Original Article

Comparison of efficacy of thioridazine with clonidine acting through different mechanisms in Acute Opioid Abstinence Syndrome

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Objective: To compare the efficacy, safety and tolerability of thioridazine with clonidine in patients with Acute opioid Abstinence Syndrome.

Methodology: This single blind comparative clinical trial was carried out at Department of Pharmacology, Basic Medical Sciences Institute (BMSI), Jinnah Postgraduate Medical Center (JPMC), Karachi. Fifty two addicts were selected randomly and were grouped into, group-A to receive thioridazine 100 mg/day and group-B to receive clonidine 150mcg/day. All participants completed the treatment program and stayed in hospital for ten days.

Results: The efficacy safety and tolerability of thioridazine was scant, while clonidine showed statistically significant turn down in the objective signs of acute opioid abstinence syndrome.

Conclusion: Clonidine had more powerful effects than thioridazine. While treating the withdrawal signs of opioid abstinence syndrome may possibly pointed out that over activation of norepinephrine is a major factor contributes to the commencement of opioid abstinence syndrome. (Rawal Med J 2013;38: 121-124).

Key words: Opioid abstinence syndrome, thioridazine, clonidine.

INTRODUCTION

Opioid abstinence syndrome is a serious clinical problem especially in Pakistan and worldwide. Opioid consumption, its abstinence associated with relapses cannot be efficiently treated without an appropriate treatment program. Buprenorphine is a long acting opioid drug very commonly used for the treatment of opioid abstinence syndrome all over the world due to its extremely sluggish dissociation from opioid receptor but it possess abuse potential and withdrawal symptoms.[1] Opioid addiction and abstinence is characterized by behavioral, psychological and psychiatric incongruity.[2,3] An up-to-date acquaintance of neurotransmitter system arbitrating the withdrawal consequences has prime importance for exploring its treatment.[4] Existing therapeutic options to treat and manage opioid abstinence syndrome are scant; so to investigate the efficacy safety and tolerability of different therapeutic regimens is extremely important.[5] The aim of this study was to compare and evaluate the efficiency, risk and tolerability of thioridazine with clonidine as a non-opioid treatment option for acute opioid abstinence syndrome in hospitalized patients.

METHODOLOGY

This study was carried out in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi, after the approval of ethical committee and each study participant submitted a written consent. A total of 52 opioid addicts were included in study after meeting the diagnosis for the abstinence as per DSM IV diagnostic criteria.[6] All were admitted to psychiatric ward for 10 days. All those individuals were excluded from study who had a preceding history or any record of previous psychiatric illness, existing dependence and addiction on different drugs like alcohols, sedative and hypnotics, cardiovascular and hepatic pathologies. All study participants were male, highly motivated, planned for discontinuing opioids use and staring for the management of opioid abstinence syndrome.

At random all the study participants were divided into two groups; group A (n=20) received 100 mg Thioridazine; and group B (n=20) received 150 mcg Clonidine two times a day orally from 3rd to 9th day of study. They were observed and rated for the presence or absence of abstinence signs, by principal investigator. From second day up to the

end of study, that observer maintained and completed the opioid withdrawal questionnaire (OWQ), comprising six opioid withdrawal signs like, watery eyes, runny nose, sweating, yawning, agitation, and piloerection. Intensity of every sign was graded as: 0- no sign, 1- minor, 2- fair, 3- moderate & 4- remarkable. The scores of individual signs were added to compile the final score for observer rated signs of acute opioid abstinence syndrome.[7-11]

Urine samples of all study participants were collected on day-1, day-5 and day-10 of study and screened for the presence of opioid by front line opiate dip-sticks, chromatographic test strips acquired from Boehringer Mannheim Pakistan.[7-11] It was a quantitative test and the amount of opioids excreted in the urine was ranked on 4- point scale of urine toxicology according to color index provided with dip-sticks (Table 1).

Data were 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 SPSS 10.0 for windows. P-values less than 0.05 were considered significant.

RESULTS

Fifty two opioid addicts were registered in this study with 20 in each group. Twelve participants of thioridazine group left the study against medical advice, with 37.5% dropout rate, while all patients in clonidine group completed the study. Study participants of both groups had objective signs of opioid abstinence with positive urine toxicology. Group A participants experienced drug related side effects while Group B patients were free from any adverse effect (Table 2).

Table 1. Proportional urine toxicology in participants.

Study Days		Mean ± SEM	
	Group A	Group-B	P-Value
	Thioridazine	Clonidine	
1	3.1 ± 0.01	2.9±0.06	P=0.521
5	2.6 ± 0.10	1.5±0.11	<0.0001
10	0.6 ± 0.11	0.1 ±0.06	< 0.0001

Toxicology scale: 0 = Nil, +1 = Traces, +2 = >200ng/ml, +3 = >1000ng/ml

On the other hand Diazepam 5mg for night time hypnosis, Aspirin 900mg, Hyoscine 30mg and Promethazine 30mg, in three divided doses per day were given to Group A participants for muscular pain, abdominal pain, and as antiemetic therapy respectively, while no such treatment was needed in Group B participants.

Table 2. Comparison of therapeutic outcome.

Study Days	Signs Severity Score		
	Mean ± SEM		
	Group A	Group-B	P-Value
	Thioridazine	Clonidine	
	n 20	n 20	
3	10.50± 0.29	09.85± 0.63	P=0.421
4	10.20 ± 0.31	04.85±0.65	< 0.0001
5	09.25 ± 0.26	01.95±0.51	< 0.0001
6	06.00 ± 0.27	00.60±0.36	< 0.0001
7	05.00±0.28	00.00±0.00	< 0.0001
8	03.00± 0.14	00.00±0.00	< 0.0001
9	01.95± 0.21	00.00±0.00	< 0.0001
10	01.30± 0.14	00.00±0.00	< 0.0001

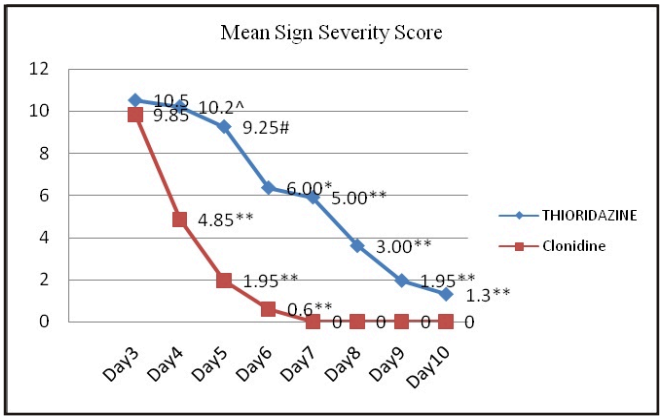
Group A participants obtained 4.85±0.28 as a mean score of withdrawal signs on day-2 while the score touches the height of 10.50±0.29 on day-3 of hospitalization. Statistically non significant decline was observed in withdrawal signs on 4th and 5th day, while the significant decrease was observed on 6th to last day of study.

Table 3. Comparison of Adverse effects.

Adverse Effects	Thioridazine (n=20) Number (%)	Clonidine (n=20) Number (%)
Blurred Vision	1	05%
Constipation	3	15%
Dry Mouth	2	10%

On the other hand, Group B participants acquired 5.55 $\pm$ 0.3 as mean withdrawal signs score on day-2 which reaches to upmost place of 9.85 $\pm$ 0.3 on day-3 of study (Table 3).

Fig 1. Comparison of Thioridazine vs Clonidine treatment groups.



All Values are articulated as mean and compared with hospitalization day-3 within the group.
^ P= 0.410, # P= 0.142, * P= 0.021, ** P< 0.001

Consequently withdrawal sign scores were significantly turn down from the very next day after clonidine therapy (Fig 1). Withdrawal signs were reduced in both A and B groups, but the difference between the groups were extremely significant in support to Group B (Table 3). At the same time the highly significant distinction in urine toxicology was observed in group B when compared with Group A (Table-I).

DISCUSSION

Opioids are known to influence the function of different brain regions through activation of serpentine type of G protein-linked opioid receptors, acting through G protein-activated inwardly rectifying K+ (GIRK) channels.[12,13] These channels play an imperative inhibitory regulatory function and on abstinence cause the excitation of ventral tegmental area and nucleus accumbance of mesolimbic system where they elevates extracellular levels of dopamine and dopaminergic impulses.[14] On the other hand noradrenergic neurons in locus coeruleus of central nervous system also increases noradrenergic neuronal firing activity and all these factors finally leads to abstinence syndrome.[15,16] So the antipsychotic dopamine (D2) receptor blockers like thioridazine might be potential non-opioid therapeutic agents for the management of opioid abstinence syndrome, acting by blocking dopamine receptors. On the other hand several studies of the locus coeruleus, the prime group of noradrenergic neurons have proved the involvement of over activation of noradrenaline during opioid abstinence syndrome.[10,11] So the clonidine, α-2 receptor agonist, acting by G protein-activated inwardly rectifying K+ (GIRK) channels generate negative feedback signals to sympathetic neurons, finally leading to decrease norepinephrine release and might be helpful in controlling opioid abstinence syndrome.[17,18,19]

This is the first and initial study to our knowledge that scrutinized and compared the efficacy and safety of non opioid antipsychotic thioridazine with a-2 agonist clonidine in patients with acute opioid abstinence syndrome. Current study recognized no remedial benefit of thioridazine in abstinence syndrome. The results have clearly shown that the a-2 receptor agonist clonidine is significantly more effective than D-2 receptor blocker thioridazine in treatment of opioid abstinence syndrome. This efficiency is in terms of early normalization of withdrawal signs, drug related adverse effects, associated symptomatic treatment and opioid clearance at the end of treatment.

This comparative clinical study recommends that clonidine is tremendously useful tool for the management of opioid abstinence syndrome, which is due to sympathetic hyperactivity and synchronized by a-2 receptors,[10,11] coupled with inwardly rectifying potassium channels (GIRK), the significant targets for the coordination of sympathetic neurotransmission.

The number of studies has shown that the opioids activate the function of GIRK channels and on abstinence they generate excitatory synaptic potentials which finally lead to opoid abstinence syndrome. So GIRK channel modulators like clonidine inhibits the noradrenergic neuronal firing and hence are very useful for the treatment of acute opioid abstinence syndrome.

CONCLUSION

The conclusion of this study established a perception that dopaminergic system does not have any elementary role in abstinence syndrome, while GIRK channel modulators like clonidine are very valuable for management of opioid abstinence

syndrome. So extensive clinical tryout should be given to other GIRK channel modulates, which might be useful non opioid treatment option for opioid abstinence syndrome.

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Concept and Design: Munawar Alam Ansari, Aijaz Amed Qureshi, Anila Kazi
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