Comparing Symptoms of Withdrawal, Rapid Detoxification and Detoxification with Clonidine in Drug Dependent Patients

Hassan Ziaaddini MD*, Abbas Qahestani MD**, Maryam Moin Vaziri MD**

* Associate Professor of Psychiatry, School of Medicine and Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran.
** General Practitioner, Kerman University of Medical Sciences, Kerman, Iran.

Abstract
Considering the fear of drug addicts from hangover symptoms and the costs of withdrawal treatment and their importance in deciding to withdraw, it is helpful to identify various ways of withdrawal and their effects. This study investigated the withdrawal symptoms of two methods of detoxification with clonidine and rapid detoxification of clonidine with naltrexone.

Background:
This was a clinical trial study. Patients referred to Shahid Beheshti hospital for narcotic addiction treatment were randomly divided into two groups. Group matching was done based on entry and excluding criteria. Data were collected using a demographic questionnaire including questions on the drug abuse and the consumption method, and a questionnaire on the symptoms of opioid withdrawal.

Methods:
Restlessness, vomiting, feeling sick and significant decrease of diastolic blood pressure was higher in rapid detoxification method group. However, considering background variables, Spearman correlation coefficient showed significant relationship just for lacrimation. Temptation for drug consumption was lower for heavy abusers in rapid detoxification method and in general, those who had higher amount of consumption and were treated by rapid detoxification, experienced less temptation for consumption.

Findings:

Conclusion:
Rapid detoxification can be the first level treatment for heavy abusers, because it reduces the temptation for drug consumption and has shorter hospitalization and, as a result, has lower cost.

Key words: Drug abuse, Rapid detoxification, Clonidine detoxification, Withdrawal symptoms.

Address of Correspondence:
Hassan Ziaaddini MD, Associate Professor of Psychiatry, Kerman University of Medical Sciences and Neuroscience Research Center, Kerman, Iran.
E-mail: h_ziaaddini@yahoo.com

Page count: 6
Tables: 3
Figures: 0
References: 14
Introduction
Drug abuse is one of the main health problems in Iran and can cause severe and deep physical, psychological and social harms. One of the goals of detoxification from drug dependency is to ease or remove the pain of withdrawal during the treatment, so that the treatment is safe and can help the patient in overcoming drug abuse.\textsuperscript{1} Drug dependency symptoms are created by stopping consumption or using drug antagonists.\textsuperscript{2,3} Based on the kind of narcotic, symptoms begin after a few hours to a few days of consumption cut. Usually, narcotics with short term-effect have severe, but short term symptoms and those with longer-term effect create mild but long term symptoms.\textsuperscript{4}

Various methods of treating withdrawal symptoms due to detoxification are recommended, such as replacing heroin with a narcotic with long-term effect like methadone\textsuperscript{5} or using LAAM (levoacetylmethadonal) and bupronorphine; of course, LAAM is not currently available in Iran.\textsuperscript{6,7} Detoxification with above mentioned methods is associated with laws and regulations of supplying them, which should be considered as a limitation.

Non-opioid treatment approaches to detoxification of opioid drugs such as clonidine were used in past years.\textsuperscript{8,9} These days, rapid detoxification and even ultra rapid detoxification are considered as detoxification with opioid in spite of their limitations. Some researchers have discussed the superiority of rapid method to detoxification with clonidine.\textsuperscript{10,11}

For rapid and ultra rapid detoxification, naloxan, an opioid antagonist with short term effects, is used. This method leads to a severe withdrawal syndrome that can be treated by constant prescription of clonidine and benzodiazepine. In detoxification with clonidine, naltrexone is prescribed for at least 5 days in case of drugs with short term effects and 10 days for drugs with long term effects such as methadone. Therefore, in rapid detoxification, detoxification is completed within 48 to 72 hours, while it is 7 to 10 days in other methods.\textsuperscript{12} Rapid detoxification has been used even at home without complications and problems.\textsuperscript{13}

Ultra rapid detoxification with general anesthesia is also reported in those who have not been able to complete their detoxification with other methods or those who has severe withdrawal symptoms.\textsuperscript{14} Considering the legal procedure of using methadone and bupronorphine in one hand and the risk factors of ultra rapid detoxification methods on the other hand, this study investigated the treatment of withdrawal symptoms in the two methods of detoxification with clonidine and naltrexone plus clonidine that do not have the above problems.

Methods
This was a clinical trial study. Participants included patients who referred to Shahid Beheshti hospital for narcotic addiction treatment. The including and excluding criteria were applied (patients should not have any psychological or physical disorder and should not leave the hospital before all detoxification symptoms are disappeared). They also provided a written consent. Patients were randomly divided into two groups and group matching was based on age, the kind of narcotic they used, the method of consumption and the amount.

After necessary clinical and paraclinical tests and considering the medical and psychiatric history of patients, if there was no problem with detoxification with clonidine or clonidine plus naltrexone, the patient would be assigned to one of the groups. For each group, 30 patients and 30 questionnaires were filled.

Data were collected using a researcher made questionnaire including questions on age, career, education, number of siblings, birth rank, type of addiction, consumption method, amount of consumption, length of addiction and trying withdrawal. The withdrawal symptoms were assessed using St George's Hospital questionnaire for narcotic withdrawal symptoms. This questionnaire includes 13 signs and 12 symptoms.\textsuperscript{14} The questionnaires were completed by a trained medical intern who was not aware of the patients' treatment method when completing questionnaire.

Signs and symptoms were checked and scored by an intern through daily clinical examination and interview. If there was no sign or symptom, the score was 0. In case of mild symptoms or lack of evidence about the existence of symptoms the score was I and obvious symptoms had score II. Signs included yawning, lacrimation, running nose, sweating, shaking, piloerection, restlessness, pupil size, lack of appetite, vomiting, diarrhea, sleeplessness, and trying to get drugs. Symptoms included muscle ache, tachycardia, sneezing, feeling pins and needles in body organs, feeling
Table 1. Frequency distribution and percentage of background variables in the two treatment groups

| Variable               | Type of treatment | Frequency | Percentage | Frequency | Percentage |
|------------------------|-------------------|-----------|------------|-----------|------------|
| Marital status         | Rapid             | 13        | 43.3       | 13        | 43.3       |
|                        | Traditional       | 17        | 56.7       | 17        | 56.7       |
| Education              | Rapid             | 2         | 6.7        | 4         | 13.8       |
|                        | Traditional       | 8         | 26.7       | 15        | 51.7       |
|                        | Rapid             | 11        | 36.7       | 9         | 31         |
|                        | Traditional       | 9         | 30         | 1         | 3.4        |
| Number of siblings     | Rapid             | 1         | 33.3       | 5         | 16.7       |
|                        | Traditional       | 18        | 60         | 11        | 36.7       |
| Birth rank             | Rapid             | 6         | 20         | 6         | 20         |
|                        | Traditional       | 24        | 80         | 24        | 80         |
| Type of drug           | Rapid             | 14        | 46.7       | 14        | 46.7       |
|                        | Traditional       | 5         | 16.7       | 5         | 16.7       |
|                        | Rapid             | 5         | 16.7       | 5         | 16.7       |
|                        | Traditional       | 3         | 10         | 3         | 10         |
|                        | Rapid             | 3         | 10         | 3         | 10         |
|                        | Traditional       | 11        | 36.7       | 14        | 46.7       |
| Consumption method     | Rapid             | 8         | 26.7       | 8         | 26.7       |
|                        | Traditional       | 16        | 53.3       | 16        | 53.3       |
|                        | Rapid             | 6         | 20         | 6         | 20         |
|                        | Traditional       | 19        | 63.3       | 16        | 53.3       |
| Job status             | Rapid             | 1         | 3.3        | -         | -          |
|                        | Traditional       | 29        | 96.7       | 30        | 100        |
| History of withdrawal  | Rapid             | 23        | 76.7       | 24        | 80         |
|                        | Traditional       | 7         | 23.3       | 6         | 20         |

cold and hot, muscle cramp, excitability, and tendency to take medicine.

This study was done under the research ethics.

Results

The mean age of participants was 28.32 ± 5.46 years. The youngest was 20 year old and the oldest was 42 years old. The frequency of background variables is presented in Table 1. Most of the participants were from crowded families. 20% were the first children in the family and 40.7% were unemployed. As mentioned before, during the study, group matching was tried by recruiting more patients. To assure group match, independent sample t-test was used, which showed no significant difference between the two groups (Table 2). Just one of the participants has addiction history of less than one year. 76.6% of participants in rapid detoxification group and 80% of clonidine group had a history of detoxification.

The mean score of 10 days observing signs and symptoms for clonidine group and 5 days for rapid detoxification group was compared using independent sample t-test. Restlessness, vomiting, feeling sick, systolic and diastolic blood pressure was significantly different between the two groups. But there was no significant difference in other signs (Table 3).

Table 2. Comparing the mean age and amount of taken narcotics in the two treatment group

| variable | Treatment method | frequency | mean     | Standard deviation | results |
|----------|------------------|-----------|----------|--------------------|---------|
| Age      | Rapid            | 30        | 28.4     | 5.77               | t = 0.117 |
| Year     | Traditional      | 30        | 28.2     | 5.23               | p > 0.9 |
| Amount   | Rapid            | 30        | 3.2      | 1.77               | t = 0.7  |
| Gram     | Traditional      | 30        | 3.3      | 8.1                | p > 0.9 |
Table 3. The mean of signs and symptoms of withdrawal during treatment period in the two groups

| Variable                        | Treatment method | P-value |
|---------------------------------|------------------|---------|
|                                 | Rapid            | Traditional |       |
|                                 | mean   | Standard deviation | mean   | Standard deviation |       |
| Yawning                         | 1.5    | 0.4               | 1.42   | 0.46               | 0.475  |
| Lacrimation                     | 1.11   | 0.49              | 0.97   | 0.54               | 0.29   |
| Running nose                    | 0.91   | 0.56              | 0.74   | 0.46               | 0.195  |
| Sweating                        | 0.7    | 0.59              | 0.69   | 0.57               | 0.947  |
| Shaking                         | 0.72   | 0.61              | 0.68   | 0.59               | 0.818  |
| Piloerection (sign)             | 0.41   | 0.47              | 0.52   | 0.47               | 0.397  |
| Restlessness                    | 1.19   | 0.54              | 0.91   | 0.52               | 0.047  |
| Lack of appetite                | 0.74   | 0.54              | 0.51   | 0.45               | 0.07   |
| Vomiting                        | 0.32   | 0.43              | 0.06   | 0.18               | 0.004  |
| Diarrhea                        | 0.57   | 0.64              | 0.38   | 0.37               | 0.159  |
| Sleeplessness                   | 0.97   | 0.7               | 0.74   | 0.63               | 0.187  |
| Temptation to take drugs        | 0.45   | 0.66              | 0.19   | 0.32               | 0.057  |
| Muscle ache                     | 0.53   | 0.6               | 0.83   | 0.56               | 0.53   |
| Heart beat                      | 0.41   | 0.42              | 0.37   | 0.41               | 0.71   |
| Sneezeing                       | 0.9    | 0.55              | 0.69   | 0.48               | 0.122  |
| Pins and needles                | 0.73   | 0.61              | 0.61   | 0.47               | 0.411  |
| Feeling cold and hot            | 0.98   | 0.68              | 0.87   | 0.58               | 0.489  |
| Piloerection (symptom)          | 0.53   | 0.54              | 0.4    | 0.33               | 0.292  |
| Feeling sick                    | 1.03   | 0.5               | 0.67   | 0.38               | 0.002  |
| Stomach ache                    | 0.75   | 0.6               | 0.62   | 0.49               | 0.339  |
| Musculoskeletal pain            | 1.06   | 0.63              | 1.23   | 0.51               | 0.265  |
| Tremor and muscle cramp         | 0.65   | 0.67              | 0.56   | 0.54               | 0.556  |
| Excitability                    | 0.62   | 0.83              | 0.63   | 0.55               | 0.971  |
| Drug seeking behavior           | 0.36   | 0.49              | 0.18   | 0.27               | 0.081  |
| Systolic blood pressure         | 114    | 6.26              | 100.06 | 5.81               | 0.000  |
| Diastolic blood pressure        | 72     | 6.34              | 67.63  | 5.76               | 0.002  |
| Heart beat                      | 84.67  | 8.21              | 87.03  | 4.71               | 0.179  |

Discussion
Comparing the groups, restlessness, feeling sick, systolic, and diastolic blood pressure were significantly different. Previous studies also reported the severity of withdrawal symptoms. This can be explained considering the consumption of antagonist in one hand and higher consumption of clonidine on the other hand. Moreover, the period of detoxification is also shorter both in the present study and in other studies.

In other cases, there was no significant difference. The severity of symptoms was easily controllable by tranquilizer. Since no significant difference was seen between the type of drug and detoxification method, there is no superiority between these two methods. To our knowledge, there are no other studies on the topic to compare.

In the rapid method group, variables of temptation to take drugs and piloerection had a negative significant relation with the amount of drugs, so that with more amount of consumption the severity of symptoms was decreased. In the only clonidine group, the mean severity of lacrimation, pins and needles, piloerection and tendency to take drugs had a positive significant relation with the amount of drugs, so that the more drugs, the higher the mean severity of these symptoms. It can be concluded that for higher amount of drug consumption, the rapid detoxification method is superior; because it decreases the temptation and sustains withdrawal. However, in long term treatment method does not have much effect on portent of sustainable withdrawal.

Considering the results of the study in one hand, and the short term hospitalization of patients on the other hand, which reduces the costs and the consumption of narcotics in hospital wards, this treatment method can be a suitable one for patients who are selected for detoxification.

Limitations: Since patients were different, it was possible for them and for other personnel to find out about the treatment method. Also, other methods of detoxification such as bupronorphine and methadone were not compared.

Conflict of interest: The Authors have no conflict of interest.

Acknowledgment
Thanks go to the personnel of third department of the Shahid Beheshti Hospital who cooperated with the researchers during the study.
References

1. Galanter M, Kleber H. The American psychiatric press textbook of substance abuse treatment. 1st ed. Washington D.C: American Psychiatric Publishing; 1994. p. 1407-2411, 2352-6.

2. O'Connor PG, Selwyn PA, Schottenfeld RS. Medical care for injection-drug users with human immunodeficiency virus infection. N Engl J Med 1994; 331(7): 450-9.

3. Kosten TR, McCance E. A review of pharmacotherapies for substance abuse. American Journal on Addictions 1996; 5(Suppl 1): S30-S37.

4. Sadock BJ, Sadock VA. Kaplan and Sadock's synopsis of psychiatry: Behavioral Sciences / Clinical Psychiatry. 10th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.

5. Cooper JR. Including narcotic addiction treatment in an office-based practice. JAMA 1995; 273(20): 1619-20.

6. Lowinson JH, Ruiz P, Millman RB, Langrod JG. Substance abuse: A comprehensive textbook. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1997. p. 10-20, 115-30, 158-80, 460-540.

7. O'Connor PG, Carroll KM, Shi JM, Schottenfeld RS, Kosten TR, Rounsaville BJ. Three methods of opioid detoxification in a primary care setting. A randomized trial. Ann Intern Med 1997; 127(7): 526-30.

8. O'Connor PG, Waugh ME, Carroll KM, Rounsaville BJ, Diagkogiannis IA, Schottenfeld RS. Primary care-based ambulatory opioid detoxification: the results of a clinical trial. J Gen Intern Med 1995; 10(5): 255-60.

9. Riordan CE, Kleber HD. Rapid opiate detoxification with clonidine and naloxone. Lancet 1980; 1(8177): 1079-80.

10. O'Connor PG, Kosten TR. Rapid and ultrarapid opioid detoxification techniques. JAMA 1998; 279(3): 229-34.

11. van Dorp EL, Yassen A, Dahan A. Naloxone treatment in opioid addiction: the risks and benefits. Expert Opin Drug Saf 2007; 6(2): 125-32.

12. Hensel M, Kox WJ. Safety, efficacy, and long-term results of a modified version of rapid opiate detoxification under general anaesthesia: a prospective study in methadone, heroin, codeine and morphine addicts. Acta Anaesthesiol Scand 2000; 44(3): 326-33.

13. Carreno JE, Bobes J, Brewer C, Alvarez CE, San Narciso GI, Bascaran MT, et al. 24-Hour opiate detoxification and antagonist induction at home—the 'Asturian method': a report on 1368 procedures. Addict Biol 2002; 7(2): 243-50.

14. Ghodse, AH. Drugs and Addictive Behaviour: A Guide to Treatment. 2nd ed. Oxford: Wiley-Blackwell; 1995.
Clinical Trials

Clinical Trials are research studies conducted with human participants to test the safety and efficacy of medical treatments. These studies are essential for advancing medical knowledge and improving healthcare outcomes. Clinical Trials are typically divided into phases, each with specific objectives and requirements.

Phase 1 Clinical Trials

Phase 1 Clinical Trials are the first stage of research in human volunteers. These trials are designed to determine the safety, tolerability, and appropriate dose levels of a new treatment. Phase 1 trials are often conducted in small groups of healthy volunteers or patients with a specific disease.

Phase 2 Clinical Trials

Phase 2 Clinical Trials are conducted to further evaluate the safety and efficacy of a treatment in a larger group of patients with the disease. These trials are usually randomized controlled trials (RCTs) and may compare the new treatment to an existing standard of care. Phase 2 trials aim to provide preliminary evidence of the treatment's effectiveness.

Phase 3 Clinical Trials

Phase 3 Clinical Trials are large trials that confirm the effectiveness of a treatment relative to an established treatment or placebo. These trials are usually randomized controlled trials (RCTs) and involve thousands of participants. The results of Phase 3 trials are used to support the approval of new treatments by regulatory agencies.

Phase 4 Clinical Trials

Phase 4 Clinical Trials are conducted after a treatment has been approved by regulatory agencies. These trials are used to gather additional information about the effectiveness of a treatment in different populations or to monitor long-term effects.

Clinical Trials are crucial for ensuring that new treatments are safe and effective before they are approved for use. They provide evidence-based insights into the best practices for treating various conditions, leading to improved healthcare outcomes for patients.