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Role of Diffusion-Weighted MRI (DWI-MRI) in the Diagnosis of Brain Complications caused by Heroin Substance Abuse

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Background: Magnetic resonance imaging (MRI) offers higher diagnostic accuracy for brain lesions caused by heroin abuse compared to compute tomography (CT) scan. These lesions have a low signal on T1-weighted (T1W) images and a high signal on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images. This study aimed to evaluate the role of diffusion-weighted MRI (DWI-MRI) in heroin addicts.

Methods: This cross-sectional study was conducted on 20 patients with heroin addiction (vapor inhalation/injection) referring to Imam Reza Hospital of Mashhad, Iran. Patients in whom heroin abuse was only cause of consciousness, loss and neurological symptoms were enrolled in this study. Demographic data of the patients were recorded, including MRI, FLAIR, T1W and T2W images. In addition, DWI of axial and sagittal sections of the brain was performed in the following sequences.

Results: In this study, mean age of patients was 40.15±7.673 years, and 95% of patients were male. The most common mode of heroin use was inhalation, and mean duration of addiction was 5.48±3.393 years. Mean daily intake of heroin was 13.4±15.30 grams, and mean duration of heroin abuse was 10.3 and 4.6 years in patients with and without MRI changes, respectively. A significant correlation was observed between MRI changes and duration of heroin use ($r=0.721$) ($p=0.001$). In addition, a significant correlation was observed between MRI changes and daily intake of heroin ($p=0.006$).

Conclusion: According to the results of this study, brain lesions caused by heroin abuse have a low signal on T1W images and a high signal on T2W and FLAIR images. Therefore, it could be concluded that heroin intake has significant effects on the brain of users.

▶*Implication for health policy/practice/research/medical education:* Role of Diffusion-Weighted MRI (DWI-MRI) in the Diagnosis of Brain Complications caused by Heroin Substance Abuse

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1. Introduction:

Heroin abuse is a global issue with an increasing rate over the past few decades (1). Heroin addiction has a higher prevalence in Asia compared to other countries in the world (5.75 versus 1.5 million users) (2, 3). According to statistics, one person per minute and 52,600 people per year become addicted to heroin in Pakistan. In 1990, 75% of the total number of patients with substance abuse accounted for heroin addicts (4).

According to several reports, mortality rate caused by drug abuse is on a rising trend worldwide. In 1964, substance abuse was the cause of death in only six cases, while this rate increased to 600 people during 1964-1997. Heroin abuse is the major cause of recorded mortalities in this regard (5).

One of the most common modes of heroin use is vapor inhalation (6). Neurological complications caused by heroin abuse depend on the type, amount and mode of substance use. Among the most frequent neurological damages caused by heroin abuse are cerebral abscess, transverse myelitis, neuropathy, rhabdomyolysis and myoglobinuria. Pathophysiology of these complications is probably secondary to hypoxic-ischemic injury, hypotension, cerebral edema and infection (7).

In several cases, overdose or complications caused by intravenous (IV) use of heroin, such as human immunodeficiency virus (HIV) and hepatitis C, could lead to death. Heroin-induced leukoencephalopathy is a significant disorder caused by heroin vapor inhalation. Heroin abuse is considerad cause of 23-25% of all leukoencephalopathies, and this rate has recently been reported to be on the rise. This syndrome is normally diagnosed through neurological disorders involving the white matter of brain (7, 8).

Early diagnosis of heroin-induced leukoencephalopathy could result in effective treatment of this disorder, as well as heroin withdrawal. Therefore, prevention of the associated complications and modification of new diagnostic methods to differentiate between heroin-induced leukoencephalopathy and other leukoencephalopathies are paramount (9).

Magnetic resonance imaging (MRI) is believed to have higher diagnostic accuracy for most disorders, such as infarcts and demyelinating diseases, compared to compute tomography (CT) scan. In addition, MRI is more accurate in the diagnosis of brain lesions caused by heroin use compared to CT-scan. These lesions have a low signal on T1-weighted (T1W) images and a high signal on T2-weighted (T2W) and fluid-attenuated inversion recovery (FLAIR) images (1).

This study aimed to evaluate the diagnostic accuracy of diffusion-weighted MRI imaging (DWI-MRI) in heroin addicts referring to Imam Reza Hospital of Mashhad, Iran.

2. Materials and Methods:

This cross-sectional study was conducted on all patients with heroin addiction referring to Imam Reza Hospital of Mashhad, located in the northeast of Iran. In total, 20 patients were selected by census sampling.

Inclusion criteria of the study were the presence of altered consciousness level and neurological symptoms, and history of

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heroin abuse (inhaled or IV) for at least three years.

Exclusion criteria were as follows: 1) cardiovascular resuscitation; 2) underlying diseases (e.g., hypertension, diabetes, hyperlipidemia, chronic renal disease and liver damage); 3) history of myocardial infarction or cerebrovascular accident; 4) neurological disorders; 5) history of HIV infection or any diseases causing white matter changes during MRI and 6) contraindications to MRI.

Written informed consent was obtained from all the patients prior to the study.

Required data were collected via interviews with patients, as well as laboratory and clinical examinations. Initially, patients presented with loss of consciousness or drug-induced brain damage (e.g., cerebellar disorders, extrapyramidal symptoms and selective mutism) referring to the emergency ward of the medical toxicology center of the hospital were evaluated by a specialist.

After investigating medical records, determining the rate and duration of heroin abuse, and ruling out other probable causes of consciousness, loss in the presence of symptoms, patients in whom heroin use was the only cause of consciousness loss and neurological symptoms were enrolled in this study. Moreover, laboratory tests and clinical examinations were performed by a clinical toxicologist and demographic data of patients, including age, gender, severity, duration of heroin use, and mode of heroin use were recorded by a radiology assistant.

MRI, FLAIR, T1W and T2W images, and DWI were obtained from axial and sagittal sections of the brain. Afterwards, the images were investigated, and the results were analyzed by a radiologist. Data analysis was performed in SPSS V.17, and P value of 0.05 was considered as significant.

In the present study, data provided from the medical records of patients remained confidential by using codes. In addition, patients were allowed to leave the study at any time without any charges. The objectives of the study were fully explained to patients prior to participation.

3. Results:

In this study, 95% and 5% of patients were male and female, respectively, within the age range of 28-59 years (mean age: 40.15±7.673 years). In terms of education status, 10% (n=2) of patients had primary education, and 20% (n=4) had secondary education. In addition, 50% (n=10), 5% (n=1), and 15% (n=3) of patients had diploma, associate degree and bachelor's degree, respectively.

Among the studied patients, 75% used other drugs in addition to heroin, 92.85% of whom (n=13) were opium addicts, and one patient (7.15%) used Tramadol. According to our findings, the most common mode of heroin use was inhalation in 90% of patients (n=18), while 10% (n=2) of participants applied both inhalation and injection.

In our patients, minimum and maximum duration of addiction were 3 years and 18 years, respectively. In 45% and 40% of participants, duration of addiction was between 3-5 years and 5-7 years, respectively, while in 5%, history of heroin abuse was between 7-9, 9-11, and over 11 years (n=1). In total, mean of substance abuse duration was estimated at 5.48±3.393 years.

Among the studied patients, minimum and maximum daily intake of heroin was between 2-60 grams, and mean of daily consumption was estimated at 13.4±15.305 grams. Frequency of daily heroin intake is presented in Diagram A.

Relationship between MRI changes and other variables: According to the results of this study, minimum and maximum of time intervals between the onset of symptoms and patients MRI were between 4-20 days. According to the results of MRI and DWI, restriction changes were observed in none of the studied patients with heroin addiction presented with neurological symptoms.

On the other hand, results of routine clinical brain MRI sequences (T2W, T1W and FLAIR) were indicative of increased signal intensity in periventricular white matter of the brain in 15% (n=3) of patients. Moreover, no signal changes were observed in 85% (n=17) of participants, and no

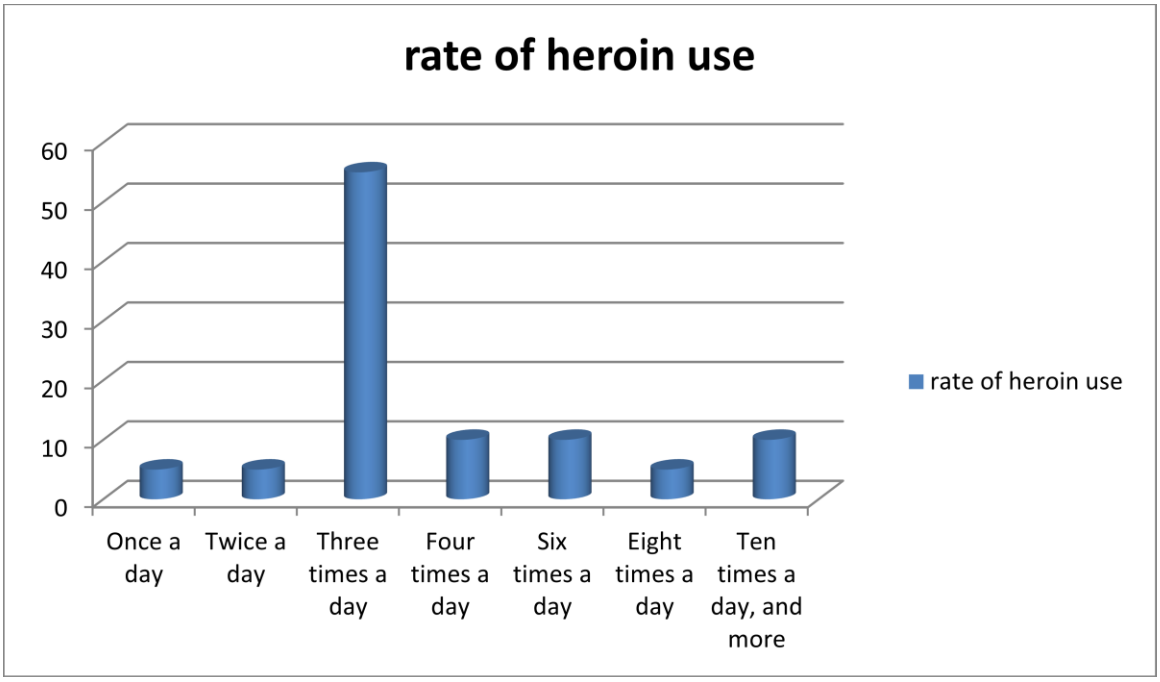

Fig. 1. Frequency of Daily Heroin Intake by Patients.

significant difference was observed between these two variables (p=0.23).

As for the relationship between MRI changes and age of patients, mean age of patients with and without MRI changes was 40.67 and 40.06 years, respectively, and results of Mann-Whitney test were indicative of no significant difference between the study groups in this regard (p=0.79).

Since only one of our patients was female with no MRI changes, we were not able to deduce a significant correlation between MRI changes and gender of drug users.

With respect to the mode of heroin use, the majority of our patients applied inhalation, and only two cases used other drugs in addition to heroin. Therefore, no significant correlation was observed between MRI changes and mode of heroin use.

In this study, mean duration of heroin use was estimated at 10.3 and 4.6 years in patients with and without MRI change. However, no significant correlation was observed between MRI changes and duration of substance abuse (p=0.28). By contrast, results of Pearson's correlation-coefficient were indicative of a significant correlation between MRI changes and duration of heroin use (r=0.721) (P=0.001).

Mean of daily heroin intake was calculated at 7.76 and 45.3 times per day in patients with and without MRI changes. Moreover, evaluation of the relationship between MRI changes and daily intake of heroin was indicative of a significant correlation between these two variables (p=0.006).

4. Discussion:

According to the results of this study, the majority of patients with heroin addiction were male, which is a finding confirmed by similar studies (2, 5, 6, 8).

Furthermore, evaluation of the relationship between MRI changes and age of patients was indicative of no significant difference between patients with and without MRI changes in this regard. Mean age of patients in our study was higher than similar studies (10), which might be due to the lower age range of addiction in other countries compared to Iran.

According to one study by Haihong et al., frontal lobe atrophy is a common complication caused by heroin substance abuse, and cingulated cortex is the most affected brain region by heroin neuropathology (11). On the other hand, Liu *et al* concluded that disrupted white matter integrity in right frontal white matter might occur as a result of continuous heroin abuse (12). Additionally, Wang et al. claimed that fractional anisotropy of cerebral white matter is more likely to decrease in patients with heroin addiction compared to control subjects (5).

DWI was first used by Chen et al. in order to distinguish between heroin-induced leukoencephalopathy and other types of leukoencephalopathy. According to their findings, DWI-MRI could be an appropriate measure to differentiate between heroin-induced spongiform leukoencephalopathy and other leukoencephalopathies, as well as other demyelinating diseases and brain edema, which are considered as two major factors associated with MRI changes. Furthermore, they claimed that heroin-induced leukoencephalopathy could be detected with high sensitivity by the assessment of white matter signal on T2W images. Also, they stated that accumulation of fluid between myelin lamellae could lead to increased anisotropic water diffusion in the white matter, which would ultimately increase the imaging signal of DWI (10). This finding was confirmed in another study by Siue *et al* (7).

In another research, Hall and Offish investigated six patients diagnosed with heroin-induced leukoencephalopathy and reported that cerebellar white matter was involved in all these patients. In addition, brain stem signal changes were observed in five cases, and no restriction changes were detected in any regions of DWI signal abnormality, which is compatible with the results of the current study.

Therefore, it could be concluded that highly specific MRI signal abnormalities may contribute to the diagnosis and identification of the main mechanisms involved in heroin-induced leukoencephalopathy, which could be practical in the administration of drug treatment regimens (13).

In their study, Bga et al. evaluated one patient with heroin-induced spongiform leukoencephalopathy and observed restricted diffusion in globus pallidus and bilateral cerebral cortex in MRI. Development of atrophy and T2-hyperintensity in the subcortical white matter of patient were also detected via MRI and FLAIR (14).

Similar to studies performed by Bartlett, and Hall and Offish, none of our patients with heroin addiction and neurological symptoms had restriction changes on their DWI. This might be due to relatively large time intervals between the onset of brain symptoms and time of MRI, as well as significantly lower time intervals between the onset of addiction and appearance of MRI changes. Mean of time intervals between the onset of brain symptoms and time of MRI was 1.5 days in the present study, while it was 11 days in the study by Hall and Offish (13). This variable was significantly higher in the study by Chen *et al*, which undermined the role of DW-MRI in the diagnosis of heroin-induced leukoencephalopathy (10). In this regard, further detailed studies with larger sample sizes are required in order to obtain more accurate results.

In another study by Blase *et al*, three patients with toxic leukoencephalopathy caused by heroin abuse were evaluated. MRI and DWI were performed on all patients, and MRI was indicative of similar symmetric supratentorial hyperintense signal changes involving the frontal, parietal, occipital and temporal lobes in all three cases. Since cerebellum and brainstem were not affected by toxic leukoencephalopathy, which is a rare occurrence in leukoencephalopathy, heroin-induced toxic leukoencephalopathy on MRI could be related to in these patients (15).

In the current study, inhalation of heroin vapor was the most frequent mode of substance use by the majority of patients, and increased signal intensity in the periventricular white matter was observed in three cases, only one of whom applied both heroin vapor inhalation and injection. Frequency of heroin vapor inhalation in our study might be due to the limited number of injecting drug users, as well as the higher safety of inhalation mode compared to injection regarding the risk of infectious diseases, such as HIV and hepatitis.

In the present study, T2W images in three patients were indicative of the reappearance of high signal intensity areas in deep white matter and periventricular white matter, while other regions remained unaffected. However, since the majority of similar studies consisted of case reports or case series, we were not able to reach a definitive conclusion on this issue.

To date, no studies have evaluated the relationship between the duration and amount of heroin substance abuse and MRI signal changes of the brain. According to the results of our study, there were no significant differences in the duration and amount of heroin use between patients with and without MRI changes, which might be due to the different dosage of the substance used by our patients over the course of addiction.

Our findings indicated that increased amount of heroin intake is highly associated with increased duration of addiction, which implies the significance of confounding variables in this regard. Therefore, it is recommended that future studies be conducted as to clarify this issue. Moreover, rate of MRI changes was observed to be higher in patients with higher daily intake of heroin.

This was the first study conducted to evaluate the role of heroin abuse in MRI changes. However, few similar studies have attempted to investigate the role of DWI-MRI in the detection of brain complications caused by heroin use. One of the limitations of this study was the small sample size, which led to the lack of definitive conclusions in some of the assumptions. Consequently, it is recommended that confounding variables be examined in large sample sizes in future studies. Furthermore, metabolic changes and brain functions associated with MRI changes need to be further studied in order to achieve better clinical prognosis.

5. Conclusion:

In conclusion, heroin intake has been shown to have a direct effect on the brain of substance users. Brain lesions caused by heroin use have a low signal on T1W images and a high signal on T2W and FLAIR images. Since early diagnosis of heroin-induced leukoencephalopathy could contribute to the rapid treatment of this disorder, modification of new diagnostic measures to distinguish between heroin-induced leukoencephalopathy and other forms of this syndrome is of paramount importance.

6. Conflict of Interest:

The authors of the present work declare no conflict of interest.

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