Preventive effects of hydroalcoholic extract of *Passiflora incarnata* on morphine withdrawal syndrome and its comparison with clonidine in mice

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**ABSTRACT**

Chronic use of morphine lead to dependence and discontinuation of the drug causes physical and emotional changes which needs pharmacological intervention. In the present study, the preventive effects of various doses of *Passiflora incarnata* extract on morphine withdrawal syndrome was evaluated in comparison to clonidine as a standard method. Total withdrawal score (TWS) was calculated based on behavioral signs of naloxone precipitated withdrawal syndrome in 56 adult male mice divided in 7 groups; in 6 groups morphine dependency was induced by chronic injection of morphine for 6 consecutive days. *Passiflora incarnata* hydroalcoholic extract was administered in doses 100, 200, 400, 800 mg/kg. Clonidine and normal saline were used in the control group. Withdrawal syndrome was induced by injection of naloxone. Total withdrawal score was decreased by chronic administration of *Passiflora incarnata* and clonidine. This study showed that clonidine (0.4mg/kg i.p.) and *Passiflora incarnata* extract significantly decrease TWS in the all used doses and in comparison to normal saline with a preventive effect comparable to clonidine. The data obtained in this study suggest *Passiflora incarnata* hydro-alcoholic extract therapeutic potential in prevention and management of opiate withdrawal syndrome which is comparable to the effect of clonidine, particularly at high doses of the plant extract.

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**Keywords**

*Passiflora incarnata*, Morphine, Withdrawal syndrome prevention, Clonidine

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**INTRODUCTION**

Morphine dependency is a major problem that develops in people all around the world and is a major task to face with in many countries. Chronic use of opiates like morphine cause structural and functional alterations in central nerve system, leading to Morphine dependency. Retreat from the opiate cause physical and emotional trauma and the withdrawal syndrome management has not been satisfactory so far. In addition, animal models of addiction have shown a developing tendency of the withdrawal syndrome which exact mechanisms is not yet clear [1, 2]. The plant *Passiflora incarnata* (*P. incarnata*), a member of Passifloraceae family, is a well-known plant that is widely distributed in many parts of Asia [3]. This traditional herbal medicine is widely used as a sedative, spasmolytic and anti-allergic agent in Asia. This plant has been used in Iranian folkloric medicine for central nervous system disorders. *Passiflora incarnata* contains indole alkaloids such as Harmann, harmol, harmine, and harmaline, flavonoids such as ornitine isornitine, vitexin,
Animals were injected morphine (20-45 mg/kg) subcutaneously with increasing dosage during 6 days. Animals in the control groups received normal saline for 6 days.

**Treatments**

Control group 1 received morphine for 6 days to induce dependency but no treatments afterwards and control group 2 just received normal saline for 6 days. *Passiflora incarnata* was injected to groups 4 to 7 in doses of 100, 200, 400 and 800 mg/kg, respectively. These groups received morphine concurrently once a day from days 1 to 6. Group 3 received clonidine hydrochloride injections concurrently with morphine once a day from days 1 to 6.

**Induction and Evaluation of withdrawal syndrome**

In day 7, animals of all groups were injected naloxone (3 mg/kg) and their 14 behaviors (jumping, head shake, wet dog shake, paw tremor, writhing, walking sniffing, sniffing, penile liking, rearing, chewing, body grooming, face wiping, swallowing, and teeth chattering) were recorded by camera. After computation of the recorded data, each behavior was divided to its weighing factor and a digit was obtained. The summation of the obtained digits gives the Total Withdrawal Score (TWS).

**RESULTS**

Morphine-dependent mice challenged with naloxone reliably displayed a profound withdrawal syndrome, consisting of jumping, paw tremors, diarrhea, weight loss, etc. The weighing factors for different withdrawal signs of morphine in mice are shown in Table 1. The aqueous extract of *Passiflora incarnata* attenuated naloxone-induced morphine withdrawal syndrome in a dose-dependent manner (Figs. 1 & 2). Treatment of animals with normal saline in negative control group (with no dependency) had a significant reduction in TWS compared to positive control (dependent) group (18.2±0.8 and 58.8±1.1 respectively, p<0.05). The co-administration of various doses of *Passiflora incarnata* attenuated TWS to 55.1±1.5, 49.5±1.2, 35.2±1.2 and 28.2±0.8 for 100, 200, 400 and 800 mg/kg of the extract, respectively. This decrease is statistically significant.

**Table 1. Weighing factors for different withdrawal signs of morphine in mice**

<table>
<thead>
<tr>
<th>Number</th>
<th>Behavior</th>
<th>Weighing factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Jumping</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>Head shake</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>Wet dog shake</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Paw tremor</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Writhing</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>Walking sniffing</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Sniffing</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Penile liking</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Rearing</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>Chewing</td>
<td>20</td>
</tr>
<tr>
<td>11</td>
<td>Body grooming</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>Face wiping</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>Swallowing</td>
<td>10</td>
</tr>
<tr>
<td>14</td>
<td>Teeth chattering</td>
<td>10</td>
</tr>
</tbody>
</table>
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DISCUSSION

Opioids are the most commonly used drugs for relief of pain across the world and their chronic use is associated with development of dependence, which abrupt cessation of the drug causes precipitation of a severe withdrawal syndrome. None of the several available approaches could treat abstinence syndrome. In last few years medicinal plants have been used widely for treatment of diseases by central nervous system origin across the world [8]. *Passiflora incarnata* extract is an effective agent for management of central nervous system disorders and has been used widely in folkloric medicine in many countries. There are scientific evidence that indicate *Passiflora incarnata* can be used for generalized anxiety disorder [9]. It has been mentioned in literature to be therapeutically effective on insomnia and can be used as sedative, anticonvulsant, anxiolytic and antioxidant [5, 10, 11]. Some studies suggest that *Passiflora incarnata* can be used as a therapeutic agent for the treatment of Attention Deficit Hyperactivity Disorder.
The authors declare that this research does not have any conflict of interest with anyone or any institute.

REFERENCES