



Evaluation of Antinociceptive Efficacy of pre versus post-incisional Morphine, Tramadol or Meloxicam in Rats

Mehrzaad Foroud and Nasser Vesal*

Abstract

Objective- To evaluate antinociceptive efficacy of pre- versus post-incisional morphine, tramadol and meloxicam using tail-flick test in an incisional model of pain in rats.

Design- Prospective, randomized experimental study.

Animals- Eighty, adult, male Wistar rats weighing 250–300 g.

Procedures- Animals were randomly divided into eight groups to receive pre- or post-incisional (tail skin incision) saline (1 mL/kg, IP), morphine (4 mg/kg, IP), tramadol (12.5 mg/kg, IP), or meloxicam (1 mg/kg, IP). Antinociceptive effect of drugs was assessed using tail-flick latency (TFL) test following exposure to radiant heat.

Results- Morphine injection before or after incision prevented hyperalgesia for 120 minutes, while pre- or post-incisional administration of tramadol prevented hyperalgesia for 90 and 120 minutes, respectively. There was no significant difference between pre- or post-incisional administration of morphine or tramadol. Meloxicam, given either before or after skin incision, did not prevent hyperalgesia as compared with saline control group.

Conclusion and Clinical Relevance- The timing of treatment had no significant effects on post-operative nociception. Both morphine and tramadol were effective in reducing post-operative hyperalgesia and can be used for the control of early postoperative nociception in rats.

Key Words- Tail flick, Morphine, Tramadol, Meloxicam, Rat.

Introduction

Recent studies have focused on the effects of peripheral tissue damage on central sensitization and hyperalgesia. It has been suggested that surgical trauma may lead to altered central processing of afferent input, resulting in amplification and prolongation of postoperative pain.^{1,2} In experimental studies, the intensity of postoperative pain may be reduced if afferent transmission of nociceptive signals to the CNS is prevented by preoperative administration of analgesic drugs.^{3,4} Consequently, it has been suggested that "preoperative analgesia" may be superior to analgesic treatment initiated after surgery because of reduced sensitization of the central nervous system, and subsequently reduced post-operative analgesic requirements.⁵ Morphine is the prototypical opioid analgesic and acts as a full agonist at μ , δ and κ receptors.

It is effective for mild to severely painful conditions in many species including laboratory animals.⁶ Tramadol HCl is a synthetic opioid analgesic with a relatively weak affinity at opioid receptors. The drug and its metabolite, O-desmethyl- tramadol (M1), cause analgesia by activating μ -opioid receptors and inhibiting serotonin and norepinephrine reuptake in the CNS.^{6,7} Meloxicam is a potent non-steroidal anti-inflammatory drug (NSAID) that reduces inflammatory pain by the inhibition of prostaglandin synthesis, which is a precursor to mediators that elicit pain and inflammation. Meloxicam preferentially inhibit cyclooxygenase-2 (COX-2).^{6,8}

The aim of this study was to compare the effects of intraperitoneal (IP) drug administration (morphine, tramadol or meloxicam) either before or after skin incision on tail-flick latency test. We hypothesized that IP administration of single doses of morphine, tramadol or meloxicam would prevent incision-induced hyperalgesia in rats and pre-incisional drug administration provides a better quality of antinociception.

Department of Veterinary Clinical Studies, School of Veterinary Medicine, Shiraz University, Shiraz, Iran.
Address all correspondence to Dr. Nasser Vesal (DVM, MVSc)
E-mail: nv1340@shirazu.ac.ir

Materials and Methods

Animals

Eighty male 250–300 g Wistar rats were used in a blinded, randomized study. Rats were housed in a temperature (21–22 °C) and light (12 hours light: 12 hours dark) controlled environment. Standard laboratory pellet food and tap water were available ad libitum throughout the study. This experimental study was approved by the Institutional Animal Care and Use Committee.

Procedure

Rats were randomly assigned to 1 of 8 groups (10 rats/group) for IP administration of the following drugs before or after tail skin incision: saline (control group, 1 mL/kg), morphine (Darou Pakhsh, Tehran, Iran) (4 mg/kg), tramadol (Tehran Chemie Pharmaceutical Co., Tehran, Iran) (12.5 mg/kg), or meloxicam (Metacam, Boehringer-Ingelheim Vetmedica GmbH, Germany) (1 mg/kg) (Table 1). All drugs were diluted with sterile saline and a final volume of 1 mL/kg was administered IP into the right caudal abdominal quadrant in each rat. Identical coded 1 mL syringes were prepared by a person not involved in the study. Each rat received only one treatment.

All rats were anesthetized with 4% isoflurane (Nicolas Piramal, London, UK) in 100% oxygen (2 L/minute) using an anesthetic induction chamber container (15 × 10 × 15 cm) until the rats had lost their righting reflex. Following induction, the rat was removed from the induction chamber, placed in sternal recumbency and anesthesia was maintained by 2% Isoflurane in oxygen (2 L/minute) through an appropriate nose cone. In all groups, except anesthesia control group, a 10 mm longitudinal incision was made through skin and fascia on the dorsal surface of the tail starting 5 cm from the tip. The surgical site was aseptically prepared by using povidone-iodine solution and alcohol before surgery. The incision was sutured with 4-0 nylon in a simple interrupted pattern. Isoflurane was discontinued and the rats were allowed to recover in their cages for 15 minutes after surgery. Drugs or saline injection was performed before anesthesia induction (Time 0) and at 30 minutes after first injection (Time 30). In anesthesia control group, skin incision was not performed but all other procedures were identical to other groups (Fig 1). Antinociception was assessed by the tail-flick latency (TFL) test using an analgesiometer (Borj Sanat; Tehran, Iran). TFLs were measured as the time between tail exposure to radiant heat and tail withdrawal. An intensity setting of 25 on a scale of 1–100 and a cut-off time of 15 seconds (to prevent tissue damage) was used throughout the study. The radiant intensity was adjusted to give a baseline TFL of 4–6 seconds and animals with a baseline TFL below 4 or above 6 seconds were

excluded. The mean baseline latency of two measurements was obtained before the first injection for each rat. Determinations of TFL was performed at 45 (15 min after the second injection), 60, 75, 90 and 120 minutes after first injection. The mean of two consecutive readings with an interval of 1 minute was recorded as the TFL value at the mentioned time points. In order to test for hyperalgesia, the TFL was determined at the site of incision and at 15 mm distal to the incision site (Fig 2). The same investigator assessed the TFL in all groups and was unaware of the treatment given.

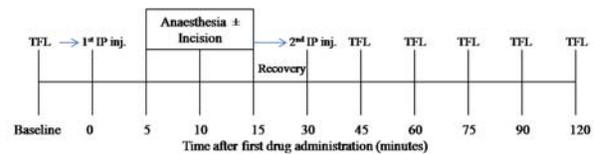


Figure 1- Experimental design employed to investigate the effect of pre- versus post-incisional administration of analgesics (refer to Materials and methods for details). TFL= tail-flick latency; 1st IP injection= first intraperitoneal drug or saline injection (Time 0); 2nd IP injection; second intraperitoneal drug or saline injection (Time 30).

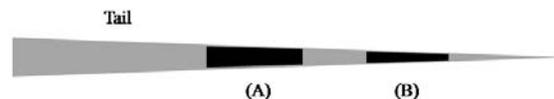


Figure 2- Diagram of the dorsal aspect of the rat tail showing sites of application of radiant heat: (A) incision site and (B) distal to the incision site.

Data and statistical analysis

Antinociception was evaluated by two different methods: (a) the means of TFLs; and (b) the percentage of maximum possible effect (% MPE). The % MPE was calculated using the following formula:

$$\% \text{ MPE} = \frac{[(\text{post-drug TFL} - \text{baseline TFL}) / (15 \text{ seconds} - \text{baseline TFL})] \times 100}{}$$

For comparing the mean of TFL within each group, one-way analysis of variance (ANOVA) for repeated measures with the pairwise comparisons of Bonferroni was used. Differences in mean of MPE among the groups were analyzed by two-way analysis of variance (ANOVA) for repeated measures with time and drug as the main factors followed by Bonferroni multiple comparison. One-way analysis of variance (ANOVA) with post hoc Tukey test was used to compare the average of TFL values (45–120 time points) between the groups. The program used to perform the statistical procedures was GRAPH PAD PRISM version 5.0 (GRAPH PAD software Inc., CA, USA). A p value of less than 0.05 was considered statistically significant. All data are presented as mean ± SD.

Results

Effect of anesthesia and surgery on TFL time

The baseline TFL was not different between anesthesia alone (Anesthesia control =A-C) (4.92 ± 0.41 seconds) and surgery (saline control) (4.77 ± 0.44 seconds) groups ($p \geq 0.05$). Isoflurane anesthesia alone did not induce any significant changes in the TFL over the 45-120 minute observational period (TFL, 4.92 ± 0.41 vs. 5.3 ± 1.0 seconds). In saline control group, TFL on the site of incision (site A) significantly decreased throughout the observational time (45-120 minutes) as compared with baseline ($p \leq 0.01$); whereas, TFL at distal to the incision site (site B) was not significantly different at any time points from the baseline values ($p \geq 0.05$) (Fig 3). Since there was no change in the TFL at distal to the incision site, only TFL values at the incision site is presented and compared in the treatment groups.

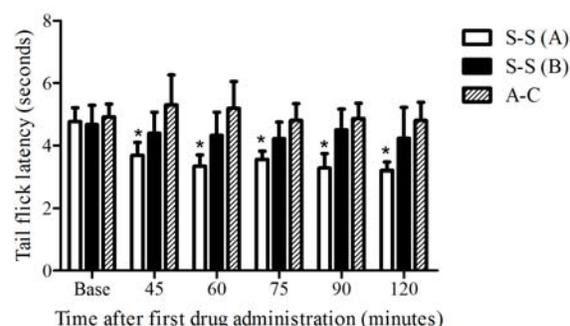


Figure 3- Changes in tail flick latency (mean \pm SD) following anesthesia alone (Anesthesia control =A-C) and surgery (saline control group) (A = the site of incision; B = distal to the incision). *Significant difference ($p < 0.05$) as compared with baseline values.

Effect of analgesic drugs on TFL time

There was no significant difference in the baseline TFL time between treatment groups and surgery control group. Mean TFL had no significant differences at any time points with the baseline values in rats received either pre- or post-incisional morphine and hyperalgesia was prevented in both groups throughout the study period (Fig 4). The TFLs of rats receiving IP morphine

peaked at 45 and 60 minutes and declined afterwards. Both pre- and post-incisional morphine groups had significantly higher MPE at 45 and 60 minutes compared with saline control group ($p < 0.01$). No significant differences in the mean MPE were observed between pre- and post-incisional morphine groups (MO-S and S-MO groups) at any time points (Fig 5). The averaged TFL (45-120 time point) values in S-MO (8.0 ± 3.8) and MO-S (7.0 ± 4.0 sec) groups were significantly higher compared with control group (3.4 ± 0.4 sec) ($p < 0.001$).

Pre-incisional administration of tramadol prevented hyperalgesia for the first 90 minutes of study, but the mean TFL was significantly lower than the baseline values at 120 minutes ($p = 0.02$). Following post-incisional administration of tramadol TFL did not show any statistical difference from the baseline value at any time point and hyperalgesia was prevented over the entire study period (i.e., 120 minutes) (Fig 6). The MPE was significantly higher than the saline control group at 45 and 60 minutes in pre-incisional tramadol group ($p < 0.001$) and at 45, 60 and 75 minutes in post-incisional tramadol group ($p < 0.05$). Although not statistically significant, rats receiving pre-incisional tramadol tended to reach their peak effects earlier (at 45 minutes). There was no significant difference in the mean MPE between pre- and post-incisional tramadol groups (T-S and S-T groups) at any time points (Fig 7). The averaged TFL (45-120 time point) values in S-T (5.8 ± 2.2 sec) and T-S (6.1 ± 3.1 sec) groups were significantly higher compared to control group (3.4 ± 0.4 sec) ($p < 0.001$).

Similar to saline control group, TFL significantly decreased in rats receiving pre- or post-incisional IP meloxicam at all time points, as compared to baseline values (Fig 8). There were no significant differences in MPE among the groups at any time points ($p > 0.05$) (Fig 9). Therefore, pre- or post-incisional IP administration of meloxicam, at the dose of 1 mg/kg, did not prevent reduction in TFLs following tail skin incision as compared to saline control group. Three rats in MO-S group (at 45 and 60 minutes), one rat in S-MO group (45-120 minutes) and one rat in T-S group (at 45 and 60 minutes) reached their maximum possible antinociceptive effects (cut off time of 15 seconds).

Table 1- Experimental groups

Treatment groups	Pre-incisional drug	Tail skin incision	Post-incisional drug
Anesthesia control (A-C)	Saline	-	Saline
Saline (surgery) control (S-S)	Saline	+	Saline
Morphine post-incisional (S-MO)	Saline	+	Morphine
Morphine pre-incisional (MO-S)	Morphine	+	Saline
Tramadol post-incisional (S-T)	Saline	+	Tramadol
Tramadol pre-incisional (T-S)	Tramadol	+	Saline
Meloxicam post-incisional (S-ML)	Saline	+	Meloxicam
Meloxicam preemptive (ML-S)	Meloxicam	+	Saline

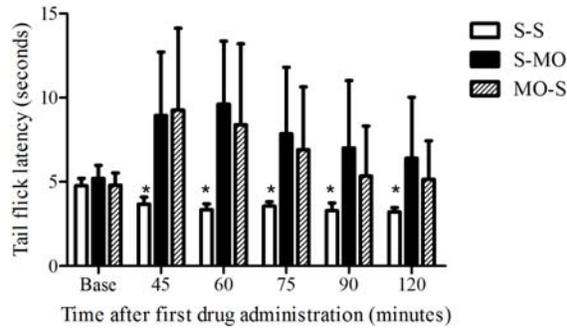


Figure 4- Effects of pre- or post-incisional IP administration of morphine (4 mg/kg) on tail-flick latency (TFL, mean ± SD) in rats.* Significant difference (p<0.05) compared with baseline. S-S= saline control group; MO-S= pre-incisional morphine; S-MO = post-incisional morphine.

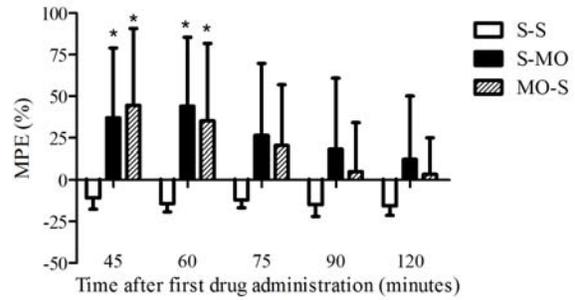


Figure 5- Effects of pre- or post-incisional IP administration of morphine (4 mg/kg) on tail-flick latency (TFL) in rats. Tail-flick latency (mean ± SD) expressed as percent maximum possible effect (MPE%).* Significant difference (p<0.05) compared with saline control group. S-S= saline control group; MO-S= pre-incisional morphine; S-MO = post-incisional morphine.

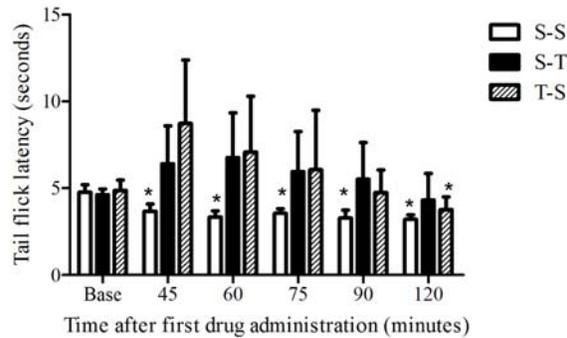


Figure 6- Effects of pre- or post-incisional IP administration of tramadol (12.5 mg/kg) on tail-flick latency (TFL, mean ± SD) in rats.* Significant difference (p<0.05) compared with baseline. S-S= saline control group; T-S= pre-incisional tramadol; S-T = post-incisional tramadol.

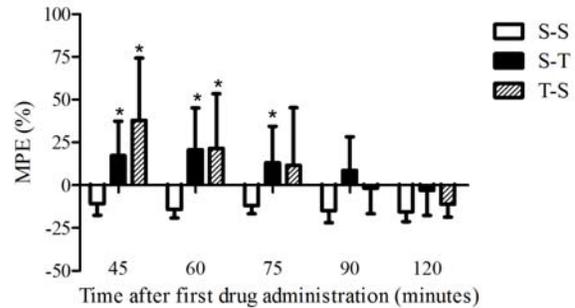


Figure 7- Effects of pre- or post-incisional IP administration of tramadol (12.5 mg/kg) on tail-flick latency (TFL) in rats. Tail-flick latency (mean ± SD) expressed as percent maximum possible effect (MPE%).* Significant difference (p<0.05) compared with saline control group. S-S= saline control group; T-S= pre-incisional tramadol; S-T = post-incisional tramadol.

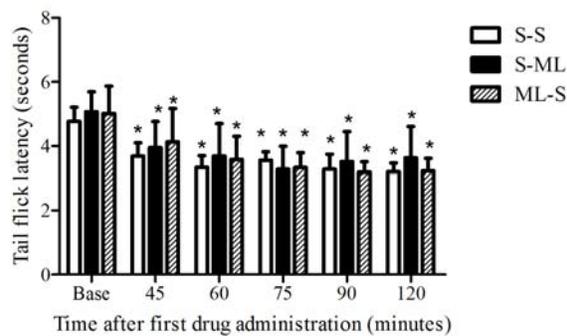


Figure 8- Effects of pre- or post-incisional IP administration of meloxicam (1 mg/kg) on tail-flick latency (TFL, mean ± SD) in rats. * Significant difference (p<0.05) compared with baseline. S-S= saline control group; ML-S= pre-incisional meloxicam; S-ML = post-incisional meloxicam

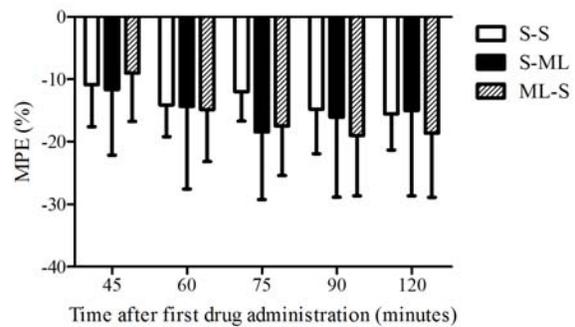


Figure 9- Effects of pre- or post-incisional IP administration of meloxicam (1 mg/kg) on tail-flick latency (TFL) in rats. Tail-flick latency (mean ± SD) expressed as percent maximum possible effect (MPE%).* Significant difference (p<0.05) compared with saline control group. S-S= saline control group; ML-S= pre-incisional meloxicam; S-ML = post-incisional meloxicam.

Discussion

In the present study, the antinociceptive effects of single-dose IP administration of morphine, tramadol and meloxicam, initiated before or immediately after surgery, on postoperative pain after tail skin incision have been evaluated. The results showed that pre or post-incisional morphine or tramadol prevents injury-induced hyperalgesia in rats, but no significant difference in TFL values were observed between pre- or post-incisional administration of morphine or tramadol. Incisional model of pain has been frequently used in laboratory animals in order to mimic postoperative pain.⁹⁻¹² In the present study, antinociception was assessed in an incisional model of pain by the tail-flick test. This test provides an objective, quantifiable and consistent measure of pain and has been used for assessing analgesic activity of drugs. The tail-flick test determines drug-induced changes in the reaction time of animals exposed to heat.¹³⁻¹⁵

Isoflurane anesthesia, tail skin incision and dosage of analgesic drugs were identical for all treatment groups. The doses were selected based on currently used doses of morphine,^{14,16,17} tramadol¹⁸ and meloxicam¹ in the rats. An anesthesia control group was incorporated to rule out any possible effect on TFL, which may be attributable to muscle relaxant or antinociceptive effect of isoflurane. Isoflurane, as an inhalation anesthetic agent, produces some muscle relaxation but has no analgesic effect.¹⁹ Weber et al. found that halothane anesthesia has no significant effects on thermal and mechanical tail withdrawal latencies in rats.²⁰

In surgery control group, tail-flick latencies at the incision site were significantly below baseline levels in rats undergoing skin tail incision throughout the study period. Hyperalgesia was observed as early as 30 minutes after skin incision. Primary mechanical and thermal hyperalgesia has also been demonstrated following plantar incision in mice.¹¹ In an incisional model of pain in rats, thermal hyperalgesia lasted for 4 days after surgical incision on hind paw.¹⁰ Weber et al. reported the development of mechanical, but not thermal, hyperalgesia following tail incision in rats.²⁰ It is likely that the method of noxious thermal challenge (immersion of the tail in hot water vs. a focused radiant heat source) is responsible for the differences observed. Hindpaw thermal hyperalgesia has been reported following the formalin injection in the rat tail.^{21,22}

The tail skin incision did not induce any change in TFL at distal to the incision site in the present study. The development of secondary mechanical hyperalgesia has occurred in a model of incisional pain using the tail of the rat.²⁰ It has been reported that the formalin injection in the tail induces a significant reduction of hindpaw (hyperalgesia), but not forepaw, withdrawal latencies in rats.²¹ Secondary thermal hyperalgesia did not occur following surgical incision on hind paw when the

radiant heat applied to the contralateral paw in rat.¹⁰ It has been suggested that the mechanism for secondary hyperalgesia to mechanical and thermal stimuli may be different and hyperalgesia to mechanical stimuli may occur in the absence of hyperalgesia to thermal stimuli.²³ However, Welsh & Nolan reported the presence of secondary hyperalgesia to heat stimuli, but not to mechanical stimuli, after abdominal surgery in sheep.²⁴ The failure of skin incision to induce thermal hyperalgesia at distal to the incision site may also be due to insufficient activation of nociceptive neurons required to induce sensitization.^{9,25} It has been shown that a longer and deeper tail skin incision produces more intense post-incisional hyperalgesia in rats.²⁰

Incision-induced hyperalgesia was prevented by both morphine and tramadol administered before or after incision. In post-incision drug administration groups, the maximal effect was observed within 15 minutes, suggesting a rapid systemic absorption after IP administration. Intraperitoneal administration of morphine (5 mg/kg) and tramadol (25 mg/kg) reduced the sevoflurane minimum alveolar concentration (MAC) in the rat by 30 and 38% for a mean duration of 63 and 67 minutes, respectively.²⁶ In the present study, the duration of action of a single dose of morphine or tramadol was 1.5-2 hours.

It has been shown that subcutaneous morphine prevents incision-induced mechanical hyperalgesia in rats.¹² Gades et al. found that morphine (10 mg/kg, SC) provides analgesia of 2 hours duration in rats as measured by tail flick test.¹³ Systemic morphine effectively prevented incision-induced primary mechanical and thermal hyperalgesia in mice.¹¹

Tramadol effectively prevents hindpaw hyperalgesia following the formalin injection in the tail when administered before or after formalin injection.²² Analgesic and antihyperalgesic effect of tramadol have been reported previously in rats.^{18,22,27} Increased TFL following IP administration of 12.5 mg/kg tramadol have also been reported in the rat.¹⁸ However, the results of another study indicated that tramadol reversed neither heat hyperalgesia nor decreased mechanical weight bearing in rats following paw incision.¹⁰ In the present study, post-incisional tramadol tended to provide longer antinociception. This result may be due to the fact that there has been a 30 minute interval between pre- and post-incisional drug administration.

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used as analgesics in laboratory animals. In the present study, pre- or post-incisional administration of meloxicam (1 mg/kg, IP) did not produce a significant change in TFL from saline control group over the 45–120 minute study period. Santos et al. found that intravenous meloxicam (1-3 mg/kg) neither reduces isoflurane MAC nor potentiates the morphine-induced decrease of isoflurane MAC in the rat.²⁸ Dose-dependent antinociceptive activities of systemic

administration of NSAIDs have been shown in tail flick test in mice and rats.^{14,29} Meloxicam (13 mg/kg, IP) has showed antinociceptive activity in tail flick test in mice.³⁰ A previous study in rat found that a high dose of meloxicam (5.8 mg/kg, IP) was not fully effective for prevention of thermal hind paw hyperalgesia following formalin injection in tail.³¹ However, meloxicam, at a dose of 1 mg/kg, attenuated post-operative pain following laparotomy or thoracotomy in rats.^{1,32} Another study has demonstrated that local, but not systemic, administration of NSAIDs induced antinociception as evaluated by the tail-flick latency test in mice.³³ It has been reported that incision-induced mechanical hyperalgesia can be reversed by oral administration of different NSAIDs, including indomethacin, celecoxib, etoricoxib and naproxen, in a rat model of post-incisional pain.³⁴

The antinociceptive activities of non-steroidal anti-inflammatory drugs (NSAIDs) are mediated, at least in part, by inhibition of the cyclooxygenase (COX) enzymes, thus blocking the synthesis of prostaglandins at the peripheral site of tissue injury. Administration of NSAIDs is always more effective when inflammation is expected. The histopathological examination revealed that only a mild inflammatory reaction is present two hours after tail incision, while moderate to severe inflammation occurred 24 hours and 8 days after incision, respectively.²⁰ In the present study, TFLs were evaluated for 2 hours after the first injection, because TFL times had returned to baseline values in all groups. In the present study, there was no significant difference in the TFL values between pre- and post-incisional administration of morphine or tramadol groups. Subcutaneous administration of morphine (5 mg/kg) before or immediately after surgery provided similar short lasting postoperative analgesia in rats.¹⁷ It has been shown that pre-incisional morphine (5 mg/kg IP) did not significantly increase paw withdrawal latency in a model of postoperative incisional pain in rats, while morphine was effective when given postoperatively.³⁵ Repeated administration of morphine starting before surgery has been shown to attenuate behavioral signs of pain more effectively than provision of pain relief post-operatively in rats undergoing ovariectomy.²⁵

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Reichert et al reported that the dose of morphine required to inhibit writhing when given before injection of acetic acid was approximately one-tenth of that required after acetic acid injection in a mouse visceral pain model.³⁶ Pretreatment with paracetamol (acetaminophen) blocked hind paw hyperalgesia following the formalin injection in the tail, while paracetamol was ineffective when administered after the formalin injection.²¹ Prado & Pontes found that pre-incisional ketoprofen, but not morphine, provides a more effective reduction in postoperative pain when compared to post-incisional administration in rats.¹⁶ A single dose preoperative analgesic administration may adequately control immediate post-operative pain responses. However, the efficacy of preoperative analgesia depends on adequate and occasionally prolonged postoperative pain control to prevent central sensitization to pain. A balanced, multimodal approach may be necessary for providing optimal analgesia for surgical patients throughout the peri-operative (pre-operative, intra-operative and post-operative) period.⁵ Our observations indicate that the rat model of incision-induced pain could be a reliable, useful tool to investigate the antinociceptive effects of commonly used analgesic drugs. TFL measurements showed that both morphine and tramadol were efficient at controlling thermal hyperalgesia after tail skin incision. Meloxicam, at the dose given, was not effective in preventing thermal hyperalgesia in male Wistar rats. We suggest that future studies should investigate the role of timing of preoperative multiple-dose analgesic treatment on the long-term postoperative nociceptive pattern.

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چکیده

ارزیابی اثر ضددردی تجویز پیش از برش در مقابل تجویز پس از برش جراحی مرفین، ترامادول و ملوکسیکام در موش صحرائی

مهرزاد فرود، ناصر وصال*

گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه شیراز، شیراز، ایران

هدف- بررسی اثر ضددردی تجویز پیش از برش مرفین، ترامادول و ملوکسیکام در مقابل تجویز پس از جراحی آنها توسط آزمون تکان دم در موش صحرائی

طرح- مطالعه تجربی آینده‌نگر

حیوانات- تعداد ۸۰ قطعه موش صحرائی نر نژاد ویستار با وزن ۲۵۰-۳۰۰ گرم

روش کار- حیوانات به صورت تصادفی در ۸ گروه جهت دریافت پیش یا پس از برش سالیین، مرفین، ترامادول و یا ملوکسیکام قرار گرفتند. یک برش جراحی در ناحیه دم ایجاد و درک درد توسط آزمون تکان دم مورد بررسی قرار گرفت. در پایان زمان تاخیری تکان دم بین تجویز پیش و پس از برش مقایسه شد.

نتایج- تزریق پیش یا پس از جراحی مرفین برای مدت ۱۲۰ دقیقه منجر به مهار هایپرآلجزیای ناشی از برش شد. تزریق پیش از برش ترامادول برای ۹۰ دقیقه و پس از برش آن برای ۱۲۰ دقیقه هایپرآلجزیای را مهار کردند. تفاوت معنی‌داری بین تجویز پیش و پس از برش مرفین و یا ترامادول مشاهده نشد. تجویز پیش و یا پس از برش ملوکسیکام منجر به مهار هایپرآلجزیای نشد.

نتیجه‌گیری و کاربرد بالینی- زمان تجویز داروی ضد درد تأثیری بر میزان درک درد پس از جراحی نداشت. مرفین و ملوکسیکام به طور موثری باعث کاهش هایپرآلجزیای بعد از جراحی شدند و تزریق داخل صفاقی این دو دارو می‌تواند در مقابله با درد حاد جراحی در موش صحرائی استفاده شود. در حالیکه ملوکسیکام با دوز مورد استفاده در این مطالعه فاقد هر گونه اثر ضد هایپرآلجزیای در آزمون تکان دم است.

کلمات کلیدی- آزمون تکان دم، مرفین، ترامادول، ملوکسیکام، موش صحرائی.