Do Opioid Addicts Require Higher Doses of Heparin During Percutaneous Coronary Intervention?

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Abstract

Background: Patients who undergo percutaneous coronary intervention (PCI) receive anticoagulants, most commonly heparin to prevent thrombotic events during the procedure. Opioid addicts may require higher doses of heparin for PCI. We aimed to compare the effect of heparin on activated clotting time (ACT) between opioid addicts and non-addicts prior to and during PCI.

Methods: This comparative study included 107 patients scheduled for elective PCI, of whom 50 were opioid addicts and 57 non-addicts. Patients’ baseline characteristics including age, gender, weight, comorbidities, drug history, and smoking were recorded. Prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and platelet count were measured in venous blood samples collected from all participants. All patients underwent PCI through femoral access. They received 100 IU/kg heparin right at the beginning of the procedure. ACT was measured at 2 and 30 minutes.

Findings: Age, gender, weight, and the amount of heparin used were comparable between groups. As for general characteristics, the number of patients with hyperlipidemia was significantly higher in non-addicts (P = 0.031), and cigarette smoking was higher in opioid addicts (P < 0.001). No significant difference was found between the groups regarding PT, PTT, INR, and platelet count (P > 0.050). ACT at 2 and 30 min were significantly lower in opioid addicts (P < 0.001). Taking other variables into account, ACT at 2 min was directly correlated with drug history of aspirin in opioid addicts (P = 0.031) and inversely correlated with cigarette smoking in non-addicts (P = 0.023).

Conclusion: Opioid addicts may require higher doses of heparin in PCI for the prevention of thrombotic complications compared to non-addicts.

Keywords: Opioids; Percutaneous coronary intervention; Heparin; Activated clotting time
Introduction

Unfractionated heparin (UFH) has been used to prevent preprocedural ischemic complications in percutaneous coronary intervention (PCI), a procedure of utmost significance in the management of patients with coronary artery disease (CAD). In fact, the availability of UFH, its cost-effectiveness, and its easy neutralization by protamine sulfate have made it the most commonly used anticoagulant agent in PCI. However, monitoring activated clotting time (ACT) has been widely recommended for the adjustment of heparin dosing during PCI, owing to the fact that UFH has a relatively narrow therapeutic window and its effect on coagulation is quite unpredictable.\(^1\)\(^-\)\(^3\) While the normal range of ACT is 70-120 s, when using anticoagulants, the target range is 150-600 s; however, these ranges can differ based on the test device and the anticoagulation therapy.\(^4\) ACT measures the duration of blood clotting via the intrinsic pathway and is mostly applicable when the partial thromboplastin time (PTT) test fails to be clinically useful or may be time-consuming to process.\(^5\)

Second only to tobacco, opioid is the most abused substance in many Asian countries.\(^6\) This may in part be due to the widespread misbelief among people about the positive effect of opioid on dyslipidemia, hypertension, CAD, and diabetes mellitus (DM).\(^7\) Contrarily, opioids have been recently suggested to be a risk factor for cardiovascular disease (CVD).\(^8\)\(^-\)\(^10\) With a dose response correlation, opioid addicts have shown to be at a higher risk of CAD compared to non-addicts.\(^11\) In addition, opioid appears to adversely influence coagulation, plasma fibrinogen level, and atherosclerosis.\(^12\)\(^-\)\(^13\) In a case-control study assessing the relationship between opioid addiction and deep vein thrombosis (DVT), the researchers showed an approximately fourfold increase in the crude odds of DVT in opioid addicts; nonetheless, opioid addiction was not an independent risk factor for DVT in multivariate logistic regression.\(^14\) The duration and route of opioid use have been associated with the detrimental effects of opioid on CVD risk factors.\(^15\) Moreover, opioids can interfere with the pharmacologic and therapeutic effects of some cardiovascular medications such as warfarin and digoxin.\(^16\)

Some studies have been carried out on the relevance of heparin use in PCI to ACT and many have evaluated UFH as a drug of choice for this intervention; nevertheless, to the best of our knowledge, the influence of heparin on ACT before and during PCI has never been compared between opioid addicts and non-addicts. Given the importance of anticoagulation in PCI, the extensive use of heparin in this regard, and the potential effect of opioid on coagulation, we aimed to investigate the effect of heparin on ACT in opioid addicts versus non-addicts prior to and during PCI.

Methods

Participants: In this comparative study, patients with ischemic heart disease (IHD) scheduled for elective PCI were recruited as study participants. The study was carried out in Shahid Mohammadi Hospital, Bandar Abbas, Iran, in 2018. The study exclusion criteria were underlying diseases affecting coagulation (either hereditary such as hemophilia or acquired such as liver failure in chronic hepatitis), drug history of warfarin, glycoprotein IIb/IIIa inhibitors, or other anticoagulant drugs, any coagulation disorder observed in the initial laboratory results [including international normalized ratio (INR) > 1.5 or platelet count < 100000/µl], and emergency PCI. Due to the lack of similar studies comparing ACT in opioid addicts with non-addicts, ACT at 2 minutes (min) was recorded for the 2 pilot groups consisting of 20 patients with opioid addiction and 20 non-addicts. The effect size was calculated as 0.7. With a power of 80%, the minimum number of patients required in each group equaled 44 individuals. Finally, 107 patients were selected though convenience sampling. Among these, 50 were opioid addicts and 57 were non-addicts. 

Study design: The protocol for this study was approved by the Institutional Review Board (IRB) of Hormozgan University of Medical Sciences (Ethics code: HUMS.REC.1397.060) and it complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from all participants. Patients’ characteristics including age, gender, weight, comorbidities including DM, hypertension, and hyperlipidemia, cigarette or hookah smoking, and aspirin or clopidogrel intake were recorded. Diagnosis of opioid addiction was made based on the Diagnostic and Statistical Manual of Mental
Disorders-5th Edition (DSM-5) criteria. For opioid addicts the type of opioid, the route of administration, and frequency of daily use were also recorded. Venous blood samples were collected from all participants prior to PCI and hemoglobin, platelet count, and coagulation indices including prothrombin time (PT), PTT, and INR were measured. All patients underwent PCI via femoral access. At the beginning of PCI, heparin (heparin sodium 1000 IU/ml solution for injection, Darou Pakhsh Pharma Chem, Iran) was intravenously injected at a dose of 100 IU/kg and 2 min later, a 2 ml blood sample was taken from the femoral catheter. ACT was immediately measured using the ACT plus™ device (Medtronic Inc., USA) after adjusting the temperature to 37 °C. ACT was measured once more 30 min after heparin injection. The total amount of heparin used for each patient was also recorded.

Statistical Package for the Social Sciences (SPSS) software (version 25, IBM Corp., Armonk, NY, USA) was used for data analysis. Mean, standard deviation, frequency, and percentages were used to describe the results. Chi-squared and Fisher’s exact tests were used to compare frequencies between different variables and ACT at 2 and 30 min. P-values ≤ 0.05 were regarded as statistically significant.

Table 1. Comparison of the baseline characteristics between opioid addicts and non-addicts

| Variables                  | Opioid addicts (n = 50) | Non-addicts (n = 57) | Total | P   |
|----------------------------|-------------------------|----------------------|-------|-----|
| Gender (male) [n (%)]      | 47 (94.0)               | 50 (87.7)            | 97    | 0.331†|
| Age (year) (mean ± SD)     | 58.44 ± 10.78           | 58.84 ± 11.38        | 58.65 ± 11.05 | 0.852†|
| Weight (kg) (mean ± SD)    | 65.86 ± 12.84           | 71.37 ± 13.06        | 68.79 ± 13.19 | 0.094‡|
| Heparin (IU) (mean ± SD)   | 6635.42 ± 1253.33       | 7215.09 ± 1338.68    | 6939.60 ± 1324.69 | 0.058‡|
| Comorbidities              |                         |                      |       |     |
| Hypertension [n (%)]       | 18 (36.0)               | 30 (52.6)            | 48 (44.9) | 0.084*|
| Diabetes [n (%)]           | 10 (20.0)               | 11 (19.3)            | 21 (19.6) | 0.927*|
| Hyperlipidemia [n (%)]     | 5 (10.0)                | 15 (26.3)            | 20 (18.7) | 0.031*|
| Drug history               |                         |                      |       |     |
| Aspirin [n (%)]            | 24 (48.0)               | 37 (64.9)            | 61 (57.0) | 0.078*|
| Clopidogrel [n (%)]        | 13 (26.0)               | 23 (40.4)            | 36 (33.6) | 0.117*|
| Smoking                    |                         |                      |       |     |
| Cigarette [n (%)]          | 25 (50.0)               | 7 (12.3)             | 32 (29.9) | <0.001*|
| hookah [n (%)]             | 8 (16.0)                | 6 (10.5)             | 14 (13.1) | 0.402*|

SD: Standard deviation
* Analyzed by χ² test, † Analyzed by independent t-test, ‡ Analyzed by Mann-Whitney test, § Analyzed by Fisher’s exact test

Results

Table 1 demonstrates the comparison between opioid addicts and non-addicts with respect to general characteristics. Patients in both groups were comparable regarding gender, age, weight, and the amount of heparin used. There was no significant difference between opioid addicts and non-addicts with regard to hypertension and DM, while hyperlipidemia was significantly more prevalent in non-addicts (10.0% vs. 26.3%; P = 0.031). The percentage of aspirin and clopidogrel use was not statistically different between the study groups (P = 0.078 and P = 0.117, respectively). A significantly higher number of opioid addicts smoked cigarettes compared to non-addicts (50.0% vs. 12.3%; P < 0.001). However, the prevalence of hookah smoking was similar between the groups (P = 0.402).

No significant difference was found between the study groups in terms of PT, PTT, INR, and platelet count (Table 2). Nevertheless, ACT at 2 min (P < 0.001), ACT at 30 min (P < 0.001), and the mean reduction of ACT between the 2nd and 30th minutes (P = 0.002) were all significantly higher in non-addicts compared to opioid addicts (Table 2).

Of the 57 opioid addicts, 3 (6%) used methadone, 37 (74%) took opium, 8 (16%) took opium extract, and 2 (4%) used both methadone and opium. The route of administration was inhalation, oral, and both inhalation and oral in 26 (52%), 18 (36%), and 6 (12%) individuals. Furthermore, 21 (42%), 16 (32%), 11 (22%), and 2 (4%) individuals used opium once a day, twice a day, 3 times a day, and 4 times a day.
The type of opioid and the route of administration had no significant correlation with ACT at 2 min, ACT at 30 min, and ACT reduction. In addition, there was no significant association between the frequency of daily opioid use and ACT at 2 min and ACT at 30 min; however, ACT reduction was significantly higher in opioid addicts with oral route of administration compared to those with both oral and inhalation routes (108.50 ± 72.66 vs. 47.67 ± 28.59 seconds; P = 0.024) (Table 3).

Backward linear regression analysis revealed a significant positive relationship between drug history of aspirin and ACT at 2 min (B = 47.247; P = 0.018) in opioid addicts which strengthened when the above mentioned variables (except for opioid-related variables) were included in the model (B = -164.508; P = 0.023). Nonetheless, no such relationships were found for ACT at 30 min in any of the groups.

**Table 2. Comparison of coagulation parameters between opioid addicts and non-addicts**

| Variables                          | Opioid addicts (n = 50) | Non-addicts (n = 57) | Total | P       |
|------------------------------------|-------------------------|----------------------|-------|---------|
|                                    | Mean ± SD               | Mean ± SD            |       |         |
| PT (sec)                           | 13.35 ± 1.08            | 13.29 ± 0.76         | 13.31 ± 0.90 | 0.718† |
| PTT (sec)                          | 31.10 ± 5.01            | 30.13 ± 4.32         | 30.52 ± 4.61 | 0.246* |
| INR                                | 1.08 ± 0.14             | 1.07 ± 0.11          | 1.08 ± 0.12 | 0.798† |
| Plt (x10^9/μl)                     | 208.61 ± 64.48          | 223.44 ± 58.31       | 217.51 ± 60.93 | 0.260* |
| ACT at 2 min (sec)                 | 292.14 ± 71.34          | 412.98 ± 150.83      | 356.51 ± 134.31 | <0.001† |
| ACT at 30 min (sec)                | 213.80 ± 49.50          | 255.23 ± 64.26       | 235.87 ± 61.20 | <0.001† |
| Change in ACT (sec)                | 78.34 ± 58.39          | 157.75 ± 152.23      | 120.64 ± 124.11 | 0.002† |

SD: Standard deviation; PT: Prothrombin time; PTT: Partial thromboplastin time; INR: International normalized ratio; Plt: Platelet; ACT: Activated clotting time
* Analyzed by independent t-test, † Analyzed by Mann-Whitney test

**Table 3. Comparison of activated clotting time (ACT) among opioid addicts by type of opioid, route of administration, and frequency of use**

| Variables                          | ACT at 2 min (sec) (mean ± SD) | P    | ACT at 30 min (sec) (mean ± SD) | P    | Change in ACT (sec) (mean ± SD) | P    |
|------------------------------------|--------------------------------|------|---------------------------------|------|---------------------------------|------|
| Type of opioid                     |                                |      |                                 |      |                                 |      |
| Methadone                          | 283.67 ± 110.44                | 0.695* | 176.00 ± 65.20                 | 0.446† | 107.67 ± 80.84                | 0.129† |
| Opium                              | 285.78 ± 51.15                |      | 213.27 ± 40.27                 |      | 72.51 ± 47.74                |      |
| Opium extract                      | 332.75 ± 127.51               |      | 223.13 ± 81.47                 |      | 109.63 ± 86.81                |      |
| Opium and Methadone                | 260.00 ± 4.24                 |      | 243.00 ± 7.07                  |      | 17.00 ± 2.83                  |      |
| Route of administration            |                                |      |                                 |      |                                 |      |
| Inhalation                         | 286.04 ± 48.36                | 0.604* | 221.50 ± 36.03                 | 0.236† | 64.54 ± 43.02                 | 0.033† |
| Oral                               | 306.56 ± 102.11               |      | 198.06 ± 67.16                 |      | 108.50 ± 72.66                |      |
| Inhalation and oral                | 275.33 ± 38.11               |      | 227.67 ± 27.54                 |      | 47.67 ± 28.59                 |      |
| Frequency of daily use             |                                |      |                                 |      |                                 |      |
| Once                               | 314.19 ± 91.03                | 0.182* | 220.86 ± 58.46                 | 0.561† | 93.33 ± 69.69                 | 0.500* |
| Twice                              | 271.00 ± 24.19               |      | 203.06 ± 40.84                 |      | 67.94 ± 40.86                 |      |
| Three times                        | 278.36 ± 71.36               |      | 210.00 ± 45.81                 |      | 68.36 ± 59.09                 |      |
| Four times                         | 305.50 ± 64.35               |      | 246.50 ± 23.33                 |      | 59.00 ± 41.01                 |      |

SD: Standard deviation; ACT: Activated clotting time
* Analyzed by Kruskal-Wallis test, † Analyzed by one-way ANOVA test

The prevalence of opium use as 3-5% among people aged 15-64 years with most users living in countries located on opium trafficking routes such as Iran. Despite the common belief that opium can have beneficial effects on CVDs, it has been suggested that opioids are a risk factor for CVDs. Furthermore, it has been proposed that opium has a role in the development of premature CAD.
Although opium addiction has been the focus of many studies, its significance in relation to coagulation and hemorrhage has rarely been addressed, especially in the context of CADs and the related procedures. In a study aimed to investigate the effect of opium addiction on post-coronary artery bypass graft (CABG) hemorrhage, inhalational opium led to more bleeding.21 However, to date no research has been performed on the association of opioid addiction with the efficacy of heparin in controlling thrombotic events during PCI monitored by ACT. Accordingly, our study appears to be the first in this regard.

In the current study, we found that ACT at 2 and 30 min was significantly lower in opioid addicts compared to controls. This suggests that blood clotting occurs faster in opioid addicts. The target ACT recommended for patients undergoing PCI with no drug history of glycoprotein IIb/IIIa inhibitors is 250 to 350 sec.22 Patients with a drug history of glycoprotein IIb/IIIa inhibitors were excluded from our study; therefore, the same range can be regarded as desirable in the current study. Although ACT reduction was significantly higher in non-addicts in our study, mean ACT at 30 min was still over 250 sec in this group, while mean ACT at 30 min in opioid addicts fell below this limit. Of note, the lower ACT reduction in opioid addicts together with the lower amount of heparin used in this group, although insignificant, may suggest the higher efficacy of this anticoagulant in this group.

Our results showed that PT, PTT, INR, and platelet count did not differ significantly between opioid addicts and non-addicts. This was in line with the findings of Nemati et al.,21 Azdaki et al.,12 and Moloudi et al.23 We also found that ACT reduction was significantly higher in opioid addicts who used the substance orally compared to those using it via both the oral and the inhalation routes. This demonstrates that ACT at 30 min reduces more rapidly in those with oral use of opium and puts them at higher risk of thrombosis. Similarly, Azdaki et al. found that drug administration route was effective on the risk of bleeding; PT was significantly lower in opium addicts who used it orally compared to those with inhalational use.12 Yet, all patients in this study were smokers compared to our study in which only some patients were smokers. In contrast, Masoomi et al. showed that opioid injection was an independent risk factor for DVT or differently put, for thrombosis.14 However, this can be attributed to opium impurities causing thrombosis via the intravenous route.

There were some limitations regarding the current study. First, in order to assess the true effect of cigarette smoking, the extent of a person’s exposure should be quantified using pack years, which we failed to record. Second, addiction to any substance is still regarded as a taboo in Iran; thus, people are generally reluctant to admit their addiction. Without appropriate testing it is impossible to ascertain whether patients in the control group were really non-addicts. Moreover, we tried to estimate the amount of opium used by each patient by recording the frequency of daily use; even so, no standard quantitative system has yet been established to determine the exact amount of opium used. Third, due to the small sample size of our study, the results should be interpreted and generalized with caution.

**Conclusion**

The present study suggests that opioid addicts may require higher doses of heparin to achieve optimum ACT during PCI compared to non-addicts. The route of administration of opioids may play a role in the efficacy of heparin in this procedure. Further studies with a larger sample size are required to confirm the findings of the current study and to determine the true influence of opioid addiction on the efficacy of heparin in maintaining ACT within the target range.

**Conflict of Interests**

The Authors have no conflict of interest.

**Acknowledgements**

The present study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences under the ethics code HUMS.REC.1397.060 and it complies with the statements of the Declaration of Helsinki.

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**Authors’ Contribution**

Conceptualization: TA; study validation and
supervision: MNT; data analysis and interpretation: EB; writing and reviewing: HF.

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آیا معتادان به مواد مخدر در حین مداخله کرونر از راه پوست به درهای بالاتر هیبارین نیاز دارند؟

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چکیده

مقیده‌های بیماری که تحت مداخله کرونر از راه پوست (Percutaneous coronary intervention، PCI) جراحی می‌گردند، از داروهای ضد انتقاد خون استفاده می‌کنند که اغلب هیبارین برای جلوگیری از وقایع ترومبوتیک در طی عمل است. معتادان به مواد مخدر ممکن است به درهای پالاتر Active clotting time (ACT) بالاتر می‌شود. در این مطالعه می‌خواستیم بهتر بشنیم تا اگر باید از درهای بالاتر هیبارین برای پتانسیال ترومبوتیک استفاده کنیم، بهترین مقدار هیبارین در معتادان در مقایسه با افراد غیر معتاد را ارزیابی کنیم.

روش‌ها: این مطالعه مقدماتی با روی 107 بیمار برنامه‌ریزی‌شده برای PCI انجام شد. در این مطالعه، 50 بیمار معتاد به مواد مخدر و 57 نفر غیر معتاد بودند. عوامل انسانی شامل سن، جنسیت، وزن، بیماری‌های سایر مصرف دارو و سیگار کشیدن یا تب شد و اینکه سایر خانوادگی افراد در نظر گرفته شد. اگر پیشرفت نداشت (P<0.05) و در مقایسه با معنی‌دار نداشت (P<0.05) و یا با سیگار کشیدن در افراد غیر معتاد رابطه معکوس وجود نداشت.

نتایج: معتادان به مواد مخدر ممکن است در مقایسه با افراد غیر معتاد در حین مداخله کرونر از راه پوست به درهای بالاتر بیشتر هیبارین را بپذیرند.

واژگان کلیدی: مواد مخدر، مداخله کرونر از راه پوست، هیبارین، زمان نیاز داشته باشند.

ارجاع: آفاق نیا طاهره، نسیم تاجیک مجید، بوشهری امیر حسین، نامی ویکی‌پرور مریم، غربی‌زاده عباس، فرشیدی حسین. آیا معتادان به مواد مخدر در حین مداخله کرونر از راه پوست به درهای بالاتر هیبارین نیاز دارند؟ مجله اعتیاد و سلامت; ۱۴۰۰:۱۲۰۰-۱۲۲۰۰.