A DOUBLE BLIND COMPARATIVE STUDY OF USEFULNESS OF CLONIDINE AND SYMPTOMATIC THERAPY IN OPIATE DETOXICATION

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SUMMARY

Several studies in West have indicated that clonidine hydrochloride, an adrenergic blocking agent is both safe and effective for detoxifying narcotic addicts. One hundred and two patients of opium addiction admitted in Psychiatry Centre Jodhpur were subjects for present study. The patients were divided into group A, B and C having thirty four in each group. These groups were identical with regards to sociodemographic variables, mean dose of opium and duration of intake. Group A was given clonidine in small doses, Group B symptomatic therapy and group C was given clonidine in high doses. Study was double blind. Record of blood pressure, pulse rate, other vital sign and withdrawal symptom (on Physician’s Rating Scale) was kept twice daily. Treatment was continued for two weeks. Clonidine in high doses proved to be more effective than other therapies.

Drug addiction exists in some form or the other in almost every country of the world. The reasons for drug addiction may be economical, physical, mental and cultural besides individual and social differences.

Opium addiction is the commonest addiction in western Rajasthan, Punjab and some parts of Madhya Pradesh. Opium is considered to be a powerful narcotic and owes its activity chiefly due to morphine, an alkaloid present in it. Many individual get to know of opium through association, group pressure and personal interests and find in them a sensation of pleasure and well being particularly in the initial phase. They then try again and again to recapture that sensation and thus develop dependence. Opium dependence has created many psychological problems by adversely influencing the physical health, earning capacity and interpersonal relationship. Due to non availability and high cost of opium and knowledge about its treatability, increasing number of addicts are visiting our centre for detoxification. Some of them on their own tried to leave opium, but could not do so, because of painful withdrawal symptoms. In fact control of withdrawal symptoms plays a vital role in the management of opium dependent patients.

The mechanism of opiate withdrawal symptoms is due to (Gold et al. 1978) increased nor adrenergic activity caused by the released inhibited activity of locus coeruleus and release of depressed transmission of spinal sympathetic preganglionic neurons. There are

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several approaches to tackle this problem –

1. To modify euphoria and withdrawal symptom by giving drugs that act on neurotransmitters. This has not been found successful.

2. Replacement by methadone. This method is slow and difficult one and there are potentials for abuse and withdrawal symptoms.

3. Others - beta adrenergic antagonists - propranolol, the alpha adrenergic antagonists, neuroleptics and nor adrenergic synthesis inhibitors. They all decrease nor adrenergic function.

   In the last group, clonidine, a imidazolidine, an alpha adrenergic agonist has been proved to be safe and effective agent for detoxifying narcotic addicts.

   Studies on rodent and primates (Gold et al. 1980) suggest that neurotransmitter nor adrenaline is involved in opiate withdrawal. Clonidine acts by inhibition of nor adrenergic activity via other inhibitory receptors on these neurons, catecholamine synthesis inhibition or by post synaptic blockage of noradrenergic projection area.

   In Western countries, opiate addicts are primarily managed by replacing it by methadone (Gold et al. 1978). In some studies methadone has been replaced by clonidine with good results (Gold et al. 1978 and 1980). Doses varying from 6 μgm - 16μgm/kg body weight has been used.

   In India not much attention has been paid regarding the management of drug addicts and opium addicts are treated by symptomatic therapy. However, in few studies clonidine (Gehlot et al. 1984, Subramanya and Channabasavanna, 1981) and DiPhenylate and Proxyphene (Gurmeet Singh et al. 1984) have been given.

   There is hardly any study available in India which has critically evaluated the effectiveness of clonidine in opium addict and compared its efficacy with symptomatic therapy and therefore the present study was planned to evaluate the effectiveness of clonidine in opiate detoxification and compare it with symptomatic therapy.

Material and Methods

Sample: The subjects of this study were 102 opium addicts who were admitted in Psychiatric Centre Jodhpur during the period between January 86 to June 86. Diagnosis of drug addiction was made as per I.C.D. 9 criteria. Functional and organic psychotic conditions were excluded. Also patients with current use of mono amino-oxidase inhibitors, neuroleptics, sedatives hypnotics, anti hypertensive drugs within two weeks of beginning of therapy, current alcohol abuse, allergy to imidazolidine drugs, any medical diseases like chronic cardiac disorder, renal, metabolic diseases, moderate to severe hypertension were not taken.

Procedure

All the subjects were male and they were divided into group A, B and C (34 patients in each group). Age range, mean dose of opium, duration of intake is given in Table 1. Thus these three groups were identical with regard to age, dose and duration of opium intake.

A physical examination and appropriate medical evaluation was performed for each case before the start of therapy. Opium was withdrawn suddenly in all patients by the turkey method.

Pharmacotherapy

Group A was given clonidine (small dose) .1mg on the 1st day and gradually increased to .5mg - .6mg during next 3-5 days. This dose is maintained during next 10 days.
Table 1  
Characteristics of the 3 Groups of Patients under study of opium withdrawal

| Name of Group | Total No. of Pts. | No. of Pts. Absconded | No. of pts. dropped out | No. of pts. completed therapy | Age range (in years) | Mean Age (in years) | Mean dose of opium (in gms) | Mean Duration of intake (in years) |
|---------------|------------------|-----------------------|-------------------------|-------------------------------|----------------------|---------------------|-----------------------------|----------------------------------|
| Group A       | 34               | 2                     | 2                       | 30                            | 21-65                | 30.2                | 14.5                        | 4.5                              |
| Group B       | 34               | 2                     | 2                       | 30                            | 20-64                | 30.5                | 14.4                        | 4.7                              |
| Group C       | 34               | 0                     | 4                       | 30                            | 25-61                | 31.2                | 14.2                        | 4.6                              |

Group B was given symptomatic therapy which included chlorpromazine (150 mg/day), Nitrazepam (10 mg bedtime), antiemetics, analgesics and other symptomatic therapy as needed. Group C was given clonidine (high doses) 0.5 mg to start with and increased to 1 mg - 1.2 mg/day till symptoms were controlled. Pharmacotherapy in the three groups was given for 2 weeks and the patients were hospitalised for 3 weeks. No attendants were allowed to meet the patients and close watch was kept so that no drug or opium was smuggled inside.

Evaluation: Each patient was examined in the morning and evening and record of blood pressure, pulse rate and other vital signs was kept regularly just prior to and one hour after each drug administration. Withdrawal symptoms were recorded independently by Psychiatrist who completed Withdrawal Symptoms Rating Scale having 24 items by giving 0 to no symptoms and 3 to severe symptoms (Methodology used by Charney S. Dennis et al. 1980). The drugs were given in identical capsules and patients and evaluating doctor did not know about the drugs patient was taking.

Assessment of somatic and psychological side effects and analysis of severity of withdrawal symptoms were done on Symptoms Rating Scale.

Discussion

Opium withdrawal is reported to be associated with intolerable symptoms of palpitation, restlessness, muscular and joint pain, insomnia, anorexia yawning etc. These symptoms discourage the addicts not to leave opium.

In western countries, opium addicts are being treated with methadone replacement therapy. Experience has shown that this process is slow and difficult one and also there are potentials for its abuse (Gold et al. 1978).

It is seen in this study that low doses of clonidine as well as symptomatic therapy influence the withdrawal symptoms of opium but clonidine in high doses was found to be superior to both the therapies
regarding the control of severity of withdrawal symptoms and its duration. When we made the comparison of each symptom of clonidine low dose therapy in controlling withdrawal symptoms at the end of 1st and 2nd week on Symptom Rating Scale with that of high dose therapy, we found that significant differences emerged on 15 symptoms out of 24 in the former, whereas significant difference were found in all these symptoms with high dose therapy. Furthermore, all these differences were significant at .01 level in comparison to low dose therapy where significant difference emerged only for 3 symptoms. In symptomatic therapy significant difference were found on 9 symptoms and 6 were significant at .01 level. On the basis of these statistical analysis we can safely infer that clonidine given in high dose is far superior to low dose clonidine and symptomatic therapy in controlling withdrawal symptoms of opium.

Twenty six patients (86%) with high doses and eight (27.5%) patients on low doses of clonidine developed hypotension and associated tachycardia. None of the patients required any specific therapy to control it.

### Table 2
Mean and S.D. of each symptom on clonidine low dose therapy in controlling withdrawal symptoms of opium at the end of I & II weeks on physician rating scale using ‘T’ test

| Symptom       | I Week M | I Week S.D. | II Week M | II Week S.D. | Significance |
|---------------|----------|-------------|-----------|--------------|--------------|
| Loss of appetite | 31.3     | 9.6         | 30.02     | 6.6          | N.S.         |
| Sweating      | 29.4     | 5.8         | 21.8      | 9.9          | <0.05        |
| Difficulty in Sleeping | 41.7     | 8.29       | 39.98     | 12.77        | N.S.         |
| Chills        | 18.6     | 6.4         | 17.8      | 8.4          | N.S.         |
| Hot flashes   | 29.6     | 9.5         | 28.3      | 11.72        | N.S.         |
| Nervousness   | 30.8     | 6.7         | 31.9      | 9.6          | N.S.         |
| Low energy    | 43.9     | 9.61        | 41.78     | 12.69        | N.S.         |
| Irritability  | 30.3     | 13.2        | 31.8      | 10.6         | N.S.         |
| Stomach cramp | 11.88    | 3.1         | 6.4       | 2.2          | <0.01        |
| Nausea        | 11.8     | 2.7         | 8.3       | 1.6          | <0.05        |
| Vomiting      | 13.3     | 2.6         | 11.8      | 2.7          | <0.05        |
| Feeling ‘Blah’ | 23.9     | 8.3         | 24.2      | 6.6          | N.S.         |
| Diarrhoea     | 8.3      | 3.3         | 6.4       | 2.28         | <0.05        |
| Joint pain    | 33.2     | 5.8         | 28.8      | 9.2          | <0.05        |
| Muscle pain   | 37.9     | 5.6         | 23.6      | 8.9          | <0.05        |
| Tremor        | 6.8      | 2.3         | 2.3       | 1.1          | <0.01        |
| Drowsiness    | 20.9     | 9.6         | 8.4       | 3.5          | <0.01        |
| Running nose  | 23.3     | 7.4         | 20.2      | 8.3          | <0.05        |
| Tearing       | 13.9     | 3.9         | 10.4      | 2.8          | <0.05        |
| Craving       | 18.7     | 5.3         | 16.1      | 2.7          | <0.05        |
| Yawning       | 28.6     | 6.74        | 26.9      | 4.8          | N.S.         |
| Drymouth      | 18.3     | 4.7         | 16.4      | 3.8          | <0.05        |
| Sneezing      | 24.4     | 6.3         | 21.2      | 3.7          | <0.05        |
| Palpitation   | 31.3     | 11.6        | 29.1      | 6.6          | <0.05        |

### Table 3
Mean and S.D. of each symptom by symptomatic therapy in controlling opium withdrawal symptoms in I and II week of therapy

| Symptom       | I Week Mean | I Week S.D. | II Week Mean | II Week S.D. | Significance |
|---------------|-------------|-------------|--------------|--------------|--------------|
| Loss of appetite | 38.6        | 7.6         | 39.1        | 8.7          | N.S.         |
| Sweating      | 20.8        | 6.4         | 19.6        | 6.7          | N.S.         |
| Difficulty in Sleeping | 41.0      | 10.5        | 39.0        | 13.6         | <0.05        |
| Chills        | 21.6        | 5.3         | 20.4        | 6.3          | N.S.         |
| Hot flushes   | 29.4        | 5.2         | 20.4        | 9.9          | <0.01        |
| Nervousness   | 38.6        | 7.6         | 37.9        | 9.9          | N.S.         |
| Low energy    | 40.6        | 7.2         | 38.9        | 11.7         | N.S.         |
| Irritability  | 34.4        | 6.6         | 32.9        | 8.8          | N.S.         |
| Stomach Cramps | 13.0        | 2.8         | 4.8         | 5.11         | <0.01        |
| Nausea        | 11.6        | 4.6         | 10.8        | 4.8          | N.S.         |
| Vomiting      | 10.4        | 6.6         | 9.3         | 3.8          | N.S.         |
| Feeling ‘Blah’ | 20.4        | 6.3         | 19.2        | 2.6          | N.S.         |
| Diarrhoea     | 5.4         | 3.2         | 4.6         | 2.6          | N.S.         |
| Joint Pain    | 45.0        | 7.5         | 18.8        | 4.2          | <0.01        |
| Muscle Pain   | 47.2        | 9.3         | 19.6        | 5.4          | <0.01        |
| Tremors       | 7.0         | 1.2         | 1.6         | 1.9          | <0.01        |
| Drowsiness    | 23.2        | 6.9         | 9.1         | 5.4          | <0.01        |
| Running nose  | 26.0        | 4.4         | 24.6        | 12.8         | N.S.         |
| Tearing       | 23.8        | 9.4         | 22.1        | 10.8         | N.S.         |
| Craving       | 11.4        | 3.7         | 12.8        | 2.9          | N.S.         |
| Yawning       | 38.8        | 4.8         | 32.1        | 14.8         | N.S.         |
| Dry mouth     | 22.0        | 1.7         | 13.4        | 5.8          | <0.05        |
| Sneezing      | 31.0        | 6.6         | 29.4        | 11.4         | N.S.         |
| Palpitation   | 22.4        | 3.6         | 19.2        | 6.2          | <0.05        |
Table 4

Mean and S.D. of each symptom on clonidine high dose therapy in controlling withdrawal symptoms of opium at the end of I and II week

| Symptom          | I Week Mean | S.D. | II Week Mean | S.D. | Significance (P) |
|------------------|-------------|------|--------------|------|------------------|
| Loss of appetite | 38.4        | 6.1  | 16.0         | 11.5 | <0.01            |
| Sweating         | 23.0        | 5.3  | 4.0          | 2.9  | <0.01            |
| Difficulty in sleeping | 46.6   | 11.3 | 21.0         | 12.9 | <0.01            |
| Chills           | 22.0        | 5.0  | 5.2          | 4.4  | <0.01            |
| Hot flushes      | 27.0        | 5.1  | 10.4         | 3.8  | <0.01            |
| Nervousness      | 40.6        | 10.5 | 12.6         | 9.8  | <0.01            |
| Low energy       | 44.8        | 11.1 | 14.4         | 10.5 | <0.01            |
| Irritability     | 37.8        | 8.4  | 11.6         | 8.5  | <0.01            |
| Stomach cramp    | 15.2        | 5.2  | 4.2          | 3.2  | <0.01            |
| Nausea           | 19.2        | 7.0  | 4.6          | 4.9  | <0.01            |
| Vomiting         | 12.6        | 6.1  | 3.0          | 3.7  | <0.01            |
| Feeling ‘Blah’   | 31.5        | 11.2 | 19.4         | 12.8 | <0.01            |
| Diarrhoea        | 10.4        | 3.7  | 1.6          | 1.8  | <0.01            |
| Joint Pain       | 47.8        | 10.2 | 21.8         | 14.2 | <0.01            |
| Muscle pain      | 50.8        | 9.8  | 19.6         | 12.1 | <0.01            |
| Tremor           | 6.6         | 2.4  | 2.4          | 1.5  | <0.01            |
| Drowsiness       | 27.8        | 8.3  | 7.2          | 5.7  | <0.01            |
| Running nose     | 30.8        | 7.3  | 8.6          | 6.3  | <0.01            |
| Tearing          | 30.8        | 7.3  | 8.6          | 6.3  | <0.01            |
| Craving          | 8.2         | 2.7  | 0.8          | 1.0  | <0.01            |
| Yawning          | 41.0        | 6.8  | 14.8         | 8.4  | <0.01            |
| Dry mouth        | 27.2        | 5.7  | 7.6          | 4.7  | <0.01            |
| Sneezing         | 32.3        | 6.0  | 16.4         | 8.1  | <0.01            |
| Palpitation      | 20.6        | 3.2  | 8.4          | 5.5  | <0.01            |

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