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Original Research Paper

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ROLE OF AN INERT SUBSTANCE IN THE MANAGEMENT OF NON-RESOLVING PAIN IN F11 WITHDRAWAL DURING EMERGENCIES.

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ABSTRACT

BACKGROUND: Pain is among the most troublesome of the Heroin withdrawal symptoms, where routine analgesics are difficult to work. Enhanced use of tramadol and buprenorphine to overcome the withdrawal pain resulted in tramadol abuse and buprenorphine dependence. To avoid the risk of iatrogenic drug dependence the placebo, an inert compound was used in addition to routine treatment to find its role in the management of heroin withdrawal. Methods:A total of 42 male patients in Heroin withdrawal were enrolled in the study. The severity of heroin withdrawal was assessed by using the Clinical Opioid Withdrawal Scale. The severity of pain was assessed by using a numerical rating scale for pain both before and after receiving a placebo

RESULTS: Out of 42 patients 24 who were in mild to moderately severe withdrawals received placebo and 18 patients received tramadol. The mean score of pain before receiving placebo was 4.916±1.8 and after receiving placebo the mean score of pain was 1.708±1.9. There was a significant reduction in pain after recieving placebo. The difference was statistically significant (p=0.0001).

CONCLUSION: These preliminary data suggest that a placebo may be used in the management of mild to moderately severe heroin withdrawal pain. Placebo being inert in action is understudied but can aid in cases of emergency where other options are limited or if used risk of abuse liability is high.

KEYWORDS : Placebo, Heroin, Withdrawal Pain, Emergency.

INTRODUCTION

BACKGROUND

Opioid use disorder in Kashmir valley, a resource-limited region, has risen to sweeping proportions. Heroin overdose cases have been a frequent occurrence in the medical emergency departments of the valley. As confirmed by the drug de-addiction centre of 'Institute of Mental Health and Neurosciences' Kashmir, opioid use disorder has become the most prevalent substance use disorder in Kashmir, heroin being the prevailing one and the majority among them were intravenous drug users (Bhat, B. A., et al. 2019). Heroin being a short-acting opioid (Gupta, A. K., & Jha, B. K. 1988) and withdrawal pain is the main reason why patients visit hospitals for treatment and rely more on injectable painkillers or over-the-counter drugs. Tramadol a centrally acting synthetic analgesic agent plays a role in the treatment of opiate withdrawal (Tamaskar, R., et al 2004) However, frequent use of such drugs to manage opioid withdrawal has become challenging in the context of misuse of prescribed medication, iatrogenic drug dependence and subsequent relapse of opioid use disorder (Chand, P., et al 2017). Placebo use for pain management has been a controversial practice although a promising one (Miller, F. G., et al 2009). It is believed that the "power of placebo" has remained under-researched and underutilised, especially in situations where challenges are posed by side-effects from an active pharmacological agent or its limited availability (Lofwall, M. R., et al 2007). The hypothesis of the present study was to institute placebo in place of opioid agonist analgesics (tramadol) and opioid partial agonists (buprenorphine) when pain persisted even after receiving routine treatment. An unprecedented surge in the number of cases seeking treatment for heroin withdrawals in the Kashmir causing unforeseen constraints on the already stretched resources. High caseload demanded rationalised utilisation of the available medication. An innovative triage system based on existing knowledge and experience, allowed them to utilise the resources judiciously and tide throughout an unprecedented crisis.

AIM

The present study aimed to analyse the efficacy of placebo in non-resolving pain in F11 withdrawal during emergencies.

METHODS

Study Design

It was a cross-sectional observational study.

Setting and Participants

The study was conducted in the Drug De-addiction Centre of the Institute of Mental Health and Neurosciences, Kashmir an associated hospital of Government Medical College, Srinagar from August to September 2019, a week following unprecedented lockdown in the Valley. The population included male patients admitted to the in-patient unit of De-addiction Centre with Heroin use disorder in uncomplicated heroin withdrawal. A total of 42 male patients who complaint of pain after reciving routine treatment were enrolled in the study. The patients with substance use disorder other than heroin with underlying medical conditions or organic brain syndromes were excluded from the study.

Procedure

The patients were admitted to the opioid withdrawal state. Detailed assessment in terms of history, examination, relevant laboratory investigations and urinary drug screen were included in the study. Furthermore, patients have been screened for DSM-5 (Hasin, D. S., et al 2013) eligibility criteria for opioid use disorder and drug screen solely positive for opioids to establish a diagnosis of opioid use disorder. The medical history was perused to rule out underlying medical causes of pain. Due to the high prevalence of nicotine smoking in the population, those who had nicotine dependence could not be excluded from the study. Clinical Opioid Withdrawal Scale was administered and cases were classified into the mild, moderate, moderately severe and severe withdrawal states (Wesson, D. R., & Ling, W. 2003). The usual protocol to manage the opioid withdrawal symptoms was by giving non-opioid analgesics, muscle relaxants, benzodiazepines and alpha agonists. Patients who had recieved the recommended daily dosage of treatment and complain of pain, after 6 hours of mean half-life from the last dose of prescribed medication were recruited in the study. To minimise over-medication when psychotherapy and counselling were not conducive the patients were given a placebo IV (normal saline 2ml) for unresolved pain. The aim of giving a placebo instead of other opioid analgesics like tramadol and opioid partial agonists (buprenorphine) was to avoid the use of drugs at high risk of abuse liability and a study was conducted to see whether

placebo can replace tramadol to manage opioid withdrawals. The written informed consent was taken from the patients, the inertness of the substance was explained and quality reassurance with strong suggestions was given regarding the beneficial effects of the drug. The numerical rating scale (Bijur, P. E et al 2003) for the pain was applied before and after giving (at least at a gap of 1 hour) placebo.

Measurement

The study instruments included Clinical Opioid Withdrawal Scale (COWS) (Wesson, D. R., & Ling, W. 2003) and the Numeric Rating Scale for pain (Bijur, P. E et al 2003). The COWS an 11-item easily applicable objective scale, utilized to measure the intensity of withdrawal symptoms in both in and out-patient settings. As per the total score, the opioid withdrawal state is classified into mild (5-12), moderate (13-24), moderately severe (25-36) and severe (>36). The pain numeric rating scale is a simple and most commonly used, single-item validated, uni-dimensional, subjective scale used to measure pain intensity. It is a continuous scale with scores from 0 (no pain), 1-3 (mild), 4-6 (moderate), 7-9 (severe) to 10 (worst pain). DSM-5 Criteria was used to diagnose heroin withdrawal (Hasin, D. S., et al 2013).

STATISTICAL METHODS

The study was conducted after getting ethical clearance from the institutional ethical committee and data was tabulated in Microsoft Excel and statistically analysed using SPSS 20.0 version, presented as percentages. An unpaired sample t-test was used to compare the groups. The mean, standard deviation, confidence interval at 95% and P-values were calculated. A P-value of less than 0.05 was taken as statistically significant.

RESULTS

Descriptive Data

Socio-demographic characteristics and Clinical profile of placebo

The majority of the participants belonged to the age group of 20-35 years, were unmarried and literates. More than half of the patients were from the rural background. Over half of the patients were employed, 23.8% were unemployed, and 21.4% were students. The Heroin dose of more than 2gms was in 57.1% and majority 61.79% of our patients were abusing heroin for more than 2yrs. Out of 42 patients 28.57% were in mild withdrawal, 38.09% were in moderate withdrawal and 33.3% were in moderately severe type as per COWS score (Table 1). Nicotine dependence was present in all patients and underlying psychiatric diagnosis (depression and personality issues) was found in 6% of patients.

Socio-demographic characteristics and Clinical profile

Variables		N=42(%)
Age group	<20	13 (30.95%)
	20-35	25 (59.52%)
	>35	04 (9.52%)
Background	Rural	24 (57.14%)
	Urban	18 (42.85%)
Marital status	Married	14 (33.33%)
	Unmarried	28 (66.66%)
Education	Illiterates	17(40.47%)
	Literates	25 (59.52%)
Employment	Employed	23 (54.76%)
	Unemployed	10(23.8%)
	Student	09 (21.42%)
Heroin dose	<1g	08 (19.04%)
	1-2g	11 (26.19%)
	>2g	24 (57.14%)
Duration	1-2yrs	16 (38.09%)
	>2yrs	26 (61.9%)
Type of withdrawal as per COWS score	Mild (5-12)	12 (28.57%)
	Moderate (13-24)	16 (38.09%)
	Moderately severe (25-36)	14 (33.33%)
	Severe (>36)	0

Table 1 Pain assessment

Out of 42 patients 07 had reported mild intensity pain while 23 had reported a moderate intensity and 12 had the pain of severe intensity on the numerical rating scale. One hour after receiving placebo there were 16 patients with no pain, 18 with mild pain, and 08 patients had moderate pain. None of the patients reported severe pain after receiving (Table 2).

Severity of pain before and after receiving Placebo and Tramadol

Severity of Pain	Score	Placebo N=42	
		Before	After
No pain	0	0	16
Mild	1-3	07	18
Moderate	4-6	23	08
Severe	7-9	12	0
Worst pain	10	0	0

Table 2 Outcome Data

Unpaired sample t-test: the below-given table shows the significant reduction in pain as reported by patients after receiving placebo. The results were statistically significant (table 3). The duration of effect was not measured but after one intramuscular placebo injection, the need for further injectable was delayed until the next day.

Significant reduction in pain after receiving Placebo and tramadol

	Mean	N	Std. Deviation	Std. Error Mean	t-value	P-value
Before Receiving Placebo	4.916	24	1.81579	.3706	5.8708	0.0001
After Receiving Placebo	1.7083	24	1.96666	.4014		

Table 3

DISCUSSION

The majority of the participants belonged to the age group of 20-35 years, were unmarried and literates. The majority of the participants had been using more than 2 grams of heroin by an intravenous route for more than 2 years. Nicotine dependence was present in all patients and underlying psychiatric diagnosis (depression and personality issues) was found only in 6% of patients. Results from this study had shown favourable effects of placebo in heroin withdrawal pain and there was a significant reduction in pain severity after receiving placebo.

Opiate addiction is a major social and medical problem. Recent studies done in the valley indicate that currently there is an upsurge in heroin use (Bhat, B. A., Dar, S. A., & Hussain, A. 2019). One of the important reasons for hospital visits among opiate abusers is the management of withdrawal symptoms. For treatment of withdrawals over the years many drugs have been used including methadone, buprenorphine and opioid analgesics (Comer, S., et al 2015). Tramadol is a centrally acting analgesic agent with opiate activity, though it does not cause classic opioid physical dependence opiate withdrawal-like symptoms after discontinuation of tramadol is a matter of concern (Tamaskar, R., et al 2004). Like buprenorphine, it also complicates the post-detoxification transition to naltrexone (Shah, K., Stout, B., & Caskey, H. 2020). So, in the current study, we tried a placebo as an alternative to opioid analgesics. And it was found placebo helped in reliving the opioid withdrawal pain so can be of help in the management of pain. The significant reduction in pain due to a placebo can be because of many possible reasons. Placebo analgesia represents a situation where the administration of a substance reported to be non-analgesic produces an analgesic response and the effect which follows the administration of an inert treatment, be it pharmacological or otherwise is known as the "placebo effect" (Bar-Or, Det al

2017). Studies have shown that placebo administration can produce the desired effects even when the subject is informed about the inert properties of the placebo. Hence, safeguarding the therapeutic alliance and the ethical practice of practioner (Colloca, L. et al 2013). The clinical improvement in withdrawal symptoms like pain by placebo induced analgesia may be due to acupuncture induced release of endogenous opioids (Colloca, L. et al 2008). Like every drug, the placebo is also preceded by a certain level of expectations, wish to get relief from the diseases and apprehension of side effects, which implies placebo analgesia is a complex cognitive process of the brainstem opioid system and higher-order cortical neurons (rostral anterior cingulate cortex and ventral prefrontal cortex), a common pathway or cognitive network involved in opioid and placebo analgesia (Ter Riet, et al 1998). Earlier studies have shown a behavioural correlation between opioid analgesia and placebo analgesia (Colloca, L et al 2013). The opioid receptor binding capacity during rest and pain is highly specific to an individual, leading to the hypothesis that high placebo responders have a more efficient opioid system (Petrovic, P. 2005, and WB Saunders.Petrovic, et al 2002). The pain may have had spontaneous temporal variation and a placebo may have been given just before their discomfort starts decreasing, and the patient may believe that the placebo was effective, although that decrease would have occurred anyway (Bar-Or, Det al 2017).

CONCLUSIONS

While managing opioid withdrawal we face a lot of challenges. Use of tramadol for opioid withdrawal prolongs hospital admission because opioids need to get washed out from the body only then patients can be put on opioid antagonist therapy naltrexone after 7days. Similarly, Buprenorphine which on one hand is short in supply and cases of opioid abuse is rising and on the other hand, imposes a risk for being misused by patients. To minimise over-medication when psychotherapy and counselling were not conducive the placebo can be of use in opioid management to help in recovery from pain and prevent indulging in iatrogenic drug dependence, which also shortens the period of hospital admission.

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