

The analgesic efficacy of intra-articular acetaminophen in an experimental model of carrageenan-induced arthritis

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BACKGROUND: Acetaminophen is one of the most common drugs used for the treatment of pain and fever.

OBJECTIVES: To examine the effects of intra-articular (IA) acetaminophen on carrageenan-induced arthritic pain-related behaviour and spinal c-Fos expression in rats.

METHODS: The present study was performed using 20 Sprague Dawley rats. Forty microlitres of IA 0.9% NaCl was injected in the control group, and 40 µL of IA carrageenan was injected in the carrageenan group. One hour after carrageenan injection, 400 µg of IA acetaminophen was injected in the IA acetaminophen group, and 400 µg of intraperitoneal (IP) acetaminophen was injected in the IP acetaminophen group. One day before injection, and 4 h and 8 h after injection, diameters of both knee joints, motility of the rat, paw loading and joint mobility were assessed. After the rats were euthanized, L3 and L4 spinal segments were excised for c-Fos assessment.

RESULTS: IA acetaminophen decreased both the severity and distribution of c-Fos expression. IP acetaminophen decreased only the distribution of c-Fos expression. IA acetaminophen decreased knee diameter at 8 h. IA and IP acetaminophen increased rat motility and paw loading scores. Joint mobility scores of IP acetaminophen were similar to saline at 8 h.

CONCLUSIONS: Results of the present study indicate an analgesic and/or possible anti-inflammatory effect of IA acetaminophen and provide further evidence on the efficacy of systemic acetaminophen injection in reducing arthritic pain.

Key Words: Arthritic pain; Carrageenan; c-Fos; Intra-articular acetaminophen

Osteoarthritis (OA) is one of the most common joint disorders, and is believed to be the most prevalent among the group of musculoskeletal diseases (1). Due to aging populations with longer life expectancies, the incidence and prevalence of OA is projected to increase in the future (2).

Arthritis pain is common, and is associated with worse functional outcomes and poorer quality of life compared with a range of other chronic conditions (3). Published systematic reviews and meta-analyses have confirmed that pharmacological therapies, such as acetaminophen, nonselective and cyclooxygenase-2 selective nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, opioids, antidepressants, topical capsaicin, chondroitin sulfate and intra-articular (IA) steroid injections, have efficacy in the management of arthritic pain (4); however, there are currently no treatments capable of markedly altering its progression. Investigations are still being performed on a wide range of pharmacological and nonpharmacological treatment options to find ideal management strategies for arthritic pain.

Despite its widespread use as a systemic analgesic and antipyretic, the mechanism of action of acetaminophen remains poorly defined. Acetaminophen has a narrow therapeutic window, but has a

L'efficacité analgésique de l'acétaminophène intra-articulaire dans un modèle expérimental d'arthrite induite par le carraghénane

HISTORIQUE : L'acétaminophène est l'un des médicaments les plus utilisés pour traiter la douleur et la fièvre.

OBJECTIFS : Examiner les effets de l'acétaminophène intra-articulaire (IA) sur l'expression c-Fos comportementale et rachidienne liée à la douleur arthritique induite par le carraghénane chez les rats.

MÉTHODOLOGIE : Les chercheurs ont effectué la présente étude au moyen de 20 rats Sprague Dawley. Ils ont injecté 40 microlitres de NaCl 0,9 % IA au groupe témoin, et 40 µL de carraghénane IA au groupe de carraghénane. Une heure après l'injection de carraghénane, ils ont injecté 400 µg d'acétaminophène IA au groupe d'acétaminophène IA, et 400 µg d'acétaminophène intrapéritonéal (IP) au groupe d'acétaminophène IP. La veille de l'injection, puis quatre heures et huit heures après l'injection, ils ont évalué le diamètre des deux articulations des genoux, de la motilité, de la charge des pattes et de la mobilité articulaire des rats. Une fois les rats euthanasiés, ils ont excisé les segments rachidiens L3 et L4 pour évaluer l'expression c-Fos.

RÉSULTATS : L'acétaminophène IA a réduit la gravité et la répartition de l'expression c-Fos. L'acétaminophène IP en réduisait seulement la répartition. L'acétaminophène IA avait réduit le diamètre du genou au bout de huit heures. L'acétaminophène IA et IP accroissait la motilité du rat et ses indices de charge des pattes. Les indices de mobilité conjointe de l'acétaminophène IP étaient similaires à la solution saline au bout de huit heures.

CONCLUSIONS : D'après les résultats de la présente étude, l'acétaminophène IA a un effet analgésique et peut-être anti-inflammatoire, ce qui s'ajoute aux données probantes sur l'efficacité de l'injection d'acétaminophène systémique pour réduire la douleur arthritique.

well-established safety profile in recommended doses. There is no information on the safety and efficacy of IA acetaminophen in the current literature.

c-Fos expression, at the spinal level, is one of the long-term intracellular events used as an indirect marker of nociceptive processes (5). Neuronal excitation leads to a rapid and transient induction of c-Fos (6). Once expressed, c-Fos protein acts as a transcriptional factor binding to DNA, thereby regulating the expression of nearby promoters, which in turn regulate the activation of a target gene (7). Previous studies have demonstrated that noxious stimulation of various peripheral regions, including the knee joint, evokes c-Fos expression in the dorsal horn of the spinal cord (8,9). Therefore, spinal c-Fos expression may be involved in central nociceptive processes or integration associated with inflammatory pain.

The present study was designed to assess the analgesic and/or anti-inflammatory efficacy of IA acetaminophen in an experimental carrageenan-induced arthritic rat model by means of pain-related behaviour, morphological measurement and c-Fos expression in the spinal cord. The study was also designed to differentiate the local and systemic effects of IA acetaminophen injection.

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TABLE 1
Scoring the severity and distribution of c-Fos expression in the L3–L4 medulla spinalis segments

c-Fos expression severity score	(-) = 0	No expression
	(-/+) = 1	Poor expression
	(+) = 2	Mild expression
	(++) = 3	Moderate expression
	(+++) = 4	Severe expression
c-Fos expression distribution score	Stage 0	No expression
	Stage 1	<50% of neurons and diffuse expression in grey matter
	Stage 2	>50% of neurons and local expression in grey matter
	Stage 3	>50% of neurons and diffuse expression in grey matter

METHODS

Animals

The present study was performed in accordance with a protocol approved by the University Bioethics Committee on Laboratory Animals at Hacettepe University, Ankara, Turkey. Twenty male Sprague Dawley rats (body weight 250 g to 300 g) were housed in cages (five rats to a cage) in a temperature-controlled room (22°C to 25°C). The rats were maintained in a 12 h light/12 h dark cycle (light between 08:00 and 20:00), with food and water provided ad libitum. The rats were habituated to handling before beginning the experiments.

Carrageenan model of joint inflammation

The study was performed using the model of carrageenan-induced inflammatory pain. After anesthesia induction, 2% λ -carrageenan (20 mg/mL) was injected IA into each animal's right hind knee joint, according to the modified method published previously (8,9). Pain threshold was measured one day before the experiment (baseline) and twice (4 h and 8 h) after induction of inflammation, with evaluation of articular function.

IA injections

The animals were lightly anesthetized via inhalation of sevoflurane for 2 min to 3 min in a glass chamber before each IA injection. The doses of test substances (in a volume of 40 μ L), selected on the basis of pilot studies, were administered into the right hind knee joints using 25-gauge injection needles.

Study groups

There were five rats in each group. In the control group (group 1), 40 μ L of 0.9% NaCl was injected IA and, in the carrageenan group (group 2), 40 μ L of 2% λ -carrageenan was injected IA. In the study group (group 3), 400 μ g of IA acetaminophen was injected 1 h after 40 μ L of IA 2% λ -carrageenan, and in the systemic acetaminophen group (group 4), 400 μ g of intraperitoneal (IP) acetaminophen (40 μ L) was injected 1 h after 40 μ L of IA 2% λ -carrageenan, to assess the systemic effect of 400 μ g acetaminophen.

Assessment of spinal c-Fos expression

The rats were euthanized 8 h after the carrageenan injection. Under urethane anesthesia (1.25 g/kg IP), the rats were transcardially perfused with heparinized saline (0.9%), followed by 4% paraformaldehyde in 0.1 M of phosphate buffer (pH 7.2). After the rats were euthanized, L3 and L4 spinal segments were excised to assess c-Fos expression.

Histopathological evaluation

Medulla spinalis specimens from L3–L4 were immediately frozen in liquid nitrogen and stored at -70°C until sectioned. Serial sections (6 μ m to 7 μ m) were obtained on gelatin-coated slides, dried at room temperature and stored in humidity-free boxes at room temperature for

TABLE 2
Numerical comparative scale for functional assessment of the knee joint

Motility	Lays motionless	0
	Creeps	1
	Walks with difficulty	2
	Runs and walks with difficulty	3
	Runs and walks normally	4
Paw loading	Stands only on three paws	0
	Stands on three paws, the inflamed paw is slightly bended and touches on the ground	1
	Stands slightly loading the inflamed paw	2
	Stands normally equally loading all paws	3
Joint mobility	Full immobility	0
	Limitation of flexion/extension	1
	Normal	2

one night until the immunohistochemical staining was performed. c-Fos immunoreactivity was detected using the avidin-biotin peroxidase method (Zymed Universal kit; Invitrogen, USA). Control staining was performed by omitting the primary antibody step. The immunolabelled medulla spinalis sections were examined and photographed using a Leica DM6000 digital microscope analyzing system (Leica Microsystems, Germany). The specimens were evaluated by a histologist who was blinded to the groups. Distribution of c-Fos immunoreactivity in neurons was scored on a four-point scale, and severity of c-Fos immunoreactivity was scored on a five-point scale (Table 1). The scoring system was modified from the scoring system proposed by Bagis et al (10).

Measurement of joint edema

To ensure carrageenan injection-induced arthritis and to assess joint edema, the diameters of the right and left knee joints were measured one day before and 4 h and 8 h after the carrageenan injection. The knee joint diameter was defined as the distance between the lateral and medial collateral ligament regions. This assessment procedure was performed and published earlier by Zhang et al (11).

The drug treatments and measurements were performed in a double-blinded fashion.

Functional assessment of the inflamed rat knee joint

The assessment of each rat was based on observation of the rat in a single cage, after 5 min habituation to the new conditions. The following measures of knee joint function were assessed one day before, and 4 h and 8 h after the carrageenan injection: the rat's motility and body position, paw loading and joint mobility. The assessment was performed according to the numerical scales presented in Table 2 and published earlier by Butler et al (12), with modification of the score of joint mobility.

Drugs

The drugs administered in the study were as follows: acetaminophen (Perfalgan; Bristol-Myers Squibb, France); λ -carrageenan (Sigma-Aldrich, USA); normal saline (0.9% NaCl; Biofarma, Turkey); and sevoflurane (Sevorane 240 mL; Abbott, USA).

Carrageenan was dissolved in normal saline and injected at the doses reported (in μ g per rat's knee joint).

Statistical analysis

Statistical analysis of the differences between groups was performed using a nonparametric test (Kruskal-Wallis one-way ANOVA on ranks). All significant variables, except joint diameter and rat motility, were analyzed using the Mann-Whitney U test. Joint diameter was assessed using the Freidman test, and rat motility was assessed using the Wilcoxon signed-rank test to identify the source of the significant difference. Data were presented as mean \pm SD, median and minimum-maximum score; $P < 0.05$ was considered to be statistically significant.

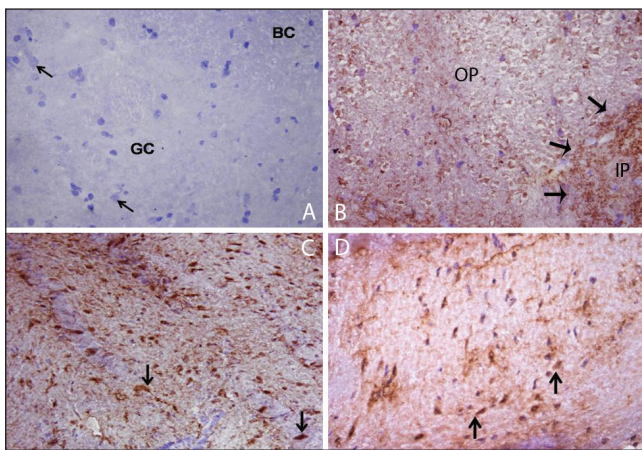


Figure 1) Histopathological assessment of c-Fos immunoreactivity. Slides were stained using the avidin-biotin peroxidase method with a c-Fos primary antibody and hematoxylin counterstain; images are original magnification $\times 400$. **A** Control group; the neurons that have normal histological appearance without immunoreactivity with glial cells (arrows) are observed in the gray matter (GC). BC White matter. **B** Carrageenan group; intense immunoreactivity in the outer part of the dorsal horn of medulla spinalis is indicated (arrows). **C** Intra-articular paracetamol group; moderate immunoreactivity in the dorsal horn is indicated (arrows). **D** Intraperitoneal paracetamol group; c-Fos-positive neurons in the gray matter are observed (arrows).

RESULTS

Histopathological findings

In group 1, gray and white matter of the medulla spinalis L3–L4 segments showed normal histological structure. In this group, neuronal c-Fos immunoreactivity was not observed (Figure 1A). In group 2, c-Fos immunoreactivity was severe, and was considered to be due to the presence of spinal nociceptive process induced by arthritic inflammation caused by the carrageenan injection. c-Fos immunoreactivity was higher in the dorsal horn and outer part of the gray matter (Figure 1B). In group 3, the distribution of c-Fos immunoreactivity was generally moderate, and was mainly observed in the dorsal horn and outer regions of the gray matter (Figure 1C). In group 4, severe c-Fos immunoreactivity was present, especially in the lateral part of the gray matter (Figure 1D). When c-Fos expression of the groups was compared with regard to severity and distribution, carrageenan injection resulted in severe c-Fos expression. IA acetaminophen decreased both the severity and distribution of c-Fos expression compared with the carrageenan group, and decreased the severity compared with the systemic acetaminophen group. Distribution of c-Fos expression also decreased in the systemic acetaminophen group compared with the carrageenan group (Table 3).

Rat knee diameters

Baseline knee diameters were similar among the groups ($P > 0.05$). In group 1, knee diameter measurements at 4 h and 8 h were similar, indicating no inflammation. In groups 2, 3 and 4, the knee diameter measurements increased after carrageenan injection, indicating joint inflammation ($P < 0.05$). At 8 h, a decrease in knee diameter was detected in group 3. The rats' knee diameter measurements are presented in Table 4.

Functional assessment of rats' knee joints

The rats' motility, paw loading and joint mobility scores for all groups at 4 h and 8 h are presented in Table 5. When the functional assessment scores of the groups were compared, regarding motility, paw loading and joint mobility, there were not any limitations in knee joint functionality after normal saline injection (group 1) at both the 4 h and 8 h assessments. Carrageenan injection (group 2) resulted in similar severe

TABLE 3
Severity and distribution of c-Fos expression

c-Fos expression	Group 1	Group 2	Group 3	Group 4
Severity	0* (0–0)	4.0† (4–4)	3.0 (3–3)	4.0† (4–4)
Distribution	0* (0–0)	3.0† (3–3)	2.0 (2–2)	2.0‡ (2–2)

Data presented as median (minimum–maximum); $n=5$ per group. * $P=0.008$ compared with other groups; † $P=0.008$ compared with group 3; ‡ $P=0.016$ compared with group 2. Group 1 Intra-articular (IA) saline; Group 2 IA carrageenan; Group 3 IA carrageenan + IA paracetamol; Group 4 IA carrageenan + intraperitoneal paracetamol

TABLE 4
Rats' knee diameter measurements

Timepoint	Group 1	Group 2	Group 3	Group 4
Baseline	1.94±0.054, 1.9	1.95±0.109, 2.0	1.96±0.054, 2.0	1.96±0.089, 1.9
4 h	1.96±0.54*, 2.0	2.52±0.148, 2.5	2.36±0.54, 2.4	2.42±0.83, 2.4
8 h	1.98±0.44*, 2.0	2.56±0.114, 2.6	2.34±0.54†, 2.3	2.40±0.10, 2.4

Data presented as mean \pm SD, median; $n=5$ per group * $P=0.008$ compared with other groups, † $P=0.008$ compared with group 2. Group 1 Intra-articular (IA) saline; Group 2 IA carrageenan; Group 3 IA carrageenan + IA paracetamol; Group 4 IA carrageenan + intraperitoneal paracetamol

limitations in motility, paw loading and joint mobility at both 4 h and 8 h. IA acetaminophen (group 3) and IP acetaminophen (group 4) increased rat motility and paw loading scores at 4 h compared with the carrageenan group (group 2), while the joint mobility scores were similar.

At 8 h, IA acetaminophen (group 3) and IP acetaminophen (group 4) motility and paw loading scores were higher than those of the carrageenan group (group 2). When joint mobility scores were assessed, IA acetaminophen (group 3) was similar to carrageenan injection (group 2), and IP acetaminophen (group 4) was similar to the control group (group 1).

In the study group, with the second injection into the joint 1 h after carrageenan injection, some of the apparent effects of IA acetaminophen may have been due to a dilution effect. The second injection simply may have diluted out some of the carrageenan. In this case, the change in c-Fos and functional end points may simply be reflecting a lower dose of carrageenan. In view of the lack of a volume control group for this experiment, the present study should be evaluated as a pilot study.

DISCUSSION

The results regarding spinal cord c-Fos expression and functional assessment of the present rat model indicate an analgesic and/or possible anti-inflammatory effect of IA acetaminophen, and provide evidence of the efficacy of low-dose systemic acetaminophen injection in reducing arthritic pain.

IA injection of acetaminophen after carrageenan-induced arthritis resulted in better histopathological results than IP injection. Our results, however, showed similar beneficial results at 4 h and 8 h with both IA and systemic acetaminophen.

OA is the most common form of arthritis, and can affect joints in different parts of the body. The main clinical problems in OA are pain and swelling due to a breakdown of the cartilage that protects the ends of the bones. There are two main types of drug treatment used as first-line therapy in OA: acetaminophen, which is used to relieve pain but does not affect swelling; and NSAIDs, such as ibuprofen, diclofenac and cyclooxygenase-2 inhibitors (celecoxib), which are used to decrease both pain and swelling (13). In a meta-analysis, Towheed et al (13) reviewed 15 randomized controlled trials in which the efficacy and

TABLE 5
Functional assessment of rat knee joints

Timepoint	Functionality	Group 1	Group 2	Group 3	Group 4
4 h	Motility	4 (4–4)*	2 (2–2)†	3 (3–4)	3 (2–3)
	Paw loading	3 (3–3)*	1 (1–1) †	2 (2–2)	2 (2–2)
	Joint mobility	2 (2–2)*	1 (1–1)	1 (1–2)	1 (1–1)
8 h	Motility	4 (4–4)*	2 (2–2)†	3 (2–3)	3 (2–4)
	Paw loading	3 (3–3)*	1 (1–1)†	2 (2–3)	2 (1–3)
	Joint mobility	2 (2–2)‡	1 (1–1)	1 (1–2)	2 (1–2)

Data presented as median (minimum–maximum); n=5 per group. *P<0.05 compared with other groups; †P<0.05 compared with groups 3 and 4; ‡P<0.05 compared with groups 2 and 3. Group 1 Intra-articular (IA) saline; Group 2 IA carrageenan; Group 3 IA carrageenan + IA paracetamol; Group 4 IA carrageenan + intraperitoneal paracetamol

safety of acetaminophen was assessed versus placebo and NSAIDs. The authors concluded that NSAIDs appear to be more effective than acetaminophen in OA subjects with moderate-to-severe levels of pain. Contrary to the conclusions of Towheed et al (13), in the present study, both IA and IP acetaminophen injection decreased the knee diameter, which may be attributed to an anti-inflammatory process. Although there are some previous trials that showed anti-inflammatory action of acetaminophen in animals and inflamed dental tissue (8,14,15), acetaminophen is generally not considered to elicit very effective anti-inflammatory action in the clinical setting (14–18). We believe that there is a need for further investigations to assess the possible anti-inflammatory properties of IA acetaminophen.

Despite its widespread use in various clinical conditions, the mechanism of the analgesic action of acetaminophen is still poorly defined. There is still controversy regarding whether acetaminophen acts peripherally and/or centrally (19). Potential mechanisms include an inhibition of prostaglandin synthesis (20), interaction with the endogenous opioid pathway and modulation of the serotonergic bulbospinal pathway (21), involvement of the nitric oxide pathway, and an increase in cannabinoid/vanilloid tone (22). Mallet et al (23) showed that pharmacological activation of TRPV1 in the midbrain periaqueductal gray matter elicits antinociception in rats. Therefore, it is possible that activation of TRPV1 in the brain contributes to the analgesic effect of acetaminophen (23). Dani et al (24) investigated the peripheral antiallostatic and antihyperalgesic effects of acetaminophen administered locally in a neuropathic pain model in the rat, and concluded that acetaminophen has peripheral antiallostatic and antihyperalgesic effects that are mediated by cannabinoid CB1 and CB2 receptors (24). In the present study, we did not aim to investigate the mechanism of the action of acetaminophen; therefore, we did not speculate on the probable mechanism of the analgesic and/or anti-inflammatory effects of IA acetaminophen.

c-Fos is a nuclear protein that is involved in the signal transduction cascade that links extracellular events to long-term intracellular adaptations. After the report by Hunt et al (25), which explained the expression of the c-Fos gene in the spinal cord of rats after a peripheral noxious stimulation, there have been studies showing that various types of noxious stimulation induce expression of c-Fos in the brain and spinal cord. There are numerous advantages of using c-Fos expression as a neural marker of nociception such as the convenience of both identifying the precise localization of neuronal populations that respond to noxious stimulation and quantitative analysis by counting the number of neurons immunoreactively labelled for c-Fos messenger RNA using in situ hybridization (26). When the c-Fos immunoreactivity results of our study were assessed, IA acetaminophen administration appeared to be more efficient when compared with the IP route in terms of analgesic efficiency. However, this finding is not supported by our observations.

Although acetaminophen can be administered via oral, rectal and intravenous routes, it is not licensed for IA use in humans, despite the absence of any reports in the literature indicating that it has toxic effects on joint structures. There is scarce information on the safety of IA acetaminophen. Bilimgut et al (27) investigated the histopathological effects of IA acetaminophen injection in the knee joint of rats, and showed that IA acetaminophen injection did not have any deleterious effects on the synovia or cartilage. We are of the opinion that

further animal research is warranted before human studies are conducted.

The dose of acetaminophen (1.3 mg/kg to 1.6 mg/kg) used in the present study, when compared with the known effective analgesic IP acetaminophen dose range (50 mg/kg to 400 mg/kg), is relatively low. The analgesic effectiveness of systemic acetaminophen in arthritic pain is well known in both human and animal research (28,29). Instead of creating a study group with the above doses, which will result in a predictable outcome, a systemic acetaminophen group with a dose similar to the IA injection was selected to rule out any systemic effect of IA acetaminophen injection. A rapid transfer of IA-injected drugs from synovial fluid to plasma is possible, resulting in plasma levels sufficient to produce centrally mediated effects such as analgesia (30). Although the rate of systemic absorption of IA acetaminophen injected through inflamed joints is unknown, we assume that a considerable portion of the IA drug may have reached the plasma. Compared with the local effects, the small systemic dose was found to be partially effective in terms of analgesia and attenuation of c-Fos activity. This finding leads us to consider that the effectiveness of IA acetaminophen may be partially attributed to central analgesic effects.

The lack of a second IA injection to the saline, carrageenan and IP acetaminophen groups, as was administered to the IA acetaminophen group, may be considered a limitation of the present study. The IA injection of acetaminophen may have caused a second trauma or a dilution of carrageenan, which may have affected the group results. Furthermore, the two treatment groups did not have any sham groups. The stress of handling and performing a manipulation following introduction of carrageenan into the joint 1 h earlier may well be significant.

CONCLUSION

In this experimental rat model, we made the intriguing novel observation that both IA and low-dose IP administration of acetaminophen may have anti-inflammatory and/or analgesic effects on arthritic pain induced by carrageenan injection. There is a need for further clinical and experimental investigations regarding the efficacy of IA acetaminophen before application in humans.

SUMMARY

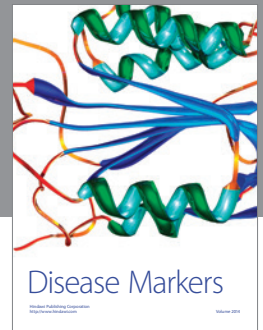
We examined the effects of IA acetaminophen on carrageenan-induced arthritic pain-related behaviour and spinal c-Fos expression in rats. IA acetaminophen decreased both the severity and distribution of c-Fos expression. IP acetaminophen only decreased distribution of c-Fos expression. IA acetaminophen decreased knee diameter at 8 h. IA and IP acetaminophen increased rat motility and paw loading scores. Joint mobility scores of IP acetaminophen were similar to saline at 8 h. Results indicate an analgesic and/or possible anti-inflammatory effect of IA acetaminophen, and provide further evidence regarding the efficacy of systemic acetaminophen injection in reducing arthritic pain.

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