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Morphine in Plasma and Cerebrospinal Fluid of Patients Addicted to Opiates Undergoing Surgery: High-performance Liquid Chromatography Method

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Original Article

Abstract

Background: The prevalence of opium addiction among Iranians is considerable. Since endogenous opioid systems may be altered as a consequence of addiction, it is very important to determine the plasma and cerebrospinal fluid (CSF) levels of morphine in Iranian patients addicted to opiates who will undergo surgery.

Methods: We obtained CSF and plasma samples from 50 volunteers with an established opioid addiction pattern. Samples were analyzed using high-performance liquid chromatography (HPLC). Additionally, frequency of nausea and vomiting, baseline heart rate (BHR), and systolic blood pressure (SBP) were recorded within the surgery and postoperatively during a 10-min interval.

Findings: 84% of participants were men with a median age of 39.08 years. Mean score of body mass index (BMI) was 23.30 and most of the participants (46%) used opium in its traditional inhaled form. A higher concentration of morphine in blood was found in comparison with CSF ($P < 0.001$) in relation to the way of use. However, no statistically significant differences were found in relation to the type of addictive substance. No other association was found between the levels of morphine and the clinical characteristics of the patients. Moreover, results revealed no difference between hemodynamic-related data with blood and CSF level in opium-dependent patients.

Conclusion: Quantification of plasma and CSF morphine, both immediately before initiation of surgery and subsequently on recovery room, showed that although clinical efficacy of systemic morphine was poor in addicted patients, it had no effect on patients' hemodynamic variable and following complications after surgery.

Keywords: Morphine; Cerebrospinal fluid; Opium addiction; Postoperative pain

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Introduction

Substance use disorder (SUD) is a pathological condition in which the use of one or more substances causes a clinically significant deterioration. According to the World Drug Report 2018, more than one quarter of billions of people in the world use drugs and 30.5 million of them suffer from SUD.[1] Two important components of this disorder are dependence and addiction, the latter is a chronic neurobiological pathology with determinants related to genetic, biopsychosocial, and environmental elements.[2] Some of these patients may be dependent as a result of long-term pain therapy[3] or opioid use disorder (OUD)[4] which is characterized by behavior that includes one or more of the following: impaired control over drug use, compulsive consumption, continued use despite harm, and craving.[5] In Europe, for instance, it has been approximately estimated from market surveillance data that there were around 2.5 million strong opioid prescriptions in the primary care setting in 2004.[6] Drug abuse and addiction in Iran are serious national problems.[7] The prevalence of opium addition in the Iranian is high, because Iran is a passage of drug and opiate trafficking from East Asia to Europe.[8] Although addictive substances are excellent analgesics, they may affect a few functions such as those of respiratory and cardiovascular systems and induce gastrointestinal (GI) symptoms (ileus, nausea and vomiting, constipation).[9]

Opium tolerance or dependence results from repeated exposure to an opioid substance causing a decreased analgesic effect through desensitization of antinociceptive mechanisms.[10] This generates a greater sensitivity to harmful stimuli, which shows that the constant administration of opioids activates the pain inhibitory systems as well as the pain facilitating systems.[11] One of the most accepted hypotheses is that acute receptor desensitization by decoupling the G-protein-coupled receptor (GPCR) generates an up-regulation of cyclic adenosine 3′,5′-monophosphate (cAMP) pathway, the subsequent activation of the N-methyl-D-aspartate (NMDA) receptor system, as well as the descending facilitation, which leads to an opioid-induced hyperalgesia.[12] Another molecular mechanism studied in this process is the mammalian target of rapamycin (mTOR), an important axis of other central nervous system (CNS) disorders such as epilepsy,[13] which has been associated with chronic pain states and their relationship with opioid-induced tolerance/hyperalgesia.[14]

For opium-dependent patients after surgery, treatment options involve further up-titration of the current opioid regimen, the addition of adjunctive agents with different mechanisms of pain control in a multimodal approach, and attempting an opioid switch or crop rotation to a different opioid analgesic; which all have further subsequent complications.[15]

Another aspect to keep in mind is that endogenous opioid systems may be altered as a consequence of addiction.[16] Although there has been considerable progress in understanding the distribution, biosynthesis, and physiology of endogenous opioids, it is not yet clear how they are affected by tolerance and dependence in patients who need surgery. There are some examples of how these systems are altered in animal models,[17] but this becomes more important considering that patients receiving long-term opioid treatment are more likely to require surgery and higher doses of opioids after the operation.[18,19]

For all the above, it is important to determine cerebrospinal fluid (CSF) and serum morphine concentration in opium addict patients that undergo surgery.

Methods

This was a cross-sectional study with approval of the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran. We studied opiate-addicted patients who were scheduled for surgery. All the volunteer patients were classified as status II according to the American Society of Anesthesiologists (ASA) physical status classification system.

Inclusion and exclusion criteria: Inclusion criteria consisted of all patients admitted for spinal anesthesia and further surgery who were claimed to be opium-dependent in the previous year.

Patients were excluded from the study when: 1. being younger than 20 or older than 60 years old, 2. having chronic inflammatory disease, hypertension, diabetes, obesity, and liver or renal disease, 3. taking regularly nonsteroidal anti-inflammatory drugs (NSAIDs), 4. having medical history of drug or alcohol abuse and psychiatric disorder, 5. having any contraindications for spinal anesthesia, 6. multiple trauma, or 7. intravenous (IV) administration of morphine.

Lumbar puncture procedure: Blood sample was obtained 5 minutes before induction of anesthesia. CSF was acquired within the surgery by lumbar puncture with the patient in the lateral decubitus position. A 22-gauge spinal needle was inserted into the L3-L4 interspace. After local anesthesia (lidocaine 2%), 1 ml of CSF was collected and subsequently transported under standard conditions to the clinical laboratory, where they were centrifuged in a refrigerated centrifuge. All samples (serum and CSF) were analyzed by high-performance liquid chromatography (HPLC) with 2000 ng Pirates Cobas Integra kits.

Baseline heart rate (BHR), systolic blood pressure (SBP), and nausea and vomiting were recorded within the surgery and postoperatively during a 10-min interval. Patient's characteristic information was gathered and data analysis was done using SPSS software (version 21, IBM Corporation, Armonk, NY, USA). Data were expressed as mean ± standard deviation (SD) (Tables) and mean ± standard error (SE) (Figure) for quantitative variables, and number and percentage for qualitative ones. Analysis of variance (ANOVA) and Pearson tests were used when appropriate, and P < 0.050 was considered as statistically significant. The statistical relationships between the serum and CSF level of morphine and the study variables were evaluated using a Pearson correlation analysis.

Results

100 patients with scheduled surgery requiring hospital admission and spinal anesthesia were enrolled in our study. No patients entered in the study were excluded from the primary analysis. The median age of participants was 39.08 years and about 84% of participants were men. Mean score of body mass index (BMI) was 23.30 and most of them (46%) used opium in its traditional inhaled form (Table 1).

There were no significant differences in terms of BMI, sex, type and form of opium abuse, length of addiction, and number of surgical spine levels with serum-spinal morphine concentrations in all time points (P > 0.050) (Tables 2 and 3). Age was the only correlated variable with serum morphine level (P = 0.030). Older patients had a higher level of morphine in their blood; it might show lower dose requirement on elderly people.

Analyzing patients hemodynamic monitoring [set by the values of heart rate (HR), as well as SBP and diastolic blood pressure (DBP)] data inter- and post-operatively showed that there was no relationship between them and plasma and CSF levels (Tables 4 and 5).

Table 1. Demographic variables of participants

Variable		Value	P (serum)	P (CSF)
Sex [n (%)]	Men	42 (84)	0.630	0.130
	Women	8 (16)		
Marital status [n (%)]	Married	43 (86)	-	-
	Single	7 (14)		
Form of abuse [n (%)]	Oral	24 (48)	-	-
	Inhalation	23 (46)		
	Both	3 (6)		
Substance type [n (%)]	Opium	42 (84)	0.770	0.600
	Thick opium	14 (28)		
	Heroin	4 (8)		
	Methadone	11 (22)		
Age (year) (mean ± SD)		39.08 ± 11.90	0.001	0.270
Weight (kg) (mean ± SD)		66.92 ± 13.02	-	-
Height (cm) (mean ± SD)		169.30 ± 5.94	-	-
BMI (kg/m^2) (mean ± SD)		23.30 ± 4.07	-	-
Years of addiction (mean ± SD)		11.32 ± 8.56	0.370	0.130
Last consumption hours (mean ± SD)		24.62 ± 2.94	-	-

P-value less than 0.050 is considered significant.
CSF: Cerebrospinal fluid; BMI: Body mass index; SD: Standard deviation

Table 2. Plasma and cerebrospinal fluid (CSF) morphine levels based on the form of opium abuse

Morphine concentration	Both form (mean ± SD)	Inhalation (mean ± SD)	Oral (mean ± SD)	P (ANOVA test)
Blood	382.66 ± 249.71	682.21 ± 127.96	799.79 ± 124.22	0.700
CSF	99.00 ± 26.00	71.56 ± 18.95	109.27 ± 33.23	0.600

P-value less than 0.050 is considered significant.
CSF: Cerebrospinal fluid

Table 3. Pearson correlation analysis of body mass index (BMI), consumption time, age, sex, and morphine levels

Variable	CSF		Blood	
	r	P	r	P
BMI	0.099	0.495	-0.007 ()	0.960
Consumption time	0.217	0.130	-0.296	0.037
Age	0.157	0.275	0.307	0.030
Sex (Men)	0.216	0.133	0.635	0.069
Sex (Women)	-0.49	0.754	0.081	0.318

r: Pearson correlation coefficient; CSF: Cerebrospinal fluid; BMI: Body mass index

There was a 8.2 folds difference between serum morphine and CSF morphine levels. These data were gathered in 10-minute interval; the only statistically significant time point was 10 minutes after patients' entrance to recovery (P = 0.001). In addition, there was no relationship between serum-CSF level with post-operation nausea and vomiting (Table 6). The results showed that the CSF morphine level of addicted patients in all forms of opium abuse (oral and inhalation) was statistically less than the serum level (P < 0.001) (Figure 1).

Discussion

Some patients who are going to undergo anesthesia for a surgery may be either opioid dependent or tolerant to opioid analgesic drugs.[20,21] For those doctors who care for opiate-dependent patients in the postoperative environment, this situation is a great challenge and also for the anesthesiologists equally; however, there is little attention drown to the other complications like nausea, vomiting, and hemodynamic instability. This problem is based on the difficulty to find the perfect balance between a useful medication for pain management and the risk that exists due to adverse reactions or the development of addiction,[22] thus raising significant ethical concerns.[23,24]

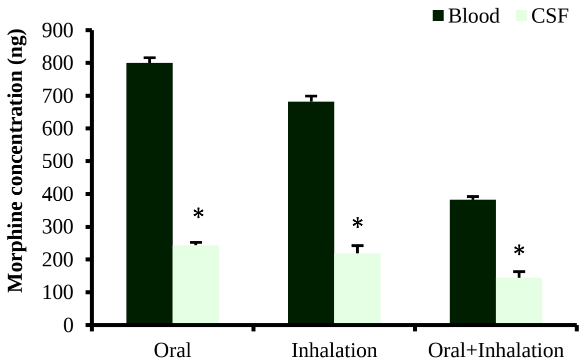

Figure 1. A decreased cerebrospinal fluid (CSF) morphine concentration was observed in all forms of opium abuse compared to the blood morphine level.
*P < 0.001 compared to the blood level
Data are presented as mean ± standard error of the mean (SEM).

Table 4. Pearson correlation analysis of systolic and diastolic blood pressures (DBP) and morphine levels

Measurement time (minute)	SBP				DBP			
	CSF		Blood		CSF		Blood	
	r	P	r	P	r	P	r	P
Base line	-0.048	0.740	-0.106	0.465	0.071	0.625	0.040	0.784
10	0.784	0.001	0.263	0.065	-0.044	0.763	-0.102	0.479
20	-0.102	0.490	0.183	0.213	0.026	0.862	-0.007	0.963
30	-0.159	0.368	-0.187	0.290	-0.074	0.676	-0.068	0.704
40	0.033	0.914	-0.227	0.457	0.464	0.110	0.602	0.300
50	0.846	0.034	0.346	0.502	0.211	0.688	0.315	0.543
60	0.939	0.061	0.296	0.704	-0.014	0.986	0.590	0.410

r = Pearson correlation coefficient
SBP: Systolic blood pressure; DBP: Diastolic blood pressure; CSF: Cerebrospinal fluid

Table 5. Pearson correlation analysis of heart rate (HR) and morphine levels

Measurement time (minute)	CSF		Blood	
	r	P	r	P
Base line	0.136	0.347	0.226	0.114
10	0.076	0.599	0.104	0.473
20	0.060	0.687	0.107	0.469
30	0.138	0.436	0.122	0.492
40	0.074	0.810	0.323	0.282
50	-0.330	0.523	0.189	0.720
60	0.486	0.514	0.970	0.300

r = Pearson correlation coefficient; CSF: Cerebrospinal fluid

The assays were performed on these 100 patients with a frequent prevalence of opium abuse and results showed that opioid-dependent patients had significantly higher mean plasma and CSF morphine levels than the normal.

Table 6. Pearson correlation analysis of nausea and morphine levels during surgery and recovery

Measurement time (minute)	CSF		Blood	
	r	P	r	P
Base line	0.072	0.622	0.139	0.336
10	0.077	0.594	0.033	0.818
20	0.099	0.495	0.026	0.856
30	0.100	0.489	-0.029	0.844
40	0.023	0.872	-0.171	0.234
50	0.086	0.580	-0.049	0.754
60	0.380	0.847	-0.051	0.795
70	0.256	0.322	-0.127	0.627
80	0.195	0.544	0.149	0.644
90	-0.132	0.716	-0.204	0.572
100	-0.889	0.111	-0.191	0.809

r = Pearson correlation coefficient; CSF: Cerebrospinal fluid

In contrast, O'Brien et al. have shown that some morphine metabolites in CSF like 6-endorphin levels were significantly lower in addicted patients as compared to the healthy people.[25] Addiction is a pathological condition in which the balance of the endogenous opioids of the human body is altered. Although the large number of variables and small sample sizes involved make interpretation of the data difficult, one reason for this controversy may be related to differences between normal people and addicts in sex ratio, race, and ethnic background in O'Brien et al. study which were not consistent with our results.

In some aspects, a particular part of the results are relevant in that opioid intake with changes in serum opioid and CSF levels could not change hemodynamic variables during surgery.

Anesthesiologists are probable to deal with a variety of opioid-dependent patients. An element to consider in order to prevent tolerance or the development of addiction, is to pay attention to the increase in the requirement of the doses used,[26] and more complications is expected. Nugent et al. evaluated transdermal fentanyl dose escalation in 73 patients with pain related to terminal malignancy. They disclosed that the initial fentanyl dose of 75 µg per hour became greater than 25% to a final median dose of 100 microgram per hour in addicted patients.[27] Our study limitation was scarce information about patient opium dosage and frequency because it is known as a shame for Iranian and addiction is not still well understood as a behavioral disorder.

Conclusion

Measuring plasma and CSF morphine in different time intervals both at once before beginning of the surgery and then on recovery room showed that although clinical efficacy of systemic morphine was poor in addicted patients, it did not affect patients' hemodynamic variable and following complications after surgery.

Conflict of Interests

The Authors have no conflict of interest.

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سطح پلاسمایی و مایع مغزی- نخاعی مورفین در بیماران معتاد به مواد مخدر در اعمال جراحی: استفاده از روش کروماتوگرافی مایع با کارایی بالا

دکتر محمد علی حق‌بین[1]، دکتر ضیاء نویدی[1]، دکتر سزار آر رومرو لگویزامون[2]، دکتر محمد شعبانی[3]

مقاله پژوهشی

چکیده

مقدمه: شیوع اعتیاد به مواد مخدر در ایران قابل توجه می‌باشد و از آن‌جا که فعالیت سیستم اپیوئیدی اندوژن به سبب اعتیاد به مواد مخدر تغییر می‌کند، بررسی سطوح پلاسمایی و مایع مغزی- نخاعی مورفین در بیماران تحت عمل جراحی به علت این که به زودی درد حاد را تجربه خواهند کرد، اهمیت ویژه‌ای دارد.

روش‌ها: در مطالعه حاضر، میزان مورفین در ۵۰ نمونه پلاسمایی و ۵۰ نمونه از مایع مغزی- نخاعی معتادان به تریاک با استفاده از روش کروماتوگرافی مایع با کارایی بالا (High efficiency liquid chromatography یا HPLC) مورد سنجش قرار گرفت. میزان ضربان قلب پایه، فشار خون سیستولیک و شیوع تهوع و استفراغ طی عمل جراحی و پس از عمل در ریکاوری با فاصله زمانی ۱۰ دقیقه ثبت گردید.

یافته‌ها: میانگین سنی بیماران ۳۹/۰۸ سال بود که ۸۴ درصد آن‌ها را مردان و ۱۶ درصد را زنان تشکیل دادند. بیماران تریاک را به فرم استنشاقی (بیشترین فرم مصرف: ۴۶ درصد)، خوراکی و یا هر دو شکل استفاده می‌کردند. سطح مورفین مایع مغزی- نخاعی در هر سه فرم خوراکی، استنشاقی و خوراکی- استنشاقی کمتر از سطح پلاسمایی آن بود ($P < ۰/۰۰۱$). ارتباط معنی‌داری بین ویژگی‌های دموگرافیک بیمار با سطح مورفین پلاسمایی و مایع مغزی- نخاعی مشاهده نشد. همچنین، رابطه معنی‌داری بین تغییرات همودینامیک بیماران معتاد به تریاک با میزان مورفین خون و مایع مغزی- نخاعی وجود نداشت.

نتیجه‌گیری: اندازه‌گیری کمی مورفین پلاسما و مایع مغزی- نخاعی در بیماران معتاد قبل و بعد از شروع جراحی و ریکاوری نشان می‌دهد که با وجود کاهش اثرات کلینیکی مصرف سیستمیک مورفین، متغیرهای همودینامیک بیماران در حین عمل و پس از عمل جراحی تحت تأثیر قرار نمی‌گیرد.

واژگان کلیدی: مورفین، مایع مغزی- نخاعی، اعتیاد به تریاک، درد پس از عمل

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