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IMPORTANCE OF AGONISTIC CLONIDIN A-2 IN REDUCTION OF HOT FLASHES IN ACUTE OPIOID ABSTINENCE SYNDROME PATIENTS

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Abstract:

Background: *The need for non-hormonal hot flush interventions is increasing due to the number of patients diagnosed with hormone-sensitive tumors, and hormone replacement therapy is not as beneficial as originally thought. Therefore, this study was conducted to investigate the efficacy of clonidine in hot flushes, the most commonly reported subjective symptom of acute opioid abstinence syndrome.*

Place and Duration: *In the pharmacology and psychiatry department of Nishtar Hospital, Multan for 2-months duration from May 1st 2020 to 30th of June 2020.*

Methods: *The study consisted of a two-month, single-blind, randomized clinical trial of clonidine in patients with opioid abstinence syndrome with very frequent flushing. 20 patients were administered clonidine 300 mcg / day in divided doses. All patients who completed the treatment program stayed in the hospital for 2 months.*

Results and Conclusions: *The mean absolute scores for the change in hot flushes per day at endpoint, from baseline, showed a very rapid and highly significant decrease in the clonidine treatment program. Researchers discovered the benefits of clonidine in hot flashes.*

Key words: *hot flushes, noradrenaline and clonidine.*

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INTRODUCTION:

The demand for non-hormonal interventions for hot flashes is increasing due to the number of patients diagnosed with hormone-sensitive cancers, and hormone replacement therapy is not as beneficial as originally thought (Barton et al., 2017, Sicat et al., 2017)[1-2]. Hot flushes are the most frequently reported symptom and occur in the vast majority of patients with acute opioid abstinence syndrome. It is similar to the heat dissipation reaction and includes sweating, dilation of blood vessels in the skin, increased heart rate, and blood pressure (Freedman et al., 2017). The hot flash appears to have behavioral and biochemical effects that include interaction with catecholamine neurotransmitter systems and autonomic imbalance (Barton et al., 2016)[3-4]. Body temperature in homeotherms is regulated by the hypothalamus between the upper thresholds of sweating and the lower thresholds of chills. There is a thermo-neutral or zero zone between these thresholds, and body temperature is regulated within these intermediate thresholds (Zacny-1982)[5]. Norepinephrine plays an important role in thermoregulation, mediated in part by alpha-2 adrenergic receptors in the hypothalamus (Charney et al., 1982). Much evidence for noradrenergic involvement comes from studies of the bluish site, which is the largest cluster of noradrenergic neurons in the brain and is the main source of noradrenergic innervation (Shanafelt et al., 2015, Frishman 2016). Recent studies have shown that elevated levels of norepinephrine in the brain in patients with acute opioid abstinence syndrome (Ansari et al., 2001, Ansari et al., 2003) narrow the thermo-neutral zone, where there are no thermoregulatory changes and most hot flashes are preceded by small but significant increases in body temperature (Kronenberg 1994, Stearns et al., 2002)[6-7]. Thus, hot flashes can be triggered when body temperature exceeds the sweating threshold (Mekjavic et al., 2011, Brengelmann et al., 2013). Thus, norepinephrine and alpha-2 adrenergic receptors in the hypothalamus may be responsible for hot flush events[8-9]. Therefore, we planned a study to investigate the effectiveness of oral clonidine in the control of hot flushes in hospitalized patients with acute opioid abstinence syndrome.

MATERIALS AND METHODS:

This study was held in the pharmacology and psychiatry department of Nishtar Hospital, Multan for 2-months duration from May 1st 2020 to 30th of June 2020. Twenty selected opioid addicts who presented for inpatient opioid abstinence treatment were enrolled and admitted to inpatient psychiatric wards for 2-months. All patients who had a history of severe mental illness, a current addiction to alcohol or other drugs such as sedatives or hypnotics, and heart and liver disease were excluded. All patients were male, expressed an interest in opioid discontinuation, and gave written consent to a study requiring abrupt opioid withdrawal upon admission to hospital. They were given placebo capsules orally on the first and second days of admission to establish a baseline frequency of hot flushes, a very common symptom of acute opioid abstinence syndrome. The subjects reported the number and intensity of hot flashes per day for which symptoms occurred. The mean number of hot flushes reported per day was obtained by summing the individual patient scores. All patients were also assessed on the basis of physiological parameters, which included systolic pressure, diastolic pressure and body temperature. Urine samples were collected on days 1, 5, and 10, 2 months and tested for the presence of opioids by means of a one-step dip and reading of chromatographic test strips. The amount of opioid in urine was assessed on a 4-point scale (Table 1). All patients were in bed on the 2nd and 3rd day of admission. Then, on the 3rd to 9th day of admission, patients received 150 mcg of clonidine orally twice daily. All patients completed the treatment program and were discharged on admission day 10. All data are expressed as means. Differences in means on different days of hospitalization were checked for significance using the Student's t-pair test. For all analyzes, P values less than 0.05 were considered significant.

RESULTS:

Twenty opioid addicts who entered the study ended treatment and were discharged from the hospital without symptoms. During the research it was observed that all subjects were men aged 21-40 (X = 29.1 ± 1.3). They had an average history of 5.7 years of opioid consumption (range 1-10 years).

Table 1 Urine Toxicology in Opioid Addicts treated with Clonidine

No. of Patients	Day 1	Day 5	Day 10
1	+3	+2	0
2	+3	+2	0
3	+3	+1	0
4	+3	+2	0
5	+3	+2	0
6	+3	+2	+1
7	+3	+1	0
8	+2	+2	0
9	+3	+2	0
10	+3	+1	0
11	+3	+2	0
12	+3	+1	+1
13	+3	+2	0
14	+3	+1	0
15	+2	+1	0
16	+3	+2	0
17	+3	+1	0
18	+3	+1	0
19	+3	+1	0
20	+3	+1	0
Mean	2.9	1.5	0.1
SEM	0.06	0.11	0.06
P value		<.001	<.001

All patients had previously failed opioid detoxification attempts, and the mean number of prior supervised opioid withdrawal attempts was 2.25 ± 0.19. They all had hot flashes, the subjective symptom of acute opiate withdrawal, and urine samples tested positive with first line opiates. The patients did not use symptomatic treatment during the treatment day, i.e. from the 3rd to the 9th day of hospitalization. The mean number of hot flushes 6.37 ± 0.5 daily was obtained on the 2nd day of admission and was increased to a maximum of 17.5 ± 0.09 in the basic period of initial treatment, that is, on the 3rd day of admission.

Table 2 Physiological parameters in patients treated with Clonidine

Physiological Parameters	Day-3	Day-10	P-Value
Mean Systolic Blood Pressure (mm of Hg)	115.7 ± 0.6	115.4 ± 0.1	N.S
Mean Systolic Blood Pressure (mm of Hg)	71.3 ± 0.9	71.0 ± 0.7	N.S
Mean Temperature (°F)	98.8 ± 0.2	98.0 ± 0.1	P< 0.01 S

However, after clonidine administration, the frequency of daytime hot flushes decreased gradually from an initial value of 17.5 ± 0.09 to zero (0) on days 8, 9, and 10 (Fig. 1).

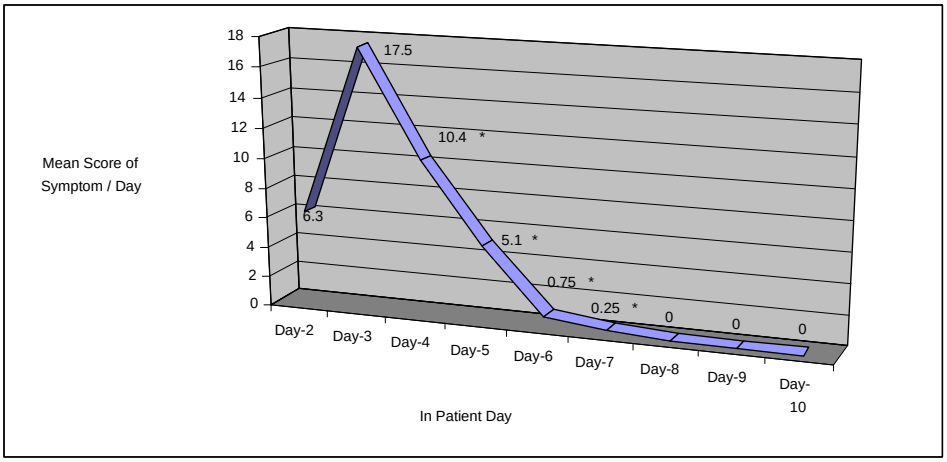

Fig. 1: Effect of Clonidine Treatment on Hot Flashes.

Thus, the effect of clonidine in reducing the frequency of daytime hot flushes was highly significant (P <0.001) on day 4 to admission compared to the initial frequency of pre-treatment symptoms on day 3 admission. Although there was no significant decrease in systolic and diastolic blood pressure. On the other hand, a slight but statistically significant decrease in body temperature was observed from the 3rd to the 10th day of admission (Table 2). Urinary toxicology decreased significantly and gradually from the mean value of 2.9 ± 0.06 on day 1 to 0.1 ± 0.06 on day 10 of admission. Thus, the effect of clonidine on opioid excretion from the body was also highly significant (P <0.001) on days 5 and 10, 2 months of admission compared with the first day of hospitalization before treatment (Fig. 2).

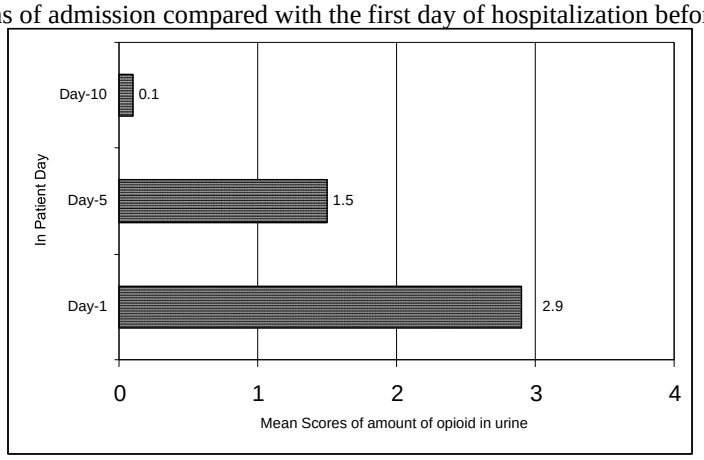

Fig. 2: Amount of Opioid in the Urine of Addicts treated with Clonidine

DISCUSSION:

Hot flushes are a significant problem for patients with acute opioid abstinence syndrome. Hot flushes can affect daily functioning, especially when they disrupt sleep, leading to tiredness and irritability during the day (Barton et al., 2014)[10-11]. Clonidine caused a rapid and statistically significant decrease in the number of hot flushes that occurred (17.5 vs.0). This study supports the hypothesis that α-2 adrenergic receptors in the central noradrenergic system are involved in the initiation of hot flushes and are consistent with the idea that central sympathetic activation and brain norepinephrine levels are elevated in this process (Barton et al. 2015). Recent studies have shown that increasing the level of norepinephrine in the brain in the hypothalamus narrows the width of the thermoregulatory inter-threshold zone[12-13]. This zone becomes so small that it is practically non-existent, and only slight increases in body temperature trigger hot flashes upon exceeding the sweating threshold (Stearns et al., 2016; Mekjavic et al., 2018; Brengelmann et al., 2017)[14]. Conversely, systemic administration of clonidine inhibits the activation of noradrenergic cells of the coeruleus locus and reduces

the secretion of noradrenergia, which raises the sweating threshold, lowers the chills threshold and relieves hot flashes (Zacny, 2018; Delaunay et al., 2015; Kronenberg 2018). Thus, these findings may have implications for the effective use of clonidine in the treatment of hot flush[15]. Although no studies have been performed to assess the efficacy or safety of various hot flush therapies. An immediate focus on some of the most promising of these therapies could broaden the treatment points available and should provide new insight into the mechanisms underlying hot flushes.

CONCLUSION:

As Clonidine has shown effects and safety in treating hot flashes, it may undergo extended clinical trials in hospitalized patients as it has not shown any side effects. Further research is needed to determine the full physiological mechanism of this common symptom.

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