Original research

Comparison of the antinociceptive effect of intrathecal versus intraperitoneal injection of paracetamol in neuropathic pain condition

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Abstract: ***Background:*** Despite the availability of several drug classes for treatment of neuropathic pain, no one provides the optimal balance of efficacy, tolerability and safety. Paracetamol (acetaminophen) is widely used for reducing pain with various origin around the world. The aim of this study was to compare the analgesic effect of intraperitoneally and intrathecally administration of paracetamol in chronic constriction Injury (CCI) model of the sciatic nerve in male rats.

Method: In this study, 24 adult male Wistar rats were randomly divided into 2 groups (n=12). The CCI model of sciatic nerve was used for induction of neuropathic pain. Catheterization was performed on the eleventh day after injury through the space between the L5 and L6. On the fourteen days after injury, paracetamol injected intraperitoneally (100mg/kg) and intrathecally (50µg / rat) in two different groups. Thermal and mechanical hyperalgesia and cold allodynia evaluated 15, 60 and 120 minutes after injection. The intact limb was used as control.

Results: Injury of the sciatic nerve induced a significant decrease in pain threshold. Both intraperitoneal ($p<0.001$) and intrathecal ($p<0.001$) administration of paracetamol reduced the pain and this effect continued until 120 minutes after injection. However, paracetamol does not increase the pain threshold of injured hind paw to the uninjured one. The effectiveness of paracetamol was similar in both methods of administration ($p>0.05$).

Conclusion: The findings of this study indicate that intraperitoneal and intrathecal administration of paracetamol had no significant difference in pain symptoms. Therefore, because of convenience and lower risk, intraperitoneal administration is recommended to relief the pain.

Keyword: Neuropathic Pain; Drug Administration Routes; Injections, Intraperitoneal; Injections, Spinal

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1. Introduction

Neuropathic pain is a kind of chronic pain, which is usually caused by disease or damage to the central or peripheral nervous system (1). Its feature is spontaneous and persistent pain along with increased sensitivity to painful stimuli (hyperalgesia) as well as feeling pain for non-painful sensation such as mechanical and cold stimuli (allodynia) (2). The prevalence of neuropathic pain is estimated about 8.5% in 2014 (3) and is more common in people older than 55 years (4). The release of inflammatory enzymes such as cyclooxygenase (COX-2) seems to be the main cellular mechanism for induction of neuropathic pain in injuries to the peripheral nerve (5). In fact, among the mediators activated in the peripheral nerve injury, the role of nitric oxide (NO) and prostaglandin (PG) is the leading cause of neuropathic pain (6).

Among Pharmacological treatments for chronic pain control, the usage of tricyclic antidepressants, gabapentin, pregabalin, and topical medications such as lidocaine and N-Methyl-D-aspartic acid (NMDA) receptor

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antagonist are common (7). Given that none of these existing drug aren't effective to control neuropathic pains, researchers are looking to find a new drug with the aim of improving the treatment and completely control the neuropathic pain. Paracetamol/acetaminophen is one of the most common drugs used as antipyretic and analgesic around the world (8).

Although over 100 years have passed since the discovery of paracetamol, it is widely used in the medical profession (9). Inhibition of the synthesis of prostaglandins from arachidonic acid by COX 1 and 2 seems to be the major mechanism of paracetamol action (10). It has central and peripheral effects. Central analgesic effects of this drug in addition to inhibiting COX, are through the descending serotonergic, L-arginine/NO pathway, cannabinoid system (11, 12) and its interaction with opioid system (10).

Paracetamol has similar properties with non-steroidal anti-inflammatory drug (NSAIDs). But unlike them, has no anti-inflammatory activity and is a drug of choice in patients who have contraindications to use NSAIDs, such as those with stomach ulcers, allergic to aspirin, blood coagulation disorders, pregnant women, nursing mothers and children who have fever with a disease (8).

The analgesic effect of paracetamol in neuropathic pain is controversial. A number of previous studies indicated the lack of analgesic effect of intrathecal injection of paracetamol in mechanical hyperalgesia in diabetic neuropathic pain model (13) and sciatic nerve ligation model (14). However, there are a small number of reports about the beneficial effect of intraperitoneal and local administration of paracetamol in reducing allodynia (15, 16) and hyperalgesia (17), the two main symptoms of neuropathic pain. Despite of these reports, the use of acetaminophen in the treatment of neuropathic pain is not common (18).

According to the bioavailability of the drugs, it is probable that the therapeutic effects of paracetamol is affected by the method of administration and this may be the reason for contradictory results being reported. In this study we evaluated and compared the analgesic effect of intraperitoneal and intrathecal injection of paracetamol in the model of peripheral nerve injury in male rats.

2. Method

2.1. Animals

In this experimental study, adult male Wistar rats weighing 200 ± 250 g were used. The animals were purchased from the center of experimental and comparative studies of Iran University of Medical Sciences and kept in controlled conditions of light (12 hours of light and 12 hours of darkness), temperature (3 ± 22 Celsius) and humidity (about 45%). They had free access to food and water. The study protocol approved by the Ethics Committee of the Iran University of Medical Sciences and experiment was conducted in accordance with the instructions of National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No . 85-23, revised 1985) (19).

2.2. CCI model of neuropathic pain

24 adult male Wistar rats were randomly divided into two equal groups (n = 12). Chronic constriction injury of sciatic nerve (CCI) was used to create neuropathic pain. The animals were anesthetized by ketamine (80 mg/kg; RotexMedica, Germany) and xylazine (10 mg/ km). After shaving the left upper thigh and sterilizing the area, a 2 cm incision created in the skin, and by blunt dissection through the biceps femoris the muscles were slowly set aside for appearing the sciatic nerve before trifurcation. Then based on the model provided by Bennett & Xie (20), sciatic nerve was separated from the surrounding tissue and four ligatures (chronic 4/0) were loosely tied around it with about 1mm spacing. Then muscle and skin were closed separately by silk 4/0.

2.3. Catheterization

Eleven days after surgery a 10 cm PE10 tube (PE-10; BD Intramedic Polyethylene Tubing) for injection to the intrathecal space was used. For this reason an incision was created in the lumbosacral area (L6 - L5) and after pushing the muscles aside, space between the two vertebrae was identified by a fine forceps and 2 cm of the catheter was led into the subarachnoid space, so that the end of the catheter is placed in the lumbar part of spinal cord. The rest of the cannula was passed rostrally under the skin of the animal to the thoracic level (21). At the end of the surgery the catheter was flashed with 10 microliter of normal saline. Three days after catheterization, in the absence of any disability, pain intensity was assessed.

2.3.1. Drug administration

Fourteen days after nerve compression, all animals were evaluated for pain threshold. To compare the effect of intraperitoneal and intrathecal injection (n = 12 in each), paracetamol (Uni Pharma, USA.1g 6,7 ml AMP) at doses of 100 mg/ kg and 50 µg/kg was administered intraperitoneally (i.p) and intrathecally (i.t.) respectively. Paracetamol was dissolved in fresh normal saline and administrated in a volume of 0.2 ml for i.p and 10 µl for i.t injection.

2.4. Behavioral tests for evaluation of neuropathic pain

All behavioral tests were performed blindly to the investigator (22, 23). Thermal and mechanical hyperalgesia and cold allodynia were evaluated fourteen days after chronic constriction injury of sciatic nerve. Animals

were tested before injection and 15, 60 and 120 min after injection of paracetamol. Uninjured hind paw was used as control.

2.4.1. Thermal hyperalgesia

Plantar test was used to determine the thermal hyperalgesia. Animals were placed in a plastic cage (14 × 17 × 22 cm) (Ugo Basile, Varese, Italy) with a glass floor. Time latency of withdrawal response to the infrared beam was automatically determined by the device. A cut-off time of 25 second was used to prevent tissue damage (24). Each hind paw was tested three times at intervals of at least 5 minutes. The mean values obtained were recorded as a response.

2.4.2. Mechanical hyperalgesia test

Mechanical hyperalgesia were evaluated by Analgesimeter device (Ugo Basile, Varese, Italy). In this test, pressure threshold of the deep tissues was measured. The animals were restrained with a towel around the trunk and treated gently during the experiments. A pusher with a rounded tip was applied to the lower hind leg extensors. The cut-off point was set at 250 g to avoid damage to the tissue. The intensity of the pressure that caused an escape reaction was defined as the withdrawal threshold. Measurements were performed two times at 30-s intervals, and the mean value was recorded as the nociceptive threshold.

2.4.3. Cold allodynia test

To measure cold allodynia, a drop of acetone applied to the hind paw based on Choi and colleagues (25). In this method, the animals were put on a mesh surface and a drop of acetone was sprayed on the hind paw by an insulin syringe. The positive response was considered when a withdrawal response appears up to 3 seconds after acetone flash. This experiment was performed 5 times and the positive response is reported as a percentage.

2.4.4. Statistical analyses

All statistical analyses were performed using SSPS version 20.0 (SPSS; USA). To evaluate the effect of time (before and 15, 60 and 120 minutes after drug administration) and the rout of drug administration (intraperitoneally and intrathecal), two-way repeated measures analysis of variance (ANOVA) with Bonferroni post hoc test was used to examine significant differences between groups. All results are presented as mean values ± standard error. For all tests, $p < 0.05$ was considered to be statistically significant.

3. Result

3.1. Cold allodynia

Intraperitoneal (df: 9, 129; F=32.4; $p < 0.001$) and intrathecal injection (df: 9, 129; F=21.7; $p < 0.001$) of paracetamol improves cold allodynia in both experimental groups. However, significant difference ($p < 0.05$) was still observed between the control (uninjured paw) and injured paw. It is worth noting that there was no differences between the i.p and i.t administration in times of 15 ($p > 0.99$), 60 ($p > 0.99$) and 120 minutes ($p > 0.99$) (Figure 1).

3.2. Mechanical hyperalgesia

Repeated Measured ANOVA showed that i.p (df: 9, 129; F18.6; $p < 0.001$) and i.t (df: 9, 129; F = 28.1; $p < 0.001$) administration of paracetamol relieved mechanical hyperalgesia. No improvement observed at 15 min after

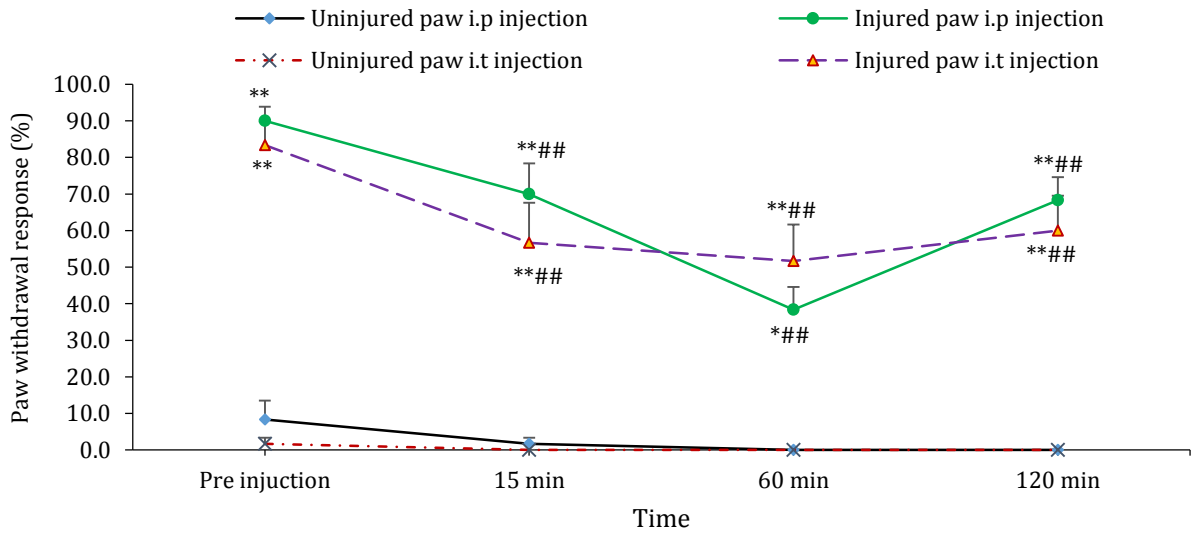

Figure 1: Evaluation of cold allodynia in experimental groups. Cold allodynia was improved by i.p (n = 12) and i.t (n = 12) administration of paracetamol. However there was no difference between the two methods of injection. * $p < 0.05$ compared to healthy (uninjured) paw; ** $p < 0.001$ compared to healthy (uninjured) paw; # $p < 0.05$ compared to the time before administration; ## $p < 0.001$ compared to the time before administration; i.p: intraperitoneal; i.t: intrathecal.

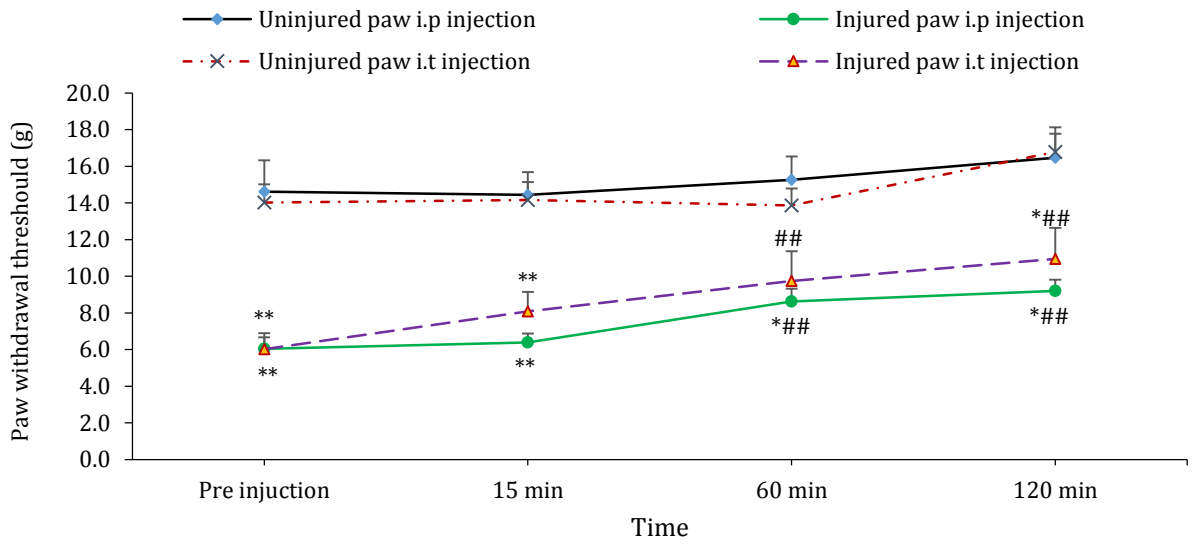

Figure 2: Evaluation of mechanical hyperalgesia in experimental group. Mechanical hyperalgesia was improved in animals with i.p (n=12) and i.t (n=12) administration of paracetamol. However there was no statistically difference between the two prescribed methods. In the 60 minute after administration, withdrawal threshold of the affected paw in the intrathecal injection group had no difference with intact limb. * p<0.05 compared to healthy (uninjured) paw; ** p<0.001 compared to healthy (uninjured) paw; # p<0.05 compared to the time before administration; ## p<0.001 compared to the time before administration; i.p: intraperitoneal; i.t: intrathecal.

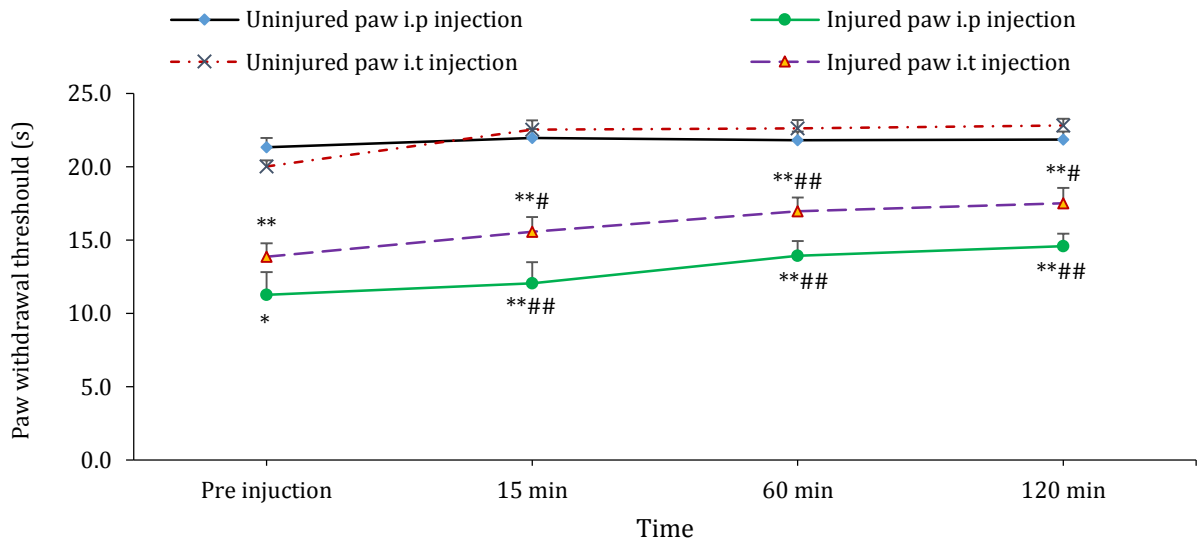

Figure 3: Evaluation of thermal hyperalgesia in experimental group. i.p (n=12) and i.t (n=12) administration of paracetamol improved thermal hyperalgesia in animals. There was no significant difference between the two administrative methods. * p<0.05 compared to healthy (uninjured) paw; ** p<0.001 compared to healthy (uninjured) paw; # p<0.05 compared to the time before administration; ## p<0.001 compared to the time before administration; i.p: intraperitoneal; i.t: intrathecal.

injection however, withdrawal threshold increased 60 min (p=0.002) and 120 min (p<0.001) after injection of paracetamol in both experimental groups. Nevertheless, mechanical threshold in the intraperitoneally administrated group never reached the level of the intact limb (p < 0.05). No differences observed between the control and injured paw in animals injected intrathecally one hour after injection (p=0.65). However, after 120 minutes a significant difference was observed between the control and injured paw in intrathecally injected animals (p = 0.04) (Figure 2).

3.3. Thermal hyperalgesia

In the evaluation of thermal hyperalgesia it was identified that both of intraperitoneal (df: 9, 129; F = 12.5; p < 0.001) and intrathecal administration (df: 9, 129; F =

15.5; $p < 0.001$) of paracetamol increase the pain threshold in injured paw. However, the level of observed improvement never reached to the level of the intact limb (uninjured paw) ($p > 0.05$). It is worth noting that there is no differences between the i.p and i.t administration groups in 15 ($p = 0.69$), 60 ($p = 0.99$) and 120 minute ($p > 0.99$) after injection (Figure 3).

4. Discussion

The findings of this study indicate that intraperitoneal and intrathecal injection of paracetamol caused improvement of neuropathic pain symptoms in the CCI model of neuropathic pain. Alleviating effect of the drug was found during the first 15 minutes and continued until the end of two hours. The results of this study showed that the administration route had no effect on the analgesic effect of paracetamol.

According to the available evidence, central and peripheral analgesic effect of paracetamol has been confirmed (8). Hinz, showed that paracetamol is a preferred inhibitor of COX-2 isoenzyme (26), which prevents the conversion of arachidonicacid to prostaglandin H2 (PGH2) and reduces the production of prostaglandin E2 (PGE2), which is an important cause of neuropathic pain (27).

Paracetamol increases the release of serotonin by stimulating the serotonergic neurons in brain stem (28). Paracetamol is also act as an opioid ligand or cannabinoid ligand and as the indirect effect is able to increase endogenous opioid and cannabinoid (CB) ligands (29). Arachidonylamide (AM404) N- (4-hydroxyphenyl) is a metabolite of paracetamol which is produced in dorsal root ganglion and prevents cellular uptake of CB (10). Inhibition of the formation of nitric oxide (NO) may be an alternative mechanism in the analgesic action of paracetamol. Activation of L-arginine/NO pathway by the substance P and NMDA receptors lead to NO- synthesis which is an important neurotransmitter in pain processing in the spinal cord (30).

The results of this experiment showed that both intrathecal (50 µg/rat) and intraperitoneal (100 mg/kg) injection of paracetamol had significant analgesic effect which last at least 2 hours after injection. This analgesic effect starts almost 15 min after injection and continued with the same intensity until 2 hour. Similar results reported by Kyong-Shil and colleagues in 2012. They reported a dose dependent analgesic effect of paracetamol (100 and 200 µg / rat) in paw-pressure test by intrathecal injection. Intraperitoneal administration of paracetamol (400 mg / kg) also had analgesic effect in the hot-plate test. They showed that intraperitoneal injection of paracetamol reduces cold allodynia and thermal Hyperalgesia in neuropathic pain model in mice, so they offered that paracetamol is useful for neuropathic pain (17).

A significant analgesic effect of paracetamol has also been reported by intrathecal injection in inflammatory pain model. Spinal serotonin receptors are responsible for the analgesic effect of paracetamol and it is not related to its anti-inflammatory effect (31). Analgesic effect of paracetamol is also approved in formalin and hot-plate test (32). The results of the present study are in accordance to the results reported by researchers.

Analgesic effect of paracetamol in neuropathic pain model has also been reported by local injection. Peripheral cannabinoid system is responsible for its dose-dependent analgesic effect when injected directly to the plantar surface of hind paw. This effect has been observed in mechanical allodynia and hyperalgesia (16). Cold allodynia were not evaluated in this study.

In contrast to data presented above Curros-Criado MM, Herrero JF reported that paracetamol , when administrated alone, is ineffective in increasing the pain threshold in neuropathic pain condition and co-administration of paracetamol with gabapentin has more effective that paracetamol alone (14). The same results was reported by Morlion (18). This result is contrary to our results. In their study, they used nitroparcetamol which is a newly synthesized NO-releasing derivative of paracetamol.

In the field of combination of paracetamol with other drugs, Antonio Gatti and colleagues in their studies on patients with neuropathic pain resulted from spinal cord injury concluded that paracetamol and oxycodone act as synergism in pain reduction and paracetamol in combination with low-dose of oxycodone, can be considered as first-line therapy in patients with various types of pain, including neuropathic pain that does not respond to paracetamol alone (33). While, co-administration of paracetamol and morphine does not have the similar impact which, was investigated in patient with cancer pain (34). Déciga-Campos M and his colleagues in 2015 evaluated the effect of N-palmitoylethanolamide (PEA) and paracetamol in diabetic rats and concluded that the combination of these two drugs can treat neuropathic pain in diabetic condition (35).

5. Conclusion

In conclusion, the results of this study showed that paracetamol can be effective as a symptomatic treatment for patients with neuropathic pain associated with allodynia or hyperalgesia. Intraperitoneal and intrathecal administration of paracetamol has similar extenuating effects for allodynia and hyperalgesia in neuropathic pain model. Because of easier and safer use, intraperitoneal administration of the drug is suggested.

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7. Conflict of interest

None.

8. Funding Source

None.

9. Author contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editor.

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