar retrospektif olarak incelendi.

Bulgular: 75 hastanın yaş ortalaması 58(34-80) olup 54 erkek ve 21 hasta kadındı. En sık metastaz yeri 40 (%53) hastada kemik iken, 20 (%26) hastada lenf nodu, 10 (%13) hastada karaciğer, ve 7 (%9) hastada beyin idi. Tüm hastalar Comparative Pain Scale (CPS) skorlaması ile takip edildi ve ortanca CPS skoru tedavi öncesi 5 (3-9) iken takiplerde anlamlı derecede azalma gösterdi, CPS değeri 2 (0-6), $P<0.001$. Korelasyon analizinde tüm biyokimyasal değerler ile analjezikler dozları ile karşılaştırıldı. Serum laktad dehidrogenaz düzeyleri fentanil dozu arasında anlamlı ilişki bulundu (Pearson correlation was 0.33, $P=0.003$).

Sonuç: Kanser tiplerinden bağımsız olarak artmış serum LDH düzeyleri fentanil dozu ve CPS skoru ile anlamlı olarak ilişkili bulunmuştur.

Anahtar Kelimeler Serum laktad dehidrogenaz, ağrı, opioid, fentanil

Introduction

The increase in prescription opioid abuse has got attention from the medical societies, and politicians¹. Prescription of the amount of opioid drugs increased by 60% over the last decade², and in 2012, 74% of prescription drug overdose deaths (14 800 deaths) were related to opioid analgesics³. On the other hand, pain is one of the most common symptoms in patients with cancer especially in advanced disease and pain usually decreased the quality of life in these populations⁴. The assessment of cancer pain is sometimes very a complex undertaking and the evaluation must begin with a history of the painful regions and the underlying malignancy. The Brief Pain Inventory (BPI) was originally designed for assessing cancer-related pain, and is now the most commonly used cancer pain assessment instruments as well as visual analog scale^{5,6}. But these methods were subjective and did not give any additional tangible clue out of patient complaints and physical examination. In this study we aimed to investigate the possible correlation with any routine biochemical parameters and drugs dosage for cancer related pain to preventing the abuse.

Material and Methods

A total of 75 locally advanced or metastatic cancer patients who had treated and follow up in the oncology clinic. The study was conducted in the Recep Tayyip Erdogan University School of Medicine between the period of Nov 2013 and Aug 2014. In the routine follow up all patients pain scale, pain assessments and pain medicines are recording in the outpatient clinic prospectively. Our medical records were evaluated and informed consents were obtained from the patients. Inclusion criteria's were diagnosed cancer with pathologic examination, in stage with locally advanced or metastatic, having chronic cancer related pain. All patients who had cancer related pain were treated nonsteroidal anti-inflammatory drugs (NSAID), paracetamol, codeine phosphate, tramadol HCL and, fentanyl transdermal which were the most common and obtainable for clinically used in patients with cancer. Palliative radiotherapy was given as needed according to the patients and disease status. Pain management was started with paracetamol or NSAID and then titrated as needed. But most of the patients needed combination therapy as NSAID/Paracetamol with codeine, tramadol HCL and fentanyl transdermal. These combinations were most commonly used drugs in our country

because health insurance services pay all of these drugs without any cost.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA). For the continuous variables, parametric test conditions were first tested. The Shapiro-Wilk test was used to determine whether the continuous variables were normally distributed. Descriptive statistics were shown as mean+standard deviation or median + IR (minimum- maximum) where appropriate. Degrees of association between continuous variables were calculated by Spearman's correlation analysis. Parameters were considered to be significant if P value was less than 0.05.

Results

This study included 75 patients with a mean age of 58(34-80) years and there were 54 men and 21 women. The most common metastatic sites were bone in 40 patients (53%), lymph nodes in 20 patients (26%), liver in 10 patients (13%) and brain in 7 patients (9%). The cancer types were summarized in the figure 1. The most common cancer types which have been treated with opioid drugs were patients with pancreatic, gastric, lung and prostate cancer. The general characteristic and analgesic dosages of the drugs were presented in the table 1. In the study population all patients needed combination therapy. The combinations were; 57 (76%) of patients received tramadol combination (\pm NSAID/Paracetamol \pm Codeine P), 45 (60%) patients received fentanyl transdermal combination (\pm NSAID/Paracetamol \pm Codeine P), and 27 (38%) patients received tramadol with fentanyl transdermal (\pm NSAID/Paracetamol \pm Codeine P) combination. All patients followed up with Comparative Pain Scale (CPS) and the analgesic dosages were adjusted as needed to patients' complaints. The median CPS score was 5 (3-9) before the pain treatment and significantly decreased during the follow up period, CPS was 2 (0-6), $P < 0.001$.

In the correlation analyses all baseline biochemical parameters and analgesics were analyzed. These parameters were serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), gamma-glutamyltransfe-

rase (GGT), alkaline phosphatase (ALP), total bilirubine (T.bil), hemoglobine (Hb), platelet count (PLT), and C reactive protein (CRP). Serum lactate dehydrogenase levels were significantly correlated with fentanyl dosage (Pearson correlation was 0.33, $P=0.003$). Also multiple regression analyses were significant only in LDH for fentanyl dosage. The regression equation was "Fentanyl Dosage" = $22,4 + 0,0161$ LDH. In addition, the baseline pain scale score were significantly correlated with serum LDH levels (Pearson correlation was 0.30, $P=0.008$) as well as fentanyl dosage (Pearson correlation was 0.49, $P=0.0001$). Serum LDH levels did not significantly different according to the cancer types ($P=0.4$)

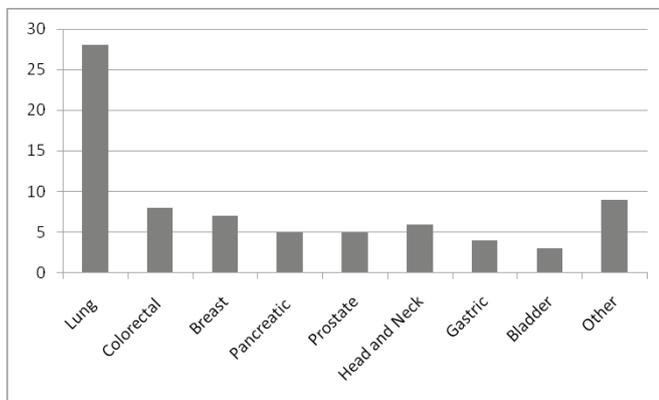


Figure 1. Cancer types of the study population.

Discussion

In the current study we found that serum LDH levels were significantly correlated fentanyl dosage in a patient with metastatic cancer. Opioids are the cornerstone of treatment for cancer pain and appropriate pain management is a hallmark of quality care⁷. On the other hand, a recent increase in prescription opioid abuse, morbidity, and mortality has transformed the landscape of prescription opioid drugs⁸, and as a result, the regulatory environment is changing, altering prescription and dispensing patterns^{7,9}. The physicians especially oncologist and algologists were in the middle of the arrow, one head of them our patients quality, and the other head was policy concerns. The Brief Pain Inventory (BPI), visual analog scale, comparative pain scale and broad physical examination are our weapons for assessing cancer-related pain, and they are now the most commonly used cancer pain assessment methods^{5,6}. But all of these methods are not adequate for the comprehensive assessment of cancer pain and prevent

to abuse of these drugs. To our knowledge there are no any laboratory parameters used in the clinical routine for predict cancer pain severity, and also correlated with any analgesic drug dosage in patients with cancer. In this study we found a significant correlation between the serum LDH levels with fentanyl dosage and there was no significant correlation between the others analgesics (paracetamol, NSAID, codeine, and tramadol HCL). Also serum LDH levels cannot be a unique marker to prescript a fentanyl but it may help to physicians with the other gold standard clinical parameters and scales, because we found a significant correlation with baseline pain scale scores and serum LDH levels as well as fentanyl dosage. The elevated serum LDH level was accepted as a prognostic factor for poor survival in lung cancer, colorectal cancer, head and neck cancer, renal cell carcinoma, prostate cancer, and as well as hematologic malignancies^{10,11}.

	Median/Mean	IR/ SD
Age,years	54	34-80
ALT, U/L	26	3.4
AST, U/L	33	4
LDH, U/L	453	98-3417
GGT, U/L	107	16-1144
ALP, U/L	184	21
Calcium, mg/dl	9.1	7.1-15
T.Bil, mg/dl	1.1	0.3-15
Hb,gr/dL	11	1.9
PLT,mm ³	271000	14000
CRP, mg/dL	8.4	0.4-29
NSAID, mg/day	850	500-1100
Paracetamol, mg/day	1000	500-1500
Codeine P, mg/day	30	10-60
Tramadol HCL, mg/day	45	0-300
Fentanyl ,mcg/72 hours	30	0-200

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase GGT: Gamma-Glutamyltransferase, ALP: Alkaline phosphatase, T.bil: Total bilirubine, Hb: Hemoglobine, PLT: platelet count, CRP: C reactive protein, NSAID: Nonsteroidal anti-inflammatory drugs, P:Phosphate, HCL: Hydro chlorine.

Suh et al found that in 93 terminally ill cancer patients, elevated LDH level (313 IU/L) was confirmed as an unfavorable indicator for survival time (14 vs 27 days). The reduction of pyruvate by nicotinamide adenine dinucleotide (NADH) to form

lactate is catalyzed by LDH. Serum LDH and lactate are known to reflect the tumor burden and invasive potential of tumor¹². Elevated LDH level caused to decreasing therapy response¹³. Thus, LDH can be accepted as a marker of tumor aggressiveness¹¹. Serum LDH was produced by many different types of cells in the body. Some of the organs have more LDH such as the heart, kidney, liver and muscle. Although tissues can have elevated LDH, blood levels of the enzyme are usually normal. When these tissues are damaged by injury or disease, they release more LDH into the bloodstream such as inflammatory conditions, degenerative processes, toxicity or malignancies¹⁴⁻¹⁷. In our study we did not find any significant differences between the LDH levels and cancer types as well as metastatic sites but the major metastatic sites were bone and lymph nodes in our study and also all patients were in locally advanced or metastatic stage. In a retrospective analysis published by Cook et al. revealed that 643 patients with bone metastases from castration resistant prostate cancer, elevated baseline serum LDH levels (>454 U/L) were associated with a nearly 3-fold increased risk of death¹⁸. In another study Brown et al showed that LDH levels correlate strongly with survival in patients with bone metastases from breast cancer and confirms the relevance of previously described prognostic factors¹⁹. Preventing abuse will always be dependent on the practitioner appropriately evaluating whether a patient has risk factors for abuse, screening their patients for abuse but sometimes oncologists or algologists cannot classify the patients symptoms and requirement of pain medicine therefore we needs some additional parameters. All these evidences may show that elevated serum LDH levels can be an additional prognostic factor for the assessing the intensity of cancer related pain as well as a prognostic factor of tumor burden and aggressiveness.

Major limitations of this study was limited number of patients and oncologic outcomes of the population but our primary aim was to find the answer of being there any possible serum marker which use in routine clinical practice, can help the pain assessment tools?. Also we could not measured plasma fentanyl concentrations.

In conclusion, regardless of the heterogeneity for cancer types, elevated serum LDH levels were significantly correlated with fentanyl dosage and baseline CPS score. So we may use

serum LDH levels to the prescribe fentanyl for cancer pain in addition to the pain assessment tools in clinical practice.



Kaynaklar

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