

Original Article



Effect of minocycline on lumbar radicular pain: a prospective pilot study

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Abstract

Introduction: Pain is an unpleasant sensory and emotional experience. Evidence suggests a role for microglia in chronic pain and inhibition of microglia leads to decrease of chronic pain intensity in animal models. Minocycline, a semisynthetic tetracycline derivative, is a selective inhibitor of microglia. Several studies have shown pain intensity improvement by minocycline in animal model of pain, but a few studies showed effectiveness on chronic pain improvement in humans. This prospective, self-controlled clinical trial investigated whether minocycline is effective for chronic pain management.

Methods: Twenty-two patients, between the ages of 20 and 80 years with radicular lumbar pain with a numerical rating scale >4, who were unresponsive to other medications and had pain duration of >6 weeks were included in the trial.

Results: Pain intensity, neuropathic pain and life quality scores assessed before and after treatment. All scores showed significant improvement after 2 weeks of treatment: 56%, 74% and 14%, respectively.

Conclusion: Findings of this study suggest minocycline can effectively improve patients' pain scores and quality of life, even in those with long-term duration of chronic pain and warrants further study.

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Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (Fernández-Carvajal et al., 2012). Alterations of pain pathways lead to chronic and debilitating pain (Basbaum et al., 2009). Emerging data are beginning to challenge the

dominant neuronal model of chronic pain. Evidence now points to a role for glia, both macroglia (oligodendrocytes, astrocytes) and microglia (Chen et al., 2009). Astrocytes and microglia in the central nervous system (CNS) each have unique roles in the modulation of neuronal microglia function (Milligan and Watkins, 2009), including well-documented roles

in pain facilitation. Microglia are heterogeneously distributed throughout the CNS. Spinal microglia activation is necessary and sufficient to induce neuropathic pain. Numerous studies have demonstrated a critical role of microglia in the development of neuropathic pain (Ji et al., 2013). Inhibition of these cells can effectively attenuate the development of neuropathic pain in animal models (Smith, 2010). Microglia and astrocytes are activated following tissue injury or inflammation and activated glia are necessary for enhanced nociception (Milligan and Watkins, 2009). Spinal glia activation is now considered as an important component in the development and maintenance of allodynia and hyperalgesia in various models of chronic pain, including neuropathic pain and pain associated with peripheral inflammation (Bradesi, 2010). Spinal cord glial activation may represent common mechanism that leads to pathological pain in a number of pain syndromes with different aetiologies.

Minocycline, a second-generation semisynthetic tetracycline derivative antibiotic, is a nonselective inhibitor of microglia. Intrathecal or systemic minocycline produces a potent and consistent antinociception in animal models of neuropathic pain induced by peripheral nerve injury or inflammation. For example, pre-treatment with minocycline before nerve injury significantly prevented the development of neuropathic pain in rats (Padi and Kulkarni, 2008). In humans, minocycline reduces acute postoperative pain, but evidence of its role in reducing the development of late-phase neuropathic pain is limited (Ji et al., 2013; Cui et al., 2008). In type 2 diabetic patients, some pain indices (Leeds assessment of neuropathic pain and pain disability index) improve following minocycline administration while others (Beck Depression Inventory and visual analog scale) do not differ from placebo (Syngle et al., 2014). While minocycline may not decrease pain intensity, it reduces the affective dimension associated with neuropathic pain (Sumitani et al., 2016). In addition to affective aspects, some psychological aspects including negative and cognitive symptoms of early-phase of schizophrenia showed improvement (Levikovitz et al., 2010; Dean et al., 2012). In an animal study, minocycline showed antidepressant effect (Molina-Hernandez et al., 2008). One study suggested a small benefit in chronic radicular pain in human (Vanelderren et al., 2015).

In view of these analgesic benefits, we undertook a study of minocycline for the treatment of lumbar radicular pain in patients who were unresponsive to other medications.

Materials and methods

Study design and setting

In this single-center, prospective, self-controlled clinical trial, we investigated the effect of minocycline on lumbar radicular pain in a group of patients. We assessed the patients' pain experience, using the patients' pre-treatment experience of pain as the comparator. Both the patients and the treating pain specialist were blinded to the identity of the study drug. Twenty-two patients, 13 female and 9 male took part in this study (according to the previous study by Valendren) with average age of 42.6. This study started in June through September 2019.

Participants

Patients referred to the outpatient pain specialty clinic at Modarres General Hospital in Saveh, Iran, were recruited for the study if they had lumbosacral radicular pain irrespective of the aetiology, leg pain predominant over back pain and with 11-point numerical rating scale (NRS) over 4. Inclusion criteria were those who were between 20 and 80 years of age, had suffered from chronic pain for a minimum of 6 weeks and had not responded to prior treatment efforts. Excluding criteria were any confirmed cognitive disorder, any confirmed sensitivity or adverse drug reactions to the study drug, any neurologic, rheumatologic or infectious diseases.

The diagnosis of neuropathic pain was documented via the Douleur Neuropathique 4 (DN4) (Vanelderren et al., 2015). Written informed consent was obtained before inclusion in the study. This research was approved by the ethics committee of Saveh University of Medical Sciences and registered in "Iran registry of clinical trials" website [Trial number: IR.SAVEHUMS.REC.1395.32].

Intervention

Enrolled patients received the study drug, minocycline 100mg (Ranbaxy Pharmaceutical Inc. Jacksonville, FL 32257 USA), once daily for 2 weeks. Patients were instructed to take the study medication in the morning, 1h before or 1h after breakfast with a

glass of water, adapted from published protocols (Vanelderden et al., 2015). Continuation of previously used paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs) was permitted. The only additional pain medications allowed during the trial were the scheduled study drug and an as-needed rescue medication. Tramadol 50mg at a maximum of three tablets daily, administered at 6h or greater intervals, was the rescue medicine.

Patients completed three visits at days 0, 7 and 14. NRS, DN4 and short form 36 (SF36) questionnaire (Sumitani et al., 2016) were completed at days 0 and 14 by the pain specialist. A one-week supply for the minocycline was given to the patient at day 0 and day 7. Patients were informed of the availability of the rescue medicine, which was kept by the nurse until the patient requested it.

Outcome measures

We compare pain sensation of patients before and after treatment with minocycline at baseline and after 14 days. An 11-point NRS, with 0 indicating no pain and 10, the worst pain ever felt was employed. Neuropathic pain intensity and life quality were also measured at these intervals by DN4 and SF36 questionnaires, respectively. Patients were asked on day 7 and 14 of the trial whether they had experienced any side effects attributable to the study drug. Improving in pain scores (NRS and DN4) could be considered as primary outcomes. Pain palliation has a positive impression on the quality of life of patients measured by SF36 questionnaire, so we considered it as secondary outcome.

Statistical methods

We analyzed the data using the Wilcoxon rank-sum test. An experiment-wise $P < 0.05$ was considered statistically significant, with $k=3$, Bonferroni's correction set the significance of the individual comparisons to $P < 0.017$. Calculations were done using SPSS ver. 25.

Results

Twenty-two patients who met the inclusion criteria consented to participate in the study. This included 9 men and 13 women. The mean age was 42 years with a range from 22 to 64 years. No patients reported side effects attributed to the study medication.

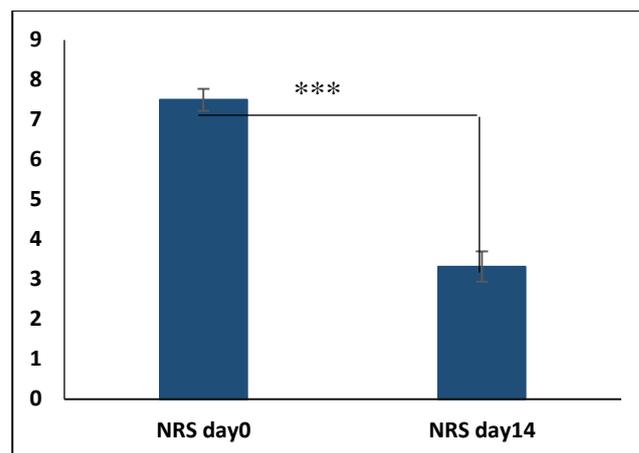


Fig.1. Numerical Rating Scale (NRS). Assessment of pain intensity by 11-point NRS ranging from 0 to 10. Higher scores indicate more pain. *** $P < 0.001$ for NRS score comparing day 14 to day 0.

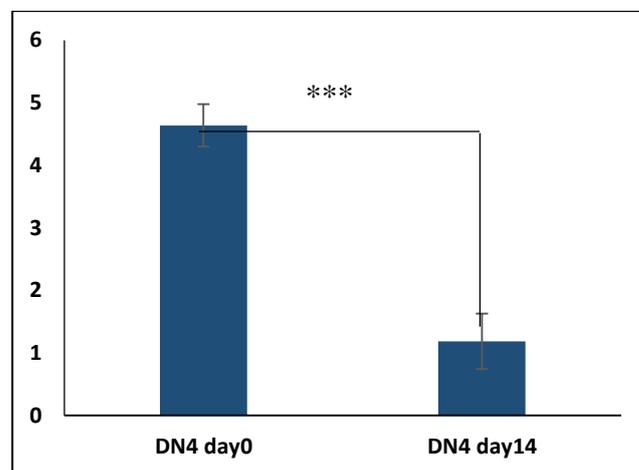


Fig.2. Douleur neuropathique 4 (DN4). Assessment of neuropathic pain. *** $P < 0.001$ for DN4 score comparing day 14 to day 0.

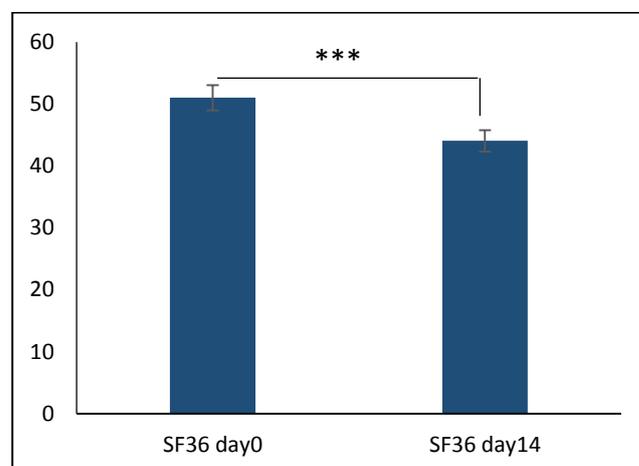


Fig.3. SF36 questionnaire. assessment of life quality. *** $P < 0.001$ for SF36 score comparing day 14 to day 0.

As shown in Figure 1, there were significant differences following two weeks of minocycline therapy in pain scores via NRS (7.50 ± 1.30 vs. 3.31 ± 1.78 , a 56% decrease, $P < 0.001$) and DN4 (4.64 ± 1.59 vs. 1.18 ± 2.08 , a 74% decrease, $P < 0.001$, Fig. 2) and also quality of life scores via SF36 (51.00 ± 9.60 vs. 44.05 ± 8.13 , a 14% improvement, $P < 0.001$, Fig.3).

Discussion

This study suggests that minocycline improves symptoms of lumbosacral radicular pain after 2 weeks of treatment. Previous studies have shown mixed results; while Sumitani et al. (2016) found that minocycline did not decrease intensity of neuropathic pain, Vanelderden and colleagues (2015) showed that minocycline reduced lumbar radicular pain, albeit by a degree of questionable clinical significance. Our results are consistent with the latter; though consistent, the two studies are not directly comparable as the control methods differed.

Life quality also showed significant improvement by SF36 questionnaire. The previous mentioned research by Sumitani also showed improvement in affective dimension of patients. Levkovitz et al. (2010) also showed that minocycline is an effective agent in treatment of negative and cognitive symptoms in early-phase schizophrenia

The only medication was taken by the patients in addition to paracetamol/NSAIDs during our trial was minocycline; there was no rescue medication use. As the patients chronic use of paracetamol/NSAIDs had up to the point of enrollment in the study failed to alleviate the participants' pain, we attribute the relief of pain sensation and neuropathic pain intensity to the use of the minocycline. While we believe the effect of minocycline is its inhibition of microglia, the actual mechanism is unknown and remains to be fully elucidated.

The use of an antimicrobial agent for analgesia may be controversial in light of antibiotic stewardship programs that endeavor to avoid development of antibiotic resistant infections. However, with an expanding world-wide opioid-dependency epidemic, the benefit of additional nonnarcotic agents in the arsenal of analgesics may outweigh the potential risks. The generalizability of this study is limited by its small size and lack of a placebo-control or active-agent comparator arms in the investigation. Such is

the nature of pilot studies.

Conclusion

We have shown that minocycline has the potential to be effective for pain reduction in chronic radiating lumbosacral pain and that it improves affective dimensions resulting in perception of higher quality of life. It warrants further investigation, including larger placebo-controlled and noninferiority comparison studies. Longer-term studies are also warranted to evaluate the duration of efficacy as well as side effects of minocycline.

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Conflict of interest

There is no conflict of interest.

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