Original Article

COMPARISON OF THE EFFICACY AND SAFETY OF CHLORPROMAZINE WITH VERAPAMIL FOR THE TREATMENT OF ACUTE OPIOID ABSTINENCE SYNDROME

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ABSTRACT

Objective: To compare the efficacy and safety of chlorpromazine with Verapamil in patients with Acute opioid Abstinence Syndrome.

Methodology: Single blind comparative clinical trial was conducted at Department of Pharmacology, BMSI, JPMC, Karachi, over the period of one year. Forty opiate-dependent subjects were chosen at random who were in search of opioid abstinence treatment. All patients were grouped into two groups, group-I received chlorpromazine 150 mg/day and group-II received Verapamil 120mg/day in divided doses. Every patient completed the management plan while admitted in the hospital for 10 days.

Results: The chlorpromazine showed decreased efficacy and safety, whereas verapamil showed clinically pertinent decline in the subjective symptoms of acute opioid abstinence syndrome.

Conclusion: The study showed Verapamil is superior to chlorpromazine in the treatment of opioid abstinence syndrome indicated by better reduction of withdrawal symptom scores, excessive opioid urinary excretion and lees side effects. The superiority of verapamil over chlorpromazine in controlling opioid abstinence syndrome may indicate that calcium is involved in the initiation and development of opioid abstinence syndrome.

KEY WORDS: Opioid abstinence syndrome, Chlorpromazine, Verapamil.

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INTRODUCTION

Drug addiction is a chronic state characterized by obsessive behavioral anomaly.[1,2] Opioids are recognized to manipulate the function of central dopaminergic systems and an excellent accord be present on the conception that opiates stimulates the striatum circuits which get input from dopamine neurons and increases firing action of dopaminergic nerve terminals.[3,4] As a result the dopamine receptors antagonist chlorpromazine at present is increasingly used for controlling opioid abstinence syndrome at various narcotic management centers which blocks the dopamine receptors in mesolimbic and mesocortical

pathways of central nervous system.[5,6] Subsequently it must restrain abstinence from opioids and may possibly be helpful for treatment of opioid abstinence syndrome.[7]

On the other hand calcium plays an essential part in action of opioids.[8-11] There is evidently an opposite association among calcium and opiate action. Opiates reduce neurotransmitter discharge by means of slowing down the depolarization-induced entry of calcium in to neurons.[4,12] Hence calcium influx may perhaps be one of the mechanisms of the activity of opioids, whereas the continual and persistent administration of morphine causes an amplified calcium entry, coupled with alterations in calcium uptake and binding.[11-13] Such augmented content of calcium at the time of precipitated opioid removal, resulting in amplified neurotransmitter discharge and increased autonomic disparity during the opioid abstinence syndrome.[14-16] Consequently the study was conducted to match up the efficacy and safety of verapamil with contemporary remedy chlorpromazine as management of acute opioid abstinence syndrome in patients.

METHODOLOGY

This study was conducted in the department of Pharmacology and Therapeutics, Basic Medical Sciences Institute and Jinnah Postgraduate Medical Centre, Karachi. Each patient gave written approval to study team that required mandatory immediate withdrawal from opioids following hospital admission.

Study population: The forty chosen addicts diagnosed according to DSM IV diagnostic criteria[17] and looking for inpatient opioid abstinence management were enrolled in study. All the patients were admitted to the inpatient psychiatry wards for ten days. All those patients were excluded from study that had a prior history of major psychiatric complaint, existing addiction on alcohol or dependence on other drugs of abuse like hypnotics, heart and hepatic diseases. All patients included in the study were male and wished-for holding up the use of opioids

Study design: Patients were randomly separated into two groups; group I (n=20) received Chlorpromazine; group II (n=20) received Verapamil. They were observed and rated for the existence or nonexistence of opioid abstinence symptoms expressed prior 24 hours by an observer. From day two of hospitalization, until discharge, an observer finished the opiate withdrawal questionnaire (OWQ), which contains 20 distinctive withdrawal symptoms, like, muscle cramps, flushing, joint pain, yawing, impatience, lacrimation, watery nose, chills, unwell stomach, sneezing, abdominal cramps, tetchiness, back pain, perspiration, dejected, insomnia, insecure, hot or cold flashes, irritable to noise, damp and clammy skin. Participants pointed out the extent to which they had practiced every symptom and then observer graded the intensity of the symptoms between 0- no symptom, 1- slight, 2- moderate, 3- quite a bit & 4- tremendous symptoms. The combined score for subject reported symptoms was obtained by totaling the scores of the individual symptoms simultaneously.[6,8,9,18,19]

Urine samples were collected on start, mid and closing of study, and tested for opioid by means of one- step dip and read chromatographic front line opiate strips, obtained from Boehringer Mannheim Pakistan.[6,8,9,18,19] The quantity of opioid in the urine was graded between 0-3 point ranges (Table-I). All patients had a bed rest on 2nd and 3rd day of hospitalization. Afterward from day 3 to day 9 the patients of group-I and group-II received 50mg of chlorpromazine and 40mg of Verapamil orally three times a day respectively. All patients were discharged from hospital on day 10 of study, when they were experiencing clinically negligible or no withdrawal symptoms.

Statistical Analysis: Complete data are expressed as means ± SEM. Differences among means of study days were tested for significance using the paired Student's t-test. Data analysis was performed using the Statistical Program for Social Sciences (SPSS) 10.0 for windows. For all analyses, P values less than 0.05 was well thought-out significant.

Table-I: Comparision of urine toxicology in Group-I and Group-II Opioid Addicts

Inpatient Day	*Mean ± SEM urine toxicology*		
	Group-I Chlorpromazine	*Group-II Verapamil*	*P-Value*
1	3.1 ± 0.01	2.8±0.09	
5	1.8 ± 0.10	1.6±0.09	< 0.0001
10	0.6 ± 0.11	0.1 ± 0.09	< 0.0001

Amount of opioid in urine graded according to color index provided with test strips.
0 = Nil , +1 = Traces.
+2 = >200ng/ml. +3 = >1000ng/ml.

RESULTS

Forty eight patients as per procedure were enrolled in this study, in order to get the target sample of twenty patients for each of two groups. Eight patients of chlorpromazine group were dropped from study with the entire breakdown of 28.5%. The fundamental characteristics of all patients in both groups were similar (Table-II). All had subjective symptoms of opioid withdrawal and urine samples showing positive outcome when tested with front line opiates dipsticks. Patients on chlorpromazine therapy experienced adverse effects and rate of recurrence of observed side effects were (45%). The experiential adverse effects were dryness of mouth (20%); blurred vision (5%), headache (10%) and postural hypotension (10%). At the same time symptomatic management like Aspirin 300mg three times a day for muscle ache, Diazepam 5mg for nocturnal sedation, Hyoscine 10mg three times a day for abdominal discomfort and Phenargon 10mg three times a day for nausea and vomiting were given to group-I & group-II patients on 3rd,4th,5th and 6th admission day.

In group-I an average score of withdrawal symptoms 15±0.205 was obtained on 2nd day of admission and the score reaches to a highest point of 32.55±0.738 during the baseline phase that is on 3rd day of admission. Following chlorpromazine treatment the mean scores of withdrawal symptoms reduced very slowly and gradually. Accordingly the effects of chlorpromazine to drop off the symptoms of acute opioid abstinence syndrome were non-significant on day 4 and day 5, significant on day 6, while highly significant on day 7 to last day of admission. (Fig-1)

Even as in group-II patients an average score of symptoms 17.5.0±0.559 was obtained on 2nd day of admission that hit the uppermost point of 31.5±0.638 during the baseline phase that is on 3rd day of hospitalization. Subsequently Verapamil therapy showed superior cutback and highly significant decline in withdrawal symptoms score from very fist post- treatment day (Fig-1) and it did not show any drug related side effect during study duration.

Withdrawal symptoms were decreased in both groups, but the distinction among the groups was highly significant in favor of verapamil group from day 4 to day 10. (Table-III) Even as the significant difference in urinary excretion of opioid was observed in group-II patients when compared with group-I patients. (Table-I)

DICUSSION

Clinically we need a standardized and secure course of therapy for opioid addicts, as addiction is highly prevalent in Pakistan. Conventionally opioid agonistic drugs like Metha-

Table-II:Baseline characteristics of Group-I and II patients

Variable	*Group-I Chlorpromazine(n=20)*	*Group-I I Verapamil(n=20)*	*P-value*
Age (Years)	29.4 (22-38)	29.1 (21-40)	0.268
Sex	Male	Male	-
Opioid consumption history (Years)	5.4 (2-9)	5.7 (1-10)	0.687
Previous detoxification attempts	2.28 (1-3)	2.13(1-3)	0.475

Values are expressed as mean (Range)
No statistical significant difference between group-I &II patients.

Table-III: Comparision of treatment outcome of Group-I and Group-II patients

Inpatient Day	*Symptoms Severity Score*		
	Chlorpromazine	*Verapamil*	*P-Value*
3	32.55± 0.73	31.50± 0.63	P=0.343
4	32.50 ± 0.75	17.45±0.65	< 0.0001
5	32.45 ± 0.76	12.50±0.51	< 0.0001
6	32.35 ± 0.75	08.05±0.36	< 0.0001
7	28.90±0.63	03.10±0.19	< 0.0001
8	12.60± 0.47	01.50±0.11	< 0.0001
9	07.05± 0.42	00.75±0.09	< 0.0001
10	05.40± 0.29	00.25±0.09	< 0.0001
n	20	20	

n = Number of patients
Values are expressed as mean + SEM
Highly significant statistical difference between group-I &II.

done is a most frequent regiman for abstinence syndrome all over the world,[19] but it is banned in Pakistan and still concerned with abuse pattern. On the whole the major object of this study was to institute a safer non-opioid treatment option which is secure and not involved in the misuse potentials. To our knowledge this is the first and initial study, to compare the efficacy and safety of chlorpromazine with calcium channel blocker verapamil in the management of acute opioid abstinence syndrome. Though Mazurier et al[7] has discussed the issue and compared chlorpromazine with morphine for the management of opioid abstinence syndrome in infants. However this study merely emphasized the comparison of duration of treatment for abstinence syndrome in neonates using chlorpromazine against morphine.

The data of chlorpromazine therapy for its effectiveness and safety is inadequate. Our study established no therapeutic advantage of chlorpromazine in acute opioid abstinence syndrome. The outcome of our study is strongly well-matched with the research of Caille and his co-workers,[20] who tested the dopamine hypothesis in acute opioid abstinence syndrome in morphine dependent rats. While Daglish et al[3] investigated the brain dopamine response in human opioid addicts. Both these studies proved that dopamine dose not play any vital role in abstinence syndrome in opioid dependent animals as well as humans. Subsequently these conclusions recommend that dopamine neurotransmission is not decisive for the initiation and precipitation of opioid withdrawal syndrome.

While the novel verapamil treatment, , for abstinence syndrome proved to be apprecia-

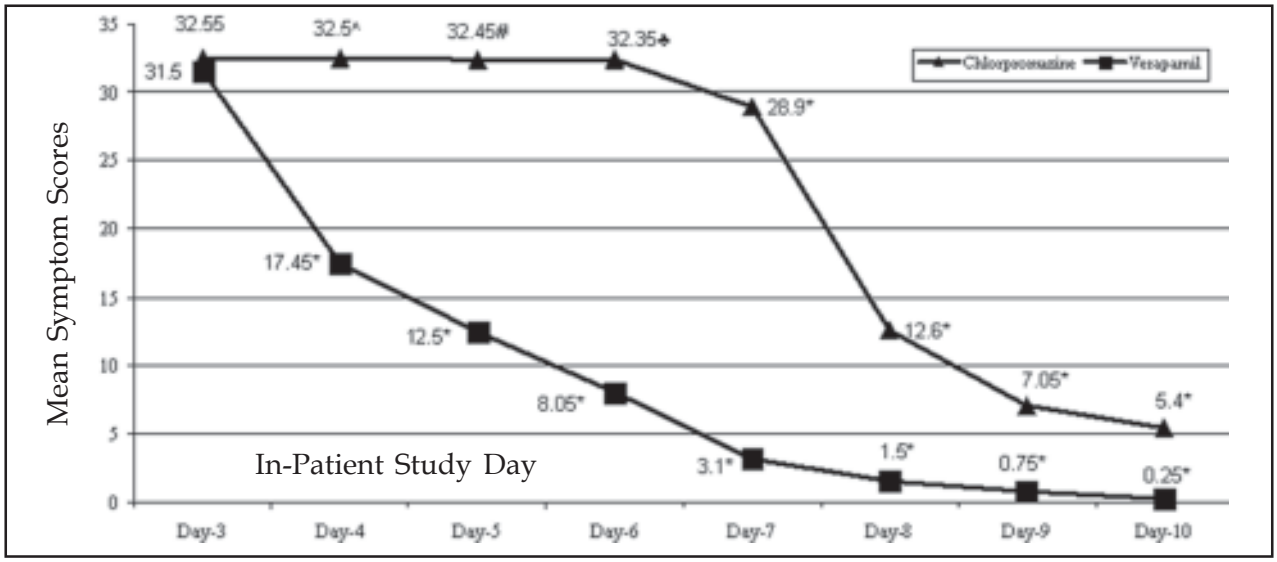

Figure-1: Comparison of chlorpromazine vs. verapamil treatment on subject reported symptoms of acute opioid abstinence syndrome.

n = 40, Values are expressed as mean. All values are compared with study day-3 of same group for significance.
^ P= 0.330, # P= 0.163, ♣ P= 0.042, * P< 0.001

bly superior than chlorpromazine therapy, in terms of declined withdrawal symptoms, excessive opioid urinary excretion as well as side effects were observed during ten days study. Generally the verapamil treatment is safe, secure, well accepted and free of adverse effects. This study also indicates, highly significant, retention in treatment was in verapamil group, almost certainly due to entire decreased load of withdrawal symptoms particularly during preliminary post-treatment days as compared to chlorpromazine group.

CONCLUSIONS

This comparative clinical trail suggests that verapamil is significantly beneficial non opioid therapeutic option for the management of opioid withdrawal syndrome. The study showed the verapamil is superior to chlorpromazine in the treatment of opioid abstinence syndrome indicated by better reduction of withdrawal symptom scores, excessive opioid urinary excretion and lees side effects. The superiority of verapamil over chlorpromazine in controlling opioid abstinence syndrome may indicate that calcium is involved in the initiation and development of opioid abstinence syndrome.

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