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Original Research Article

IVABRADINE AS AN ANALGESIC IN PATIENTS WITH LUMBAR RADICULAR PAIN: A CASE SERIES

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Abstract:
Objective - To report the effect of Ivabradine, a non-selective HCN blocker on pain in a series of patients with radicular low back aches.
Background - Neuropathic pain is one the most debilitating types of pain experienced among the various pain syndromes and is the most persistent complaint pain physicians observe. The augmented response and the allodynic features of neuropathic pain result from to spontaneous discharge of impulses from nerves, SSNRs, and DRG. This spontaneity has been attributed to pacemaker channels like HCN channels (HCN1-4). Ivabradine which is a nonselective HCN channel blocker was hence used to see its analgesic effects on neuropathic pain conditions like Lumbar radicular pain syndrome.
Material and methods – A total of six patients were given Tablet Ivabradine 5 mg twice on days 1, 2, and 3 and their demographics, vitals, pain scores (like VAS, FPS, VDS), and complications were assessed at time point 0, 1 hour and 3 hours after ingestion of the drug.
Result – Ivabradine as an analgesic showed insignificant improvement in the pain score in patients with Lumbar radicular pain syndrome and also caused marked complications such as symptomatic Bradycardia, hypotension, and palpitation.

1. Introduction

IASP in 2020 defined pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage," with the addition of six key Notes and the etymology of the word pain for further valuable context.

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena and they cannot be inferred solely from activity in sensory neurons.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience in pain should be respected.

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- Although pain usually serves an adaptive role, it may have adverse effects on function, social and psychological well-being (1).
- Verbal description is only one of several behaviours to express pain; the inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain (1).

Pain broadly is classified into Nociceptive pain, Inflammatory pain, and Pathological pain. Neuropathic pain comes under pathological pain wherein there is the occurrence of pain despite the absence of noxious stimuli owing to the maladaptive plasticity of the somatosensory nervous system (2). Due to this maladaptive plasticity, ectopic discharges get created also termed spontaneous discharges which have no protective role and lead to the development of symptoms like burning pins-needles and other neuropathic symptoms.

These spontaneous discharges have been attributed to the presence of Hyperpolarised gated cationic nucleotide channels (HCN1-4 channels). HCN-1 channel is present in the SA node and is responsible for giving it pacemaker-like characteristics. In nerve tissues, HCN-2, 3 and 4 channels are majorly responsible for the above-mentioned ectopic-spontaneous discharges leading to neuropathic pain-like symptoms (3). Interestingly, these HCN2 channels regulate inward current through intracellular cAMP, which is quite high during inflammatory conditions, in turn leading to enhanced activity of HCN 2 channels. These HCN channel subtypes are widely present at locations such as SSNR and DRG causing the emergence of ectopic impulses that result in symptoms such as pain, numbness, and tingling. The action of PGE2, another cytokine released during inflammation is also mediated by the HCN channels, whose presence has been confirmed in rat models by deletion of HCN2 channels which resulted in negated effects of PGE 2 (4).

To date, only Ivabradine, a non-selective HCN channel blocker has been FDA-approved for symptoms of stable heart failure. Its functions are more pronounced on funny currents of the SA node which is responsible for its depolarization and pacemaker qualities. It has bioavailability of 40% with its plasma concentration reaching its peak at 1 hour post ingestion. The distribution half-life of Ivabradine is 2 hours with effective half-life varying from 3 to 6 hours. Above all, it is metabolized exclusively by the hepatic system through the enzyme CYP3A4 (5).

Due to the unavailability of selective HCN2 channel blocker, we used Ivabradine which is a non-selective HCN blocker to evaluate its analgesic effect for Lumbar radicular pain syndrome. Although, Ivabradine is being used enormously for angina due to its anti-ischemic effects and is also widely accepted (6). Used in doses of 5-10 mg BD, it has shown significant improvements during the ischemic episodes along with its prominent resolution of ST-segment, which is dose-dependent. In few studies, like the *Initiative trial it* has shown no difference in the outcome of coronary artery disease patients when compared with atenolol (7).

In one study like that of K.Takasu et al, showed that the administration of selective HCN channel inhibitors has alleviated pain, due to the thermal or mechanical stimuli (8). In this study, they injected selective HCN inhibitor ZD7288 intrathecally and assessed its effects via in vitro electrophysiological studies.

We also based our evaluation on the study done by Gareth T. Young et al, where they studied neonatal mice of 4-6 weeks using patch clamp technology and concluded that Ivabradine has a measurable blocking effect on the HCN channel of sensory neurons with suppression of cAMP. Surprisingly, in nerve injury specimens the effect of Ivabradine was found to be comparable with Gabapentin in conditions such as neuropathic pain symptoms (9). This

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comparison of Ivabradine and Gabapentin was done by injecting these drugs intraperitoneally and their effects were analyzed using electrophysiological methods.
The dosage however of Ivabradine in our study was kept minimal to lower its adverse effects on the heart rate. To improve its safety profile we used a much lesser dose of 5 mg twice a day, while the dosage for conditions such as stable heart rate and angina have been 10-15 mg twice daily (10).

Objective

To report the effect of Ivabradine, a non-selective HCN blocker on the pain in a series of patients with radicular low back aches.

2. Material and methods

We studied six patients between the age of 18-65 years of age presenting with Low backache with radicular symptoms. Patients with a history of Bradycardia, Prolonged Qtc, atrial fibrillation, hypertension, coronary artery disease, and cerebrovascular disease were excluded. These patients were studied in the pain division of the Anaesthesiology department of IMS, BHU, Varanasi after getting approval from the ethical committee of the institute.
Patients were initially assessed in the Pain OPD using clinical symptoms, and signs such as straight leg raising test, crossed leg raising test, sitting leg raise test, and imaging modalities. After proper diagnosis, these patients were admitted to the ward and were explained about the study, drug, and its effects (benefits and side effects). Post admission their vitals were noted at time point 0 and then the first dose of drug Tab. Ivabradine 5 mg was given and vitals, and pain scores like NRS, VDS, and FPS were noted at time points of 0,1-, and 3 hours post-ingestion. A satisfactory pain relief was designated as a change in pain score improvement ≥ 30% and if it wasn't achieved then a rescue analgesic injection of Paracetamol 1gm was given and was termed as a failed response to achieve analgesia. Complications such as Bradycardia, hypotension, nausea, vomiting, or any visual effects were also noted.

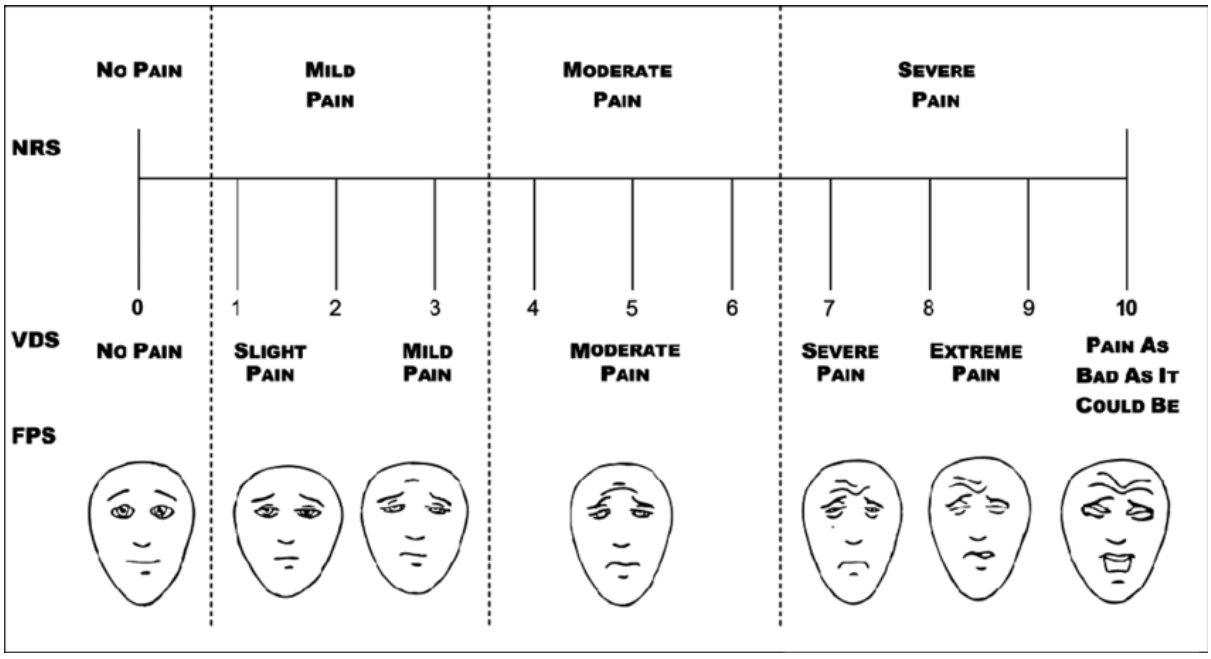

Figure 1 – Chart to document NRS, FPS and VDS

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3. Discussion

As already pointed out above these patients were having symptoms of Lumbar radicular pain syndrome (LRS) which is defined as low back ache with radiating radicular symptoms to one or both legs in a dermatomal fashion with documented evidence of band-like pain, decreased deep tendon reflexes or weakness. There are various causes for LRS but the most prominent pathophysiology, is the compression of the nerve, nerve root, or dorsal root ganglion. This compression causes inflammation or partial demyelination of the nerves leading to ectopic, paroxysmal, spontaneous firing from these areas of demyelination which we have now know is mediated by HCN channels (11).

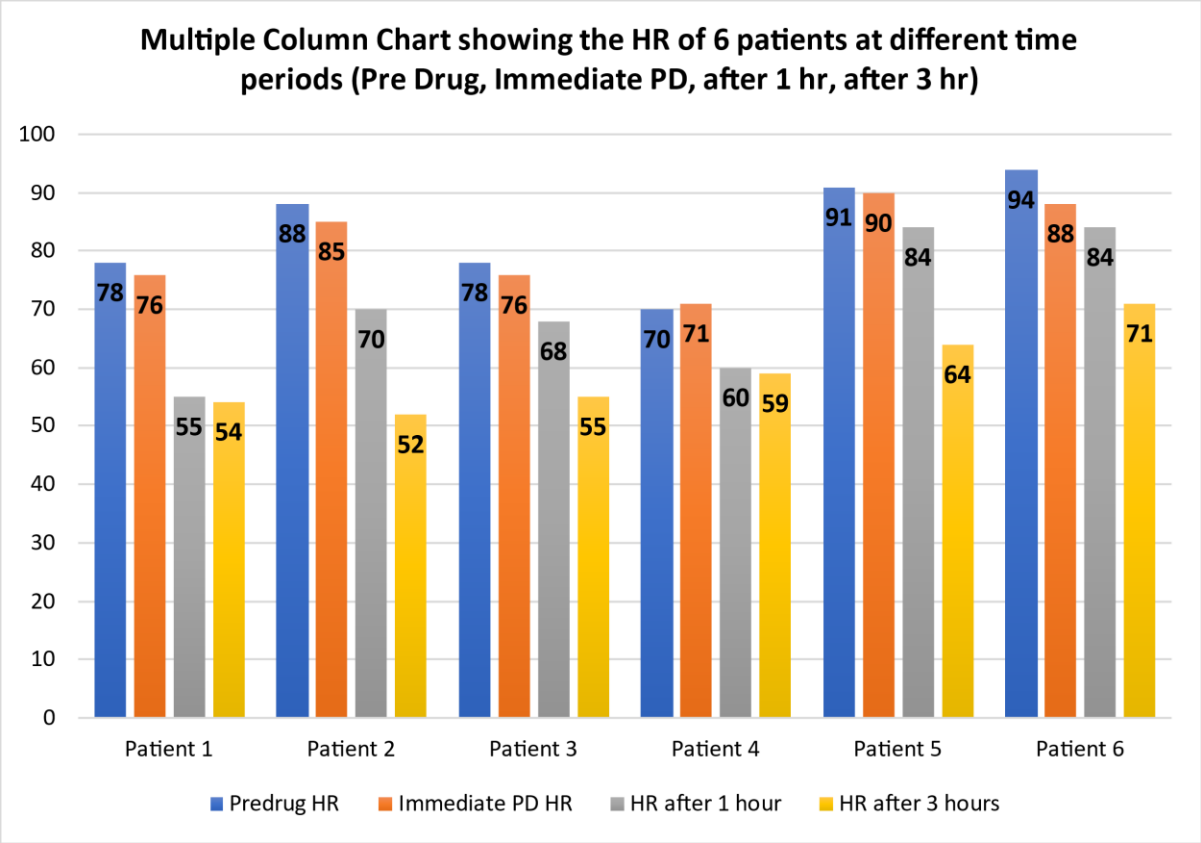

Figure 2 – Graph showing HR variabilities in six patients

One of the most prominent effects of Ivabradine is on heart rate (HR) and the adjoining graph depicts the effect of Ivabradine on HR, here there was a significant difference between the HR noted before and 3 hours after the drug administration, which was noted in all six patients. Moreover, patients also experienced the symptoms of palpitation that was reported more by the female patients. Ivabradine as a non-selective blocker of HCN, blocks the HCN 1 channels prominently present in the SA node that prevent Na ingress and prevent spontaneous discharge of the SA node, due to this it has been successfully used in the treatment of tachycardia or tachyarrhythmias (12). *Signify* study also noted the above effects as well its beneficial effects in treating patients with heart failure and Myocardial infarction which also opened new doors for its use (6). We had anticipated this complication, due to which we had used lower dose of 5 mg BD however, significant bradycardia and palpitation observed at this dose was strange.

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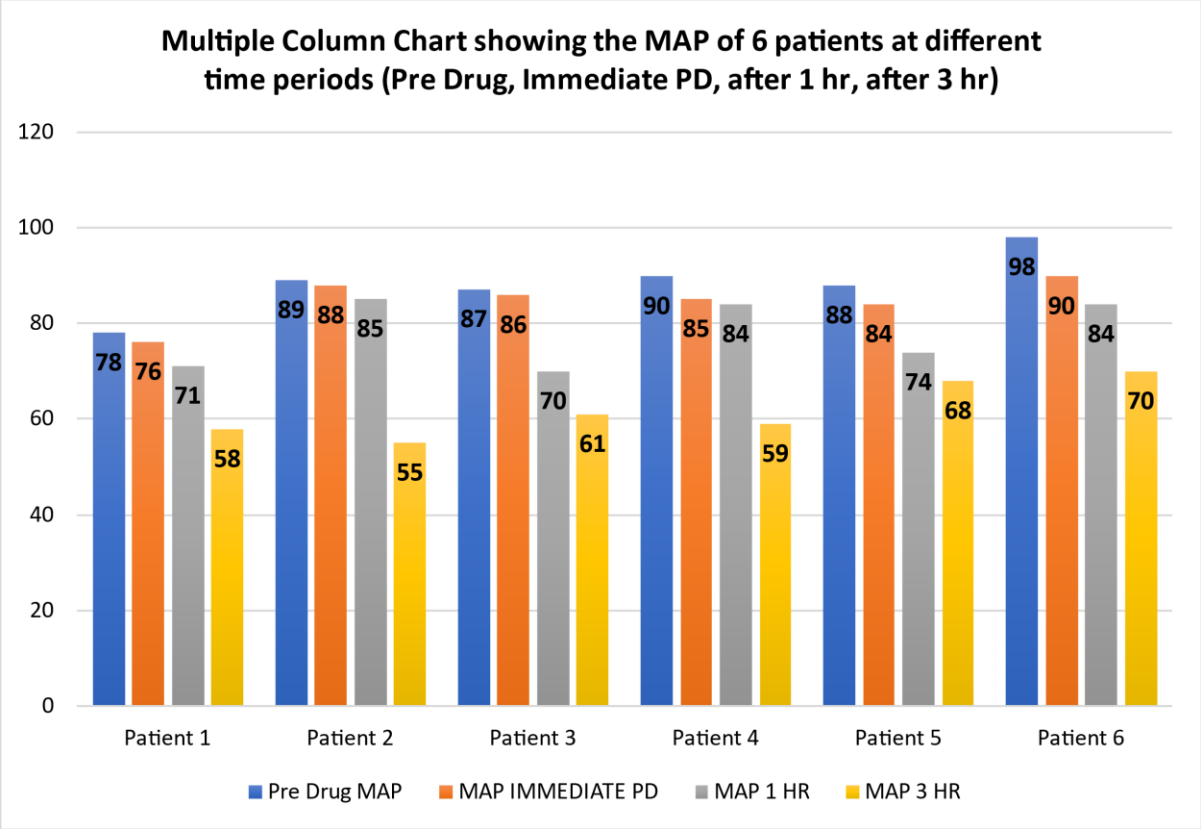

Figure 3 – Graph showing MAP variabilities in six patients

Ivabradine also shower significant changes in blood pressure. Wherein the fall in systolic blood pressure, diastolic blood pressure, and mean arterial blood pressure was prominent after 1 hour and 3 hours of drug ingestion. Many processes could explain this phenomenon, like the attenuation of oxidative stress, its anti-inflammatory action on the vasculature, decreased lipid peroxidation and decreased atherosclerotic plaque size (13). The fall in blood pressure was significant at the time point of 3 hours post-ingestion of the drug compared to the pre-drug administration value. We also noted that the fall in systolic and MAP was more than it was for the diastolic blood pressure, which could be partly explained by the lowering of heart rate and subsequent small reduction in the cardiac output.

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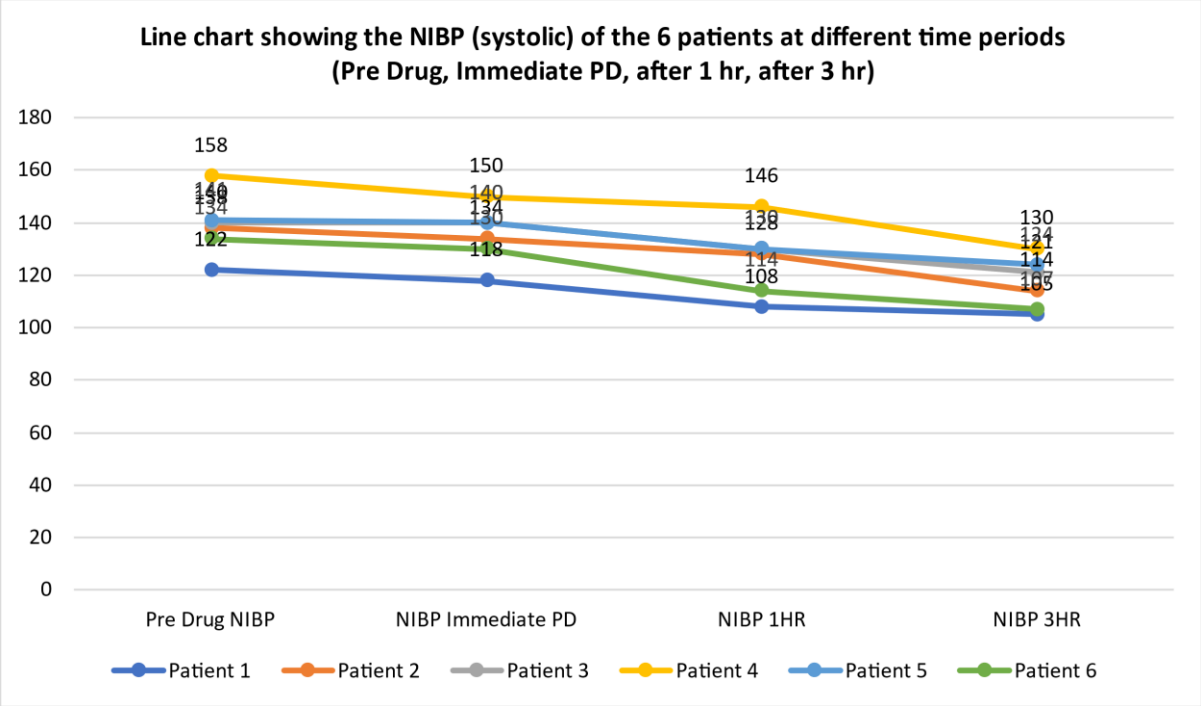

Figure 4 – Graph showing systolic pressure variabilities in six patients

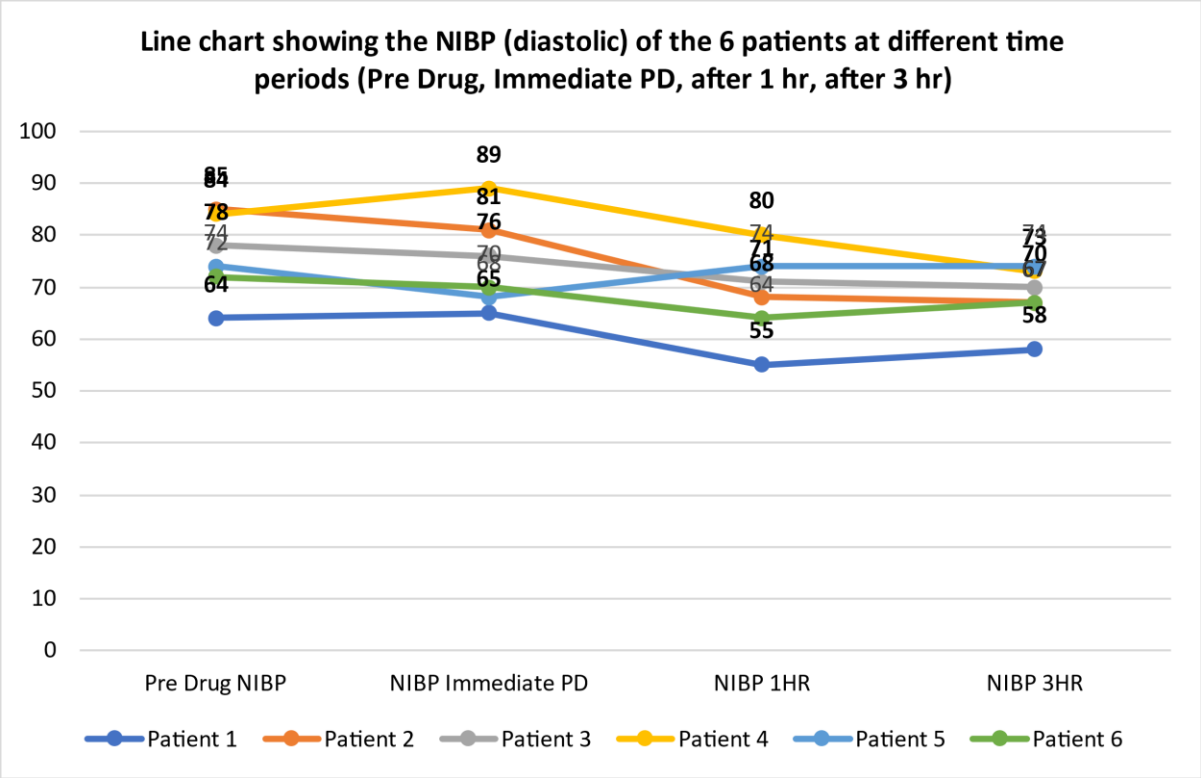

Figure 5 – Graph showing NIBP (diastolic) variabilities in six patients

Hence, the above two graphs depicts the fall in systolic and diastolic blood pressure in which the fall in systolic was appreciably more than diastolic due to the added effect of a decrease in the heart rate contributing to the lowered cardiac output. For patient 1, the highest BP

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(systolic) was observed at pre-drug (122 mmHg) followed by immediate post-drug (118 mmHg), after 1-hour post-drug (108 mmHg), and after 3 hours post-drug (105 mmHg).
In one study, Wistar-Kyoto controls using pentobarbital anaesthesia, acute administration of consecutive ivabradine doses of 1mg/kg decreased systolic, diastolic, and mean blood pressure in hypertensive rats (14). Likewise, even in our study the fall in blood pressure seen in patient 1 who was hypertensive was far higher compared to other patients with no history of hypertension.
The NRS for the 6 patients was compared in which all the values were greater than 5. The pre-drug NRS was observed highest in patients 4, 5 and 6 (10) followed by patients 1 and 3 (9), and lowest was in patient 2 (8). The immediate post-drug and after 1 hour post-drug NRS was observed highest in patient 6 (9) followed by patient 4 (8) and lowest was observed in patients 2 and 3 (7). The after-3-hour post-drug NRS was observed to be highest in patients 4, 5 and 6 (8) followed by patients 1, 2, and 3 (7).
Fairly positive results of Ivabradine on neuropathic pain have been documented by a study done by Gareth T Young et al. on mice where after using patch clamp technology they concluded that inflammatory and neuropathic pain was rapidly inhibited by blocking HCN-dependent repetitive firing in the peripheral nociceptive neurons (9). Another article written by You Wan used immunomicroscopy and immunohistochemical staining to show the location of different subtypes of HCN channels, they depicted that HCN 1 channel was predominant in the Dorsal root ganglion while HCN 2 and 3 were present in lower levels. Most importantly, HCN 4 was majorly present in smaller neurons (15).
Our case series was even based on the observations mentioned above and by the study done by Shannon A. Bernard Healey et al. in which seven participants who had documented neuropathic symptoms for more than 6 months with DN4 score of more than 4, were given maximum Ivabradine dosages of 7.5 mg twice daily with a target heart rate of 50-60/minute and their self-reported NRS was evaluated over a period of 10 days (16). Unfortunately, they failed to show any benefits of Ivabradine on pain relief.
Similarly, a crossover randomized trial conducted by Gareth T Young et al. to evaluate its effect on capsaicin-induced hyperalgesia also illustrated negative results of Ivabradine as an analgesic (17). In this study, 55 participants were selected with more than 20 cm of punctate hyperalgesia on topical application of 0.5% Capsaicin cream and were given either 15 mg of Ivabradine or a placebo, they also failed to show any improvement in the hyperalgesic symptoms. Another similar study conducted by Santoshi Tanaka et al. used Capsaicin-induced dynamic mechanical allodynia and heat pain threshold to observe the effects of Ivabradine and also negated its effects as an analgesic (18).
Nevertheless, the graph below from our study as well shows that improvements in the NRS and facial pain score were insignificant. The scores here did not improve by 30% with all six patients requiring rescue analgesics at the end of the 3 hours period. On verbal communication, all six patients reported minimal relief in their pain alongwith symptoms of palpitation and unrest. At the end of 3 hours period three out of six patients also required admission for a day. Three out of 6 patients also reported nausea and vomiting at the end of the 1-hour and 3-hour periods. Surprisingly, all six patients reported feeling of uneasiness, discomfort in chest and palpitation.
Furthermore, none of the six patients reported visual symptoms such as sudden brightness in vision that have been reported as one of the side effects of the usage of Ivabradine, which has been mostly observed with patients on long-term treatment for more than 2 months (19).

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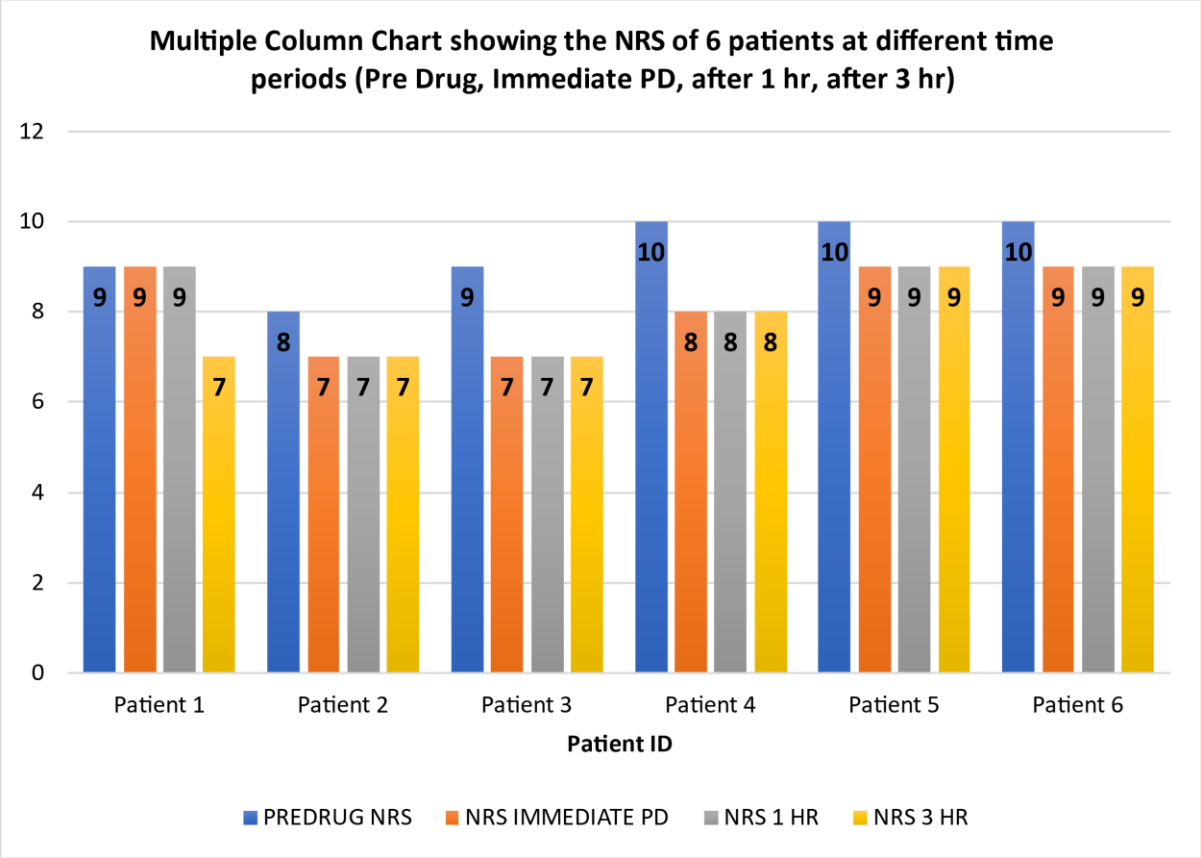

Figure 6 – Graph showing NRS in six patients

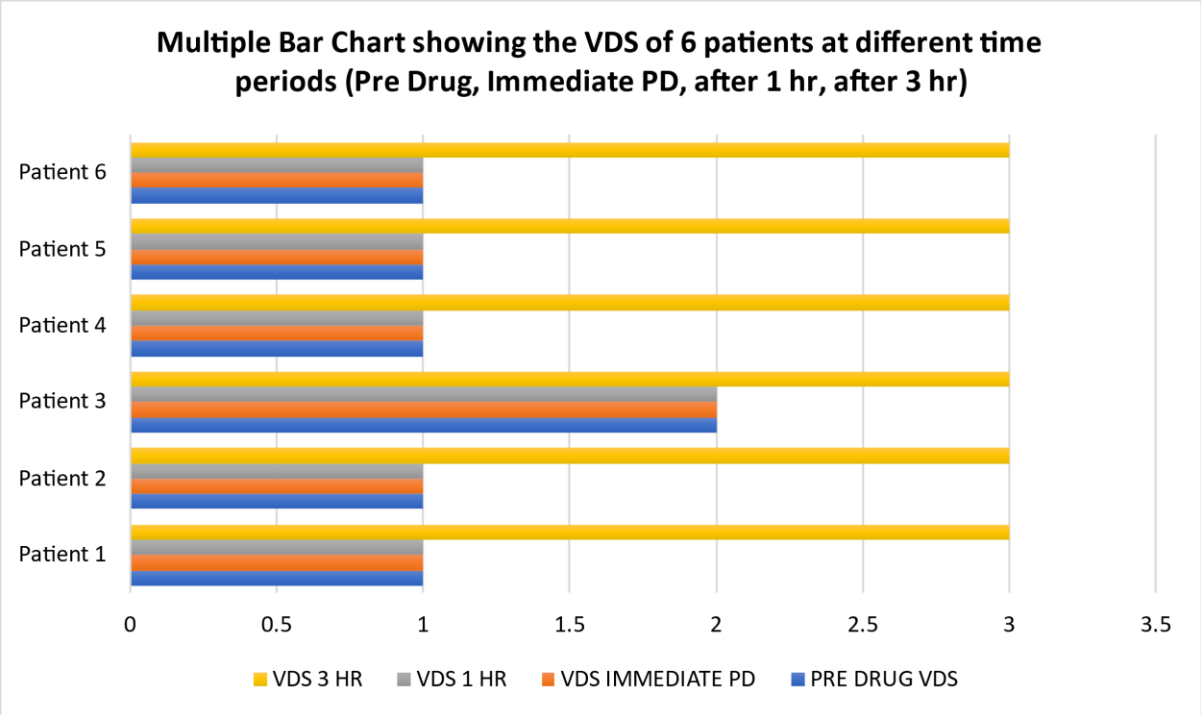

Figure 7 – Graph showing FPS in six patients

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The study done by Shannon Bernard mentioned above, that formed the basis of our study was done in the western enriched population (16), as a consequence we thought and attempted to report the outcome of Ivabradine on Lumbar radicular pain syndrome amongst our south asian population. Lumbar radicular pain syndrome (LRS) is one of the most commonly reported pain scenarios in our country and our study aimed to develop an opinion about any genetic-geologic-ethnic factors that could contribute to the effect of Ivabradine as an analgesic especially in chronic neuropathic pain cases like the LRS.

Shortcomings in our study

Many shortcomings of our observations can be observed such as fewer patients enrolled, in-homogenous age-sex demographics, and shorter duration of drug administration due to reported adverse effects of Ivabradine. Although 13 patients were enrolled in this study out of which only 6 patients completed our study while remaining 7 dropped out of the study due to its side effects such as bradycardia, palpitation, uneasiness and nausea.

4. Conclusion

To sum it up, only six patients were observed during this study with cessation of recruitment of new patients occurred obviously due to the reported bradycardia and restlessness. Regrettably, Ivabradine was not able to show any promising effect as an analgesic in patients with Lumbar radicular pain syndrome (LRS).

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