Original Article

Comparison of Effects and Side Effects of Two Naloxone-Based Regimens in Treatment of Methadone Overdose

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ABSTRACT

Background: Acute opioid overdose is a common cause of admission in emergency department. In spite of the fact that naloxone is the main therapy for decades, there are controversies about the proper way of its use. This study aimed to compare two most recommended administration modes for naloxone.

Methods: In this single-blind clinical trial, 80 patients with methadone overdose syndrome were randomly divided into two equal groups. The patients in infusion group received a constant infusion of naloxone preparation; while in the patients in PRN group, naloxone was administered only if needed clinically. Severity of withdrawal syndrome was evaluated after 30 min, 3 h, and 12 h of the treatments in both groups.

Results: Eighty patients completed the study (10 women and 70 men). Both groups were similar in terms of mean age, sex ratio, and the severity of intoxication. The severity of withdrawal symptom was significantly lower in the PRN group (P<0.001).

Conclusion: Naloxone administration as PRN mode lowers the rate and severity of withdrawal syndrome. It is recommended as the preferred mode of naloxone administration.

Keywords: Infusion, Methadone Intoxication, Naloxone, PRN, Withdrawal syndrome.

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INTRODUCTION

Replacement therapy with methadone eases access to this synthetic opioid [1]. Methadone has influential effect in relieve of almost all opioid withdrawal symptoms. However, it has low therapeutic index [2]. It has also numerous interactions with benzodiazepines, ethanol, antidepressants and many other drugs [3, 4] that make its use very challenging. The same is true in its overdose, which needs antagonism therapy [3]. On the other hand, naloxone half-life (30 to 80 min) is too short in comparison to methadone's (1 to 15 h) [2]. Therefore, clinical features of methadone toxicity may reappear again with unpleasant consequences [5-8]. Opioid overdose syndrome is true medical emergency. Naloxone is given mainly intravenously in this situation simultaneously with other supportive measures. This semi-synthetic pure opioid antagonist shows its power within seconds. However, complete drug effect cannot be observed until an hour later during which withdrawal syndrome may appear including muscle and abdominal pain and cramps, diarrhea, agitation [7, 9], decreased confidence and cooperation with medical team and leaving hospital against advises of medical staff. It may lead the patient to take another dose of methadone, and another overdose [8].

In spite of seriousness of methadone intoxication, there are no strict recommendations for way of naloxone administration in medical textbooks. Naloxone is accepted as the first line antidote, in some references as PRN mode and in as continuous IV infusion. Length of therapy and its dosing remain uncertain. 12 to18 h, 0.25-6.25 mg/h to 25 µg/kg/hour are recommended [5, 7].

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This study was primarily designed to find which naloxone administration method is more efficacious and causes fewer withdrawal symptoms during therapy.

MATERIALS AND METHODS

In this double blind clinical trial study, registered as IRCT code: 138903054033N1, overall, 80 patients diagnosed with methadone intoxication by physician of emergency ward using the triad of methadone intoxication (miosis, bradypnea with respiratory rate <10, and altered level of consciousness) and history of recent methadone ingestion entered the study. Those with history of severe heart disease, co-ingestions, treated with flumazenil or atropine during pre-hospital management, and patients admitted to intensive care unit were excluded for the study. All patients received naloxone intravenously, as well as other resuscitative measures. Based on administration mode, the patients were allocated to two equal groups with ethical issue as balancing care quality and efficiency**,** the ongoing issue of providing everyone with access to basic medical care and coordinate care, and provide many other services.

In the first step, 0.2 mg naloxone was injected and repeated if no response was seen. The third and fourth doses were given in amount of 0.4 mg, if needed after two min. In the case of no improvement in patient condition, the next doses of 0.8 mg were used every 5 min up to 10 mg total dose. This primary dosage of naloxone (referred to as X) was the same in both groups.

As half- life is about 30-60 min naloxone and 16-36 h for methadone, the patient may again demonstrate signs of intoxication after primary improvement. In this case, naloxone administration repeated as above in the case group. However, the primary total dose given to any patient by EMS or in ED (X) was administered in control group for 3 h in a diminutive way as follows:

The first hour: 2/3*X

The second hour: 2/3*the first hour

The third hour: 2/3 *the second hour

The severity of withdrawal syndrome was assessed in the patients using COWS (Clinical Opiate Withdrawal Scale) criteria [10]. All information about the patient condition, the amount of naloxone used, and severity and number of withdrawal symptoms after primary antidote therapy in were registered for three hours.

Data were analyzed with chi-square or *t*-test using SPSS software (Chicago, IL, USA).

RESULTS

Eighty patients completed the study (10 women and 80 men). Their mean age was 32.86±9.64 (32.92±9.80 in PRN (case) group and 32.80±9.61 in infusion (control) group which did not differ significantly (*P*=0.954).

Thirty-four patients (85%) were drug users in the PRN group. The figure was 37 (92%) for the infusion group. Number of previous attempts to quit addiction was 2.92±37.0 in the case group and 4.50±4.25 for the control group.

Severity of withdrawal syndrome was the same in both groups (*P*=0.089). Table 1 and Figure 1 show the severity of withdrawal syndrome in both groups during different times. Independent *t*-test showed significant difference between two groups in the severity of withdrawal symptoms which were lower in PRN group in comparison to control group (*P*<0.001).

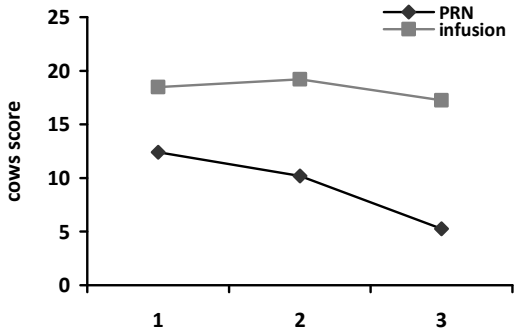

Figure 1. The severity of withdrawal symptoms (COWS scores) in both groups in different time.

- *PRN group is presented by the lower line*

Figure 1 shows that the reduction of withdrawal symptoms happened faster in PRN group than in the control group. With coupled *t*–test, the changes were statistically significant in the case group (*P*<0.001), but insignificant in the control group (*P*=0.076).

The severity of withdrawal symptoms was lower in the PRN group in all follow-up assessments, based on chi-square analysis (Table 2).

Table 1. The severity of withdrawal symptoms (COWS scores) in both groups.

Time of assessment	Group	Mean	SD	*P* value
30 min	PRN	12.40	3.49	Less than 0.001
	Infusion	18.47	6.92	
3 h	PRN	10.20	5.07	Less than 0.001
	Infusion	19.20	4.41	
12 h	PRN	5.25	1.67	Less than 0.001
	Infusion	17.25	5.25	

Table 2. The severity of withdrawal symptoms in the studied groups.

Time of assessment	Group	The severity of withdrawal syndrome				*P* value
		Severe	Moderate	Mild	None	
30 min	PRN	0	15	20	5	Less than 0.001
	Infusion	8	27	4	1	
3 h	PRN	0	10	22	8	Less than 0.001
	Infusion	6	29	5	0	
12 h	PRN	0	0	22	18	Less than 0.001
	Infusion	1	34	2	3	

Mean naloxone administration was 2.18± 0.96 mg in PRN group and 3.22±1.11 mg in infusion group. *t*-test result showed significant lower in PRN group (P =0.001).

DISCUSSION

Clarke et al. proposed a guideline for naloxone administration in severe opioid intoxication in his meta-analysis in 2005 as fallows; for patients with GCS of less than 13-14, respiratory rate<10 per min, and Pao2<92% in room air; naloxone was given by continuous IV infusion at 0.1 mg/min until the RR>10 and GCS>13-14; then if the abused opioid was short acting, the patient should remain under observe for two hours without any intervention and could be discharged from ED. Half of the dosage of primary treatment with naloxone should be given in 15 min and 2/3 of same amount should be continued in an hour for intoxications by long acting substances. For patients without IV access 0.8 mg S.Q or 0.4 mg IM was recommended [8].

Clirker et al. found that only five among 180 articles asked this question: does the way of treatment (infusion vs. PRN) might have any effect on appearance of withdrawal syndrome. None of them tried to answer the above-mentioned question [9].

The best outcome could be achieved by combination of IV and IM routes, while nasal ingestion has very long time of onset. Naloxone has an almost immediately onset when given IV [11]. They also concluded that except for the nasal way (because of very long absorption of naloxone through nasal mucosa), a combination of both other methods can be used in most of the times [11]. Intranasal naloxone is effective in treating opiate-induced respiratory depression, but is not as effective as IM or IV naloxone [12-15].

CONCLUSION

Naloxone administration in PRN manner is accompanied by less severe withdrawal syndrome and less staff work and energy. In brief, PRN method save the staff work and naloxone stock while also the patients suffer less severe withdrawal syndrome [16].

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The authors declare that there is no conflict of interests.

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