A novel approach in the detoxification of intravenous buprenorphine dependence

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ABSTRACT

Background: Opioid dependence remains a significant problem in India, and of late intravenous (IV) buprenorphine use has increased in India, especially in combination with antihistamines and benzodiazepines. Its usage has many serious consequences in the form of needle-transmitted hepatitis and HIV, which is showing an increasing trend. Buprenorphine is a partial agonist at µ-opioid receptors. In tablet form (and rarely as IV), it is widely used in the treatment of opioid detoxification. We assessed the safety and efficacy of transdermal patch of buprenorphine with week long duration of action in the treatment of detoxification of IV buprenorphine dependence in view of its many advantages.

Materials and Methods: Six consecutive patients with International Classification of Diseases diagnosis of Opioid Dependence Syndrome (IV buprenorphine) were given a buprenorphine patch for treatment of withdrawal symptoms after receiving consent. Severity of opioid dependence was assessed by using Severity of Opioid Dependence Questionnaire on the day of presentation. Subjective and objective rating for opioid withdrawal was done by subjective opiate withdrawal scale (SOWS) and objective opiate withdrawal scale (OOWS) prepatch and postpatch 3rd and 7th day. Buprenorphine side effect checklist was applied on a daily basis.

Results: The patients had a mean age of 30 years, of whom 83.3% are males. All were educated and 50% were currently employed. All of them had additional comorbid substance use as well as a comorbid psychiatric diagnosis. Each of them received a patch of varying dosage. The patch dose used initially was based on clinical considerations alone and was fairly adequate in controlling acute withdrawal symptoms. There is a significant improvement in SOWS and OOWS while comparing the baseline (prepatch) with 3rd and 7th day (postpatch) (P ≤ 0.05). None of the patients reported any side effect with the patch.

Conclusion: This study shows that transdermal buprenorphine is safe, useful, and clinically effective, and a 7-day application may provide an alternative means of detoxification. However, the result of the study needs to be replicated in a larger sample in a clinical setting, and a control group receiving a conventional mode of treatment needs to be included.

Key words: Buprenorphine patch, opiate detoxification, opioid dependence syndrome

INTRODUCTION

Opioid dependence remains a significant problem in India, and many users prefer intravenous (IV) buprenorphine whenever heroin is unavailable and often mix it with a benzodiazepine to provide adequate “kick.” A few users prefer it over brown sugar or dirty heroin whenever it is unavailable. The prevalence of IV buprenorphine use has shown a significant decline in recent years, but nevertheless remains a significant problem in many pockets of the country. The profile of buprenorphine use reported in literature
Buprenorphine is a weak partial agonist at μ-opioid receptors. It has a high affinity for μ-opioid receptors, binding more tightly to these receptors than full opioid agonists. It also exhibits pharmacological properties that are more characteristic of an antagonist and thus, may have important implications for clinical utility. It has the dual effect of producing opioid responses while blocking the effects of additional opiate use and is used for the treatment of addiction and pain. It has particularly been used as an effective alternative to methadone in the treatment of opiate dependence. It is considered an attractive compound for use in clinical settings because of reduced potential for toxicity and overdose. It is available in the form of sublingual tablets, ampoules for intramuscular or subcutaneous injection, and transdermal preparations.

Managed withdrawal has always been considered as a necessary step prior to drug-free treatment or as the endpoint of substitution treatment. The transdermal formulation of buprenorphine provides extended relief from opioid withdrawal and improves adherence, while having less potential for diversion and abuse. It is also expected to be safer than the injectable form when it is used for detoxification, if effective clinically. The significant bio-delivery of buprenorphine and the suppression of the heroin withdrawal syndrome during patch application and its reappearance after patch removal indicate its clinically useful role. With the above knowledge of the use of buprenorphine patch in the treatment of other forms of opioid dependence, we used it in a clinical setting for the detoxification of patients dependent on IV buprenorphine injections.

**MATERIALS AND METHODS**

Six consecutive patients who fulfilled the International Classification of Diseases-10 diagnosis of “opioid (buprenorphine) dependence syndrome” were given a buprenorphine patch of appropriate dosage for the treatment of withdrawal symptoms. Informed consent was obtained from all the patients after an explanation of the role of buprenorphine patch in reducing withdrawal symptoms as well as the possible need for rescue medication for pain and withdrawal symptoms. They were also explained the possible need for additional medications for their comorbid conditions. Two of the six patients were evaluated on in-patient settings while the remaining four were evaluated on an out-patient (OP) basis due to their unwillingness for in-patient care. However, all the four patients who agreed only for OP treatment were called for daily OP visits and were evaluated with vitals monitoring, physical examination, and parameters similar to the admitted patients. The dose of IV buprenorphine use per day is depicted in Table 1. Patients were using at a frequency of 2–3 times per day. One of the patients had thrombophlebitis over the IV injection site, which was treated subsequently. Each received variable doses of buprenorphine patch (5 mg, 10 mg, and 15 mg) application based on the clinical impression and their severity of opioid dependence scores. Preapplication vitals were measured and baseline complete blood count, random blood sugar, liver function and renal function tests were done along with electrocardiography prior to the application of patch. The patch was applied on the left upper third of the...

| Socio-demographic/clinical variable | Mean (SD) | Frequency |
|------------------------------------|-----------|-----------|
| Age in years                       | 29.67 (4.59) |           |
| Gender                             |           |           |
| Male                               | 5         |           |
| Female                             | 1         |           |
| Educational status                 |           |           |
| Secondary school                   | 2         |           |
| Graduate                           | 4         |           |
| Socio economic status (SES)        |           |           |
| Lower SES                          | 1         |           |
| Middle SES                         | 2         |           |
| Upper SES                          | 3         |           |
| Domicile                           |           |           |
| Rural                              | 2         |           |
| Urban                              | 4         |           |
| Current occupational status        |           |           |
| Unemployed                         | 3         |           |
| Employed                           | 3         |           |
| Dose of Buprenorphine (number of ampoules/day) |           |           |
| (1 ampoule=0.6 mg Buprenorphine)   |           |           |
| 2-3                                | 2         |           |
| 3-4                                | 2         |           |
| More than 5                        | 2         |           |
| Co-morbid substance                |           |           |
| Nicotine                           | 3         |           |
| Nicotine and marijuana             | 2         |           |
| Polysubstance                      | 1         |           |
| Co-morbid psychiatric diagnosis    |           |           |
| Personality disorder               | 5         |           |
| Depression                         | 1         |           |
| Severity of dependence (using SODQ) |           |           |
| Low                                | 3         |           |
| Medium                             | 1         |           |
| High                               | 2         |           |
| Transdermal buprenorphine patch dose |           |           |
| 5 mg                               | 4         |           |
| 10 mg                              | 1         |           |
| 15 mg                              | 1         |           |
| Rescue drug                        |           |           |
| Clonazepam                         | 4         |           |
| Quetiapine                         | 2         |           |

n – Number of patients in each subgroup
arm for a duration of 7 days. The patients were explained about the necessity of covering up the patch prior to washing. They were instructed to report immediately if they developed itching/redness in the patch area or if they experienced severe withdrawal symptoms or any medical problems. Severity of opioid dependence was assessed with the “Severity of Opioid Dependence Questionnaire” (SODQ). SODQ is a five-section questionnaire comprising 21 questions designed to assess the severity of opioid dependence. The SODQ contains items addressing the demographics of drug consumption, as well as items related to physical withdrawal, affective withdrawal, withdrawal relief drug-taking, and rapidity of reinstatement after abstinence. The SODQ has been found to have clinically acceptable levels of internal consistency. In addition, significant correlations between SODQ scores and subjective sense of dependence in the “Psychoactive Substance Dependence and Abuse” section of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-III-R were found.

A self-report and observer rating scale of opioid withdrawal and agonist effects, subjective and objective opioid withdrawal scale (SOWS, OOWS) were administered on the patients on the day of evaluation prior to the application of patch, the 3rd and 7th days after the application of patch consecutively. The SOWS contains 16 symptoms whose intensity the patient rates on a scale of 0 (not at all) to 4 (extreme). The OOWS contains 13 physically observable signs, rated present or absent, based on a time period of observation of the patient by a rater. Both SOWS and OOWS were found to be very sensitive to reduction in withdrawal scores due to buprenorphine, among in-patient opiate abusers. Good inter-rater reliability for the OOWS and good intra-subject reliability over time for both scales were found.

All the patients received additional medications for the comorbid conditions such as insomnia, body aches, and anxiety. Additional or rescue medications were provided in the form of clonazepam or quetiapine, whenever called for. A specific buprenorphine checklist was also used daily to assess for side effects of the patch and any treatment-emergent side effects.

**DISCUSSION**

Buprenorphine transdermal patch in various doses has been found effective in the treatment of chronic nonmalignant pain syndromes requiring opioids. Sublingual buprenorphine either alone or in a combination with naloxone (to prevent IV abuse) has been used in the treatment of opioid dependence. Studies have concluded it to be an effective intervention in comparison to methadone treatment. Lanier et al. did the first open-label human trial of transdermal buprenorphine in nine heroin-dependent patients and found it to be effective in reducing acute withdrawal symptoms during the detoxification. Later, another study on detoxification was done in 12 cases of heroin dependence syndrome, using a single 7-day application of buprenorphine patch, which also showed a significant reduction of withdrawal symptoms. However, no study has been done to determine its use in patients with IV buprenorphine dependence.

In our sample, the majority of the patients were found to be males with a mean age of 30 years. All of them had completed schooling with majority being graduates and half of them were currently employed. Majority of our sample belonged to the middle- and upper-middle socio-economic status (80%) and came from an urban background (66.7%) [Table 1]. This profile of our opioid-dependent population is similar to that found in several other studies. Interestingly, in our study, we had one female patient who was dependent on buprenorphine. All our patients had another co-abuse substance (benzodiazepine, nicotine, cannabis, or multiple substance use) as well as comorbid psychiatric disorders.

### Table 2: Comparison of the scores of SOWS and OOWS at baseline, 3rd and 7th day post-patch

| Patient | Average SOWS score | Average OOWS score |
|---------|---------------------|--------------------|
|         | 3rd post-patch day | 7th post-patch day |
|         | 7th post-patch day | 3rd post-patch day |
|         | 7th post-patch day | 7th post-day       |
| 1       | 25                 | 16                 | 13                 | 10               | 4               |
| 2       | 30                 | 18                 | 14                 | 10               | 4               |
| 3       | 11                 | 7                  | 9                  | 4                | 2               |
| 4       | 16                 | 8                  | 9                  | 7                | 3               |
| 5       | 18                 | 10                 | 12                 | 8                | 3               |
| 6       | 11                 | 6                  | 10                 | 4                | 2               |

SOWS = Subjective opioid withdrawal scale; OOWS = Objective Opioid Withdrawal Scale

### Table 3: Comparison between average scores on SOWS and OOWS at baseline (pre-patch) and 3rd and 7th day (post-patch)

| Scales | Baseline vs Third day | Baseline vs Seventh day |
|--------|-----------------------|-------------------------|
|        | Z (p)                 | Z (p)                   |
| OOWS   | -2.000 (0.046)*       | -2.271 (0.023)*         |
| SOWS   | -2.000 (0.046)*       | -1.857 (0.05)*          |

*Level of significance 0.05. OOWS = Subjective Opioid Withdrawal Scale; OOWS = Objective Opioid Withdrawal Scale
(5 out of 6 with personality disorders and 1 out of 6 with depression), which again are a common finding in such a population. Many previous studies have suggested that hard-core opioid use is generally associated with a more commonly accepted softer gateway substance and many users later move onto being dependent on multiple drugs. A study by Aich et al. shows that nicotine is the most common gateway drug which was evident in our study. Personality disorders are very common with opioid and poly-substance abuse. These findings make opioid dependence particularly difficult to treat and these patients often require treatment for their comorbid psychiatric disorders with mood stabilizers, anti-psychotics, and anti-depressants. However, none of our patients had sought previous psychiatric help anywhere.

In our study, 66.7% patients required a patch dose of 5 mg and 33.3% patients received a higher patch dose (10 or 15 mg). The appropriate patch dose was clinically decided based on the dose of buprenorphine taken as well as the duration and severity of opioid dependence. Clinical decision was used rather than using any guidelines in selecting the dose of buprenorphine patch. Other medicines received by the patient and his medical status also influenced our choice of patch dose.

While comparing between scores on SOWS/OOWS at baseline (prepatch) and 3rd and 7th day (postpatch), there was a significant difference between the baseline rating of OOWS and SOWS with the score on 3rd and 7th day postpatch application [Tables 2 and 3]. This shows that the patient who received buprenorphine patch had shown a significant improvement in withdrawal symptoms during the application of the patch. There was no comparison group to decipher the exact influence of buprenorphine in this reduction of withdrawal symptoms. While monitoring with buprenorphine side effects checklist, there were no reported side effects reported by the patients. Indices of withdrawal (self-reports, observer ratings, and rescue medication) were significantly reduced within 72 h of patch application, and continued to decline thereafter, and did not reappear following patch removal. Two patients needed patches for another 2 weeks and one patient who was on a 5 mg patch needed a patch of 10 mg postdischarge. All the patients and their families were given psycho-education and psycho-social support right from the beginning (even before admission) and perhaps as a result of this, the initial follow-up was better. One of our patients was a medical student and started supporting the group along with individual therapy from our psychologist, but however, patients were soon lost for follow-up from varying times. Two of our patients had moved out to Bengaluru as per the family wishes (to avoid the old company) and another patient got re-admitted after a relapse 4 months later and was detoxified with buprenorphine patch once again. Three of the patients were started on tablet naltrexone 50 mg per day which they continued for the next 6 months.

There is significant literature regarding the application of buprenorphine patch and using buprenorphine depot injections mainly for heroin dependence, but we did not come across a single study for its use in injectable buprenorphine abusers. This along with a novel use of buprenorphine transdermal patch in this population is the main reason for undertaking this small study. However, there are several limitations in our study. The sample size was particularly low, and there was no control group for a strict comparison of the reported findings. Obviously, the results cannot be generalized and calls for further research in this area with a larger sample population and controlling for rescue drugs in a research setting.

**CONCLUSION**

This study shows that transdermal buprenorphine appears to be safe, effective, and clinically useful, and suggests that a 7-day application may provide a simple and comfortable means of buprenorphine detoxification. The use of patch formulation appears to reduce concerns about compliance, as well as reducing the likelihood of buprenorphine (tablets or injections used for detox) being diverted for illicit use. The cost considerations also seem to be favorable, especially when we consider the possibility of OP detoxification without a need for admission to a hospital facility in selected patients.

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**Conflicts of interest**

There are no conflicts of interest.

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