

تاریخ: ۸/۵/۹۱
شماره:
۲۷۵/مبیا



به نام خداوند جان و خرد

همکار ارجمند

با اهدای سلام،

با کمال خوشوقتی دو شماره جدید مجله جراحی دامپزشکی ایران، که در قالب یک جلد منتشر شده است، (Vol.4, No.1 & 2, Serial No. 10 & 11 2009) خدمت شما تقدیم می شود. به استحضار می رساند که از شماره جاری این مجله به صورت دو شماره در سال منتشر خواهد گردید. ضمناً جهت رفع هرگونه ابهام، تاریخ چاپ این دو شماره بهار ۱۳۹۱ اعلام می گردد.

به امید دریافت مقالات ارزشمند شما همکار محترم

سردبیر مجله جراحی دامپزشکی ایران
پروفسور ایرج نوروزیان

Analgesic Effects of Metoclopramide Following Conventional Ovariohysterectomy in Bitches

Azin Tavakoli^{*1}, DVM, DVSc
Hossein Kazemi Mehrjerdi², DVM, DVSc
Arman Haghighi¹, DVM

¹*Department of Clinical Sciences, Faculty of Veterinary Medicine, Islamic Azad University-Garmsar Branch, Garmsar, Iran*

²*Department of Clinical Sciences, Faculty of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad, Iran*

Abstract

Objective: The aim of the present study was to evaluate the analgesic properties of Metoclopramide, a frequently prescribed antiemetic, for relieving postoperative pain following ovariohysterectomy in dogs.

Study design: Experimental study

Animals: Sixteen intact bitches, mean weight 15±2 kg.

Methods: The dogs were randomly placed into two equal groups (A and B). Prior to surgery, the dogs in group A, received Metoclopramide (0.5mg/kg/ IV) and the dogs in group B, received the same volume of saline placebo intravenously. Under general anesthesia (acepromazine [0.1mg/kg/IM], thiopental Na [8 mg/kg/IV] and inhalation of 1.6 % isoflurane in 100% oxygen) traditional midline ovariohysterectomy was performed in all dogs. Pain scores were recorded using a University Melbourne Pain Scale (UMPS) before surgery and at 0.5, 1, 3, 6 and 24 hours following surgery. All data were analyzed by SPSS software using the student's t test for normally distributed data and the Mann-Whitney U and Wilcoxon signed-rank test for skewed data. P-value less than 0.05 was considered to be significant.

Results: The mean of recovery time was significantly higher in group B (18.6±2.3) in compared to group A (11.4±2.3) ($P=0.001$). Median pain scores were significantly higher in the group B than group A at all postoperative times ($P<0.05$) except 24 hours following the surgery ($P=0.6$). Median postoperative pain scores were significantly higher than preoperative pain scores at 0.5, 1, 3 and 6 hours in both groups ($P<0.05$).

Conclusion: It is concluded that metoclopramide has analgesic properties and can alleviate postoperative pain following ovariohysterectomy in dogs during 6 hours after surgery. In addition following injection of the drug duration of recovery time is significantly decreased.

Key words: ovariohysterectomy, postoperative pain, metoclopramide, dog

*** Corresponding author:**

Azin Tavakoli, DVSc

Department of Clinical Sciences, Faculty of Veterinary Medicine, Islamic Azad University-Garmsar Branch, Garmsar, Iran

Email Address: azin.tavakoli@gmail.com

Introduction

Pain is an unpleasant sensory and emotional experience with actual or potential tissue damage¹. Severe prolonged pain after surgery is associated with complications such as increased catabolism and metabolic rate, decreased gastrointestinal motility, tachycardia, respiratory depression, decreased food intake and delayed wound healing. Additionally, acute pain causes undetectable changes in central nervous system. Providing adequate intra- and postoperative analgesia can reduce these deleterious effects. Consequently, the patient recovers sooner and returned to normal function earlier.^{2,3,4} The use of analgesics for pain management is an integral part of clinical veterinary medicine while paying attention to animals' welfare.^{5,6} At present, opioids systemically administered, are the most powerful agents for postoperative pain relief in small animals. But because of variety of adverse effects like respiratory depression, bradycardia, hypotension, dysphoria and abnormal behaviors and also limitations of prescription in many rural clinics, efforts have been done to reduce the rate of prescription of opioid agents. Thus introduction of other antinociceptive drugs as an alternative to opioids seems worthwhile.^{6,7}

Metoclopramide, a primary antiemetic, has been shown to have efficacy to alleviate pain. It was first demonstrated in 1986 by Ramswamy et al.⁸ They reported intraperitoneally administered metoclopramide can cause analgesia in albino mice. Thereafter, many studies have been conducted to assess its analgesic properties in controlling acute and chronic pain.^{5, 9, 10, 11, 12, 13} Analgesic actions of metoclopramide have been demonstrated on pain induced by intravenous injection of propofol.¹⁴ Also it decreases pain in patients suffering from urolithiasis.¹⁵ However the mechanism of action of metoclopramide to decrease pain has not been understood yet and different hypothesis have been stated.¹⁶ The drug belongs to the class of antidopaminergic drugs. It is believed that dopaminergic system is closely correlated to opioid actions. But it is not demonstrated to have affinities to opioid receptors. However, in some studies it has been attributed to endogenous opioid mechanisms and/or increased serum levels of prolactin.^{15,18} Also Genta and Fee claimed that the systemic analgesic effect of metoclopramide could be attributed to alteration of calcium transport through membranes.¹¹ According to the authors' knowledge the analgesic properties of metoclopramide in controlling postoperative pain following ovariohysterectomy is not existed in veterinary literature. Therefore, the objective of this trial was to examine the analgesic effects of metoclopramide on pain management after traditional midline ovariohysterectomy in bitches.

Materials and Methods

After approval was received from the University Research Committee, sixteen healthy mixed breed bitches, mean weight 15 ± 2 kg, randomly were divided into two groups. The dogs were maintained in a same place and lighting condition. They were assessed by a single, trained observer who allocated their pain scores, using a University Melbourne Pain Scale (UMPS). This scale included multiple descriptors in six categories incorporating both physiological data (heart and respiratory rate, rectal temperature, salivation and dilated pupils) and behavioural responses (responses to palpation, activity, mental status, posture and vocalization) that each descriptor is assigned a different numerical value. Pre-designed questionnaires according to Firth and Haldane pain score definition in 1999 were used to record the pain scale of each dog¹⁹. All scores are summed to create a total pain score for a dog at a certain time.

The dogs were premedicated with a single intramuscular dose of acepromazine (0.1 mg/kg). Anesthesia was induced using thiopental Na (8 mg/kg/IV). The anesthesia time was started at

this point. Following tracheal intubation, anesthesia was maintained using 1.6% Isoflurane/Oxygen. The animals were allowed to breath spontaneously throughout anesthesia. In group A, Metoclopramide (0.5 mg/kg/IV) was administered immediately after induction of anesthesia. Whereas in group B, as a control group, the similar volume of saline placebo was used.

All dogs in both groups, after aseptic preparation of caudal thorax to inguinal area, an 8 to 10 cm midline skin incision started from 2 cm caudal to the umbilicus extended caudally. Traditional midline ovariohysterectomy was performed in all dogs in both groups. The same surgeon performed all surgeries. At the end of the surgery, the vaporizer was turned off and duration of both surgery and recovery time were recorded in all dogs.

During 24 hours post-surgery all dogs maintained in similar place. Pain scores using UMPS were recorded at 0.5, 1, 3, 6 and 24 hours after recovery from anesthesia by a single trained observer.

Data were analyzed by a computer software SPSS, version 18 (PASW). The duration of surgery, recovery, and total pain scores were plotted as histograms. Data that were normal distributed were compared using a t-test (paired or independent) and data that were not normally distributed were compared using a Mann-Whitney U signed-rank test or Wilcoxon signed-rank test. Data were presented as mean \pm SD, or median. Values of $P > 0.05$ were considered significant in all tests.

Results

All animals survived the surgery and recovered from anesthesia without any complication. Statistical analysis indicated that the median postoperative pain scores were significantly higher than preoperative pain scores at 0.5, 1, 3 and 6 hours but they did not significantly differ at 24 hr post-surgery ($P > 0.05$) (Table 1). In addition there was not a significantly difference between means of duration of surgery between groups ($P = 0.58$) (Table 2). The mean of duration of recovery time was significantly higher in group B compared to group A ($P = 0.001$) (Table 2).

Pain scores increased within the primary hours after the operation in both groups. The dogs experienced the highest pain score at 3 hours following the surgery (Fig. 1).

The results showed that the Median pain scores were significantly higher in group B than group A, at 0.5, 1, 3 and 6 hours postoperative but 24 hours following surgery no significant difference was observed between the two groups ($P > 0.05$) (Table 2).

Table 1. Median pain scores

| Time | 0.5h | 1h | 3h | 6h | 24h |
|---------|-------|-------|-------|--------|-----|
| Group A | 2 | 3 | 5 | 3 | 0 |
| Group B | 4 | 5 | 8 | 6 | 0 |
| P.value | 0.04* | 0.04* | 0.03* | 0.001* | 0.6 |

Values are median.

* Denotes a statistically significant difference between the two groups, $P < 0.05$ (Method: Mann-Whitney test.)

Table 2. Duration of surgery and recovery time

| | Group B (Control) | Group A (Test) |
|----------------------------|-------------------|----------------|
| Duration of surgery (min) | 39.6±10.9 | 36±8.8 |
| Duration of recovery (min) | 18.6±2.3 | 11.4±2.3 |
| P. value | 0.58 | 0.001* |

Values are mean±SD

*Denotes a statistically significant difference between the two groups, P < 0.05(Method: t- test.)

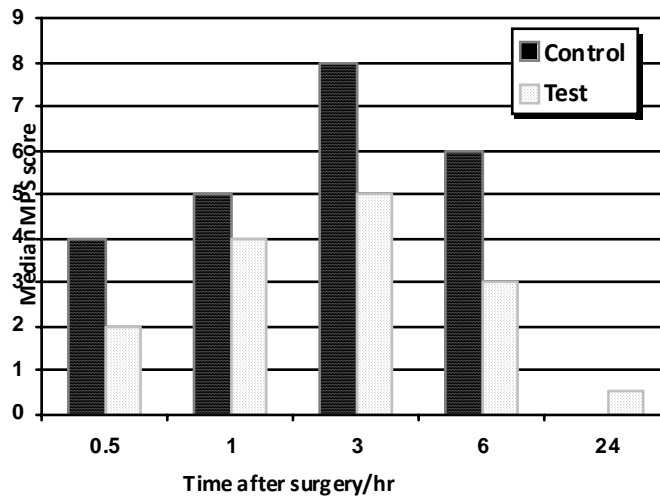


Figure 1. median MPS pain scores during the 24 hours postoperative period

Discussion

Metoclopramide, a potent antagonist of the dopaminergic D₂ receptor, is a frequently prescribed antiemetic and gastroprokinetic agent. There are many reports concerning its analgesic properties. Antinociceptive effects of metoclopramide administered intravenously in labor, termination of pregnancy, prosthetic hip surgery, knee arthroscopy, laminectomy and painful injections have been described.^{9,18,15} However the exact mechanism by which metoclopramide exerts analgesia after surgery is still unknown.¹⁶ This study was designed to examine the analgesic effects of metoclopramide following routine ovariohysterectomy in dogs.

Traditional midline ovariohysterectomy in this research was performed to induce moderate post-operative pain in bitches. The procedure is counted a relatively standardized source of soft tissue pain and is suitable for clinical studies of analgesia.¹¹ In addition this surgery is probably one of the most common surgical procedures performed on dogs in small animal veterinary practice. Acepromazine, a phenothiazine derivative that was administered as sedative in the dogs prior to induction of anesthesia in this study, has been shown to have no analgesic actions. Also isoflurane does not exhibit analgesic properties.^{21,22}

Successful pain management requires valid and reliable assessment of the degree of pain. Also accurate pain measurement is essential for clinical trials.^{1,5} Methods of recording pain in small animals had often been adaptations of rating scales developed for evaluating pain in human infants that these systems measure physiological data or evaluate behavior changes or both². University of Melbourne pain scale (UMPS), modified from Children's Hospital of Eastern Ontario Pain Scale (CHEOPS), is one example of practicable techniques that used for measurement of pain in dogs¹⁹. It is confirmed that behavioral and physiologic measurements that are considered in UMPS, can be used reliably to evaluate degree of pain in dogs during the postoperative period and their response to analgesics.¹⁹

In the present trial the lack of significant difference in median pain scores between previous and 24 hours after surgery, indicates that the use of analgesic medications is not essential after 24 hours following ovariohysterectomy. This finding has also been reported by Carpenter et al in 2004.²³

In this experiment the results showed that the mean duration of recovery from anesthesia decreased when metoclopramide was injected prior to surgery. This may be caused that metoclopramide alleviate intraoperative pain as well, therefore recovery from anesthesia is facilitated.

The highest recorded median UMPS score in this study was 8 which was in group B. Hansen et al in 2003, have been reported that the highest mean score was 8 when UMPS was used to measure the post operative pain following ovariohysterectomy in bitches as well²⁴. This finding is in consistent with the recorded scores in this study.

Variety doses of IV administration of metoclopramide to demonstrate analgesic effects after surgery have been reported. Lisander et al, used 0.5 mg/kg metoclopramide for knee arthroscopy, and 1mg/kg for prosthetic hip surgery to produce analgesia.^{18, 15} Derbent et al., administered 0.5 mg/kg metoclopramide before surgery for evaluating its analgesic effects during elective laminectomy.⁹ Similarly, in this study, we injected 0.5 mg/kg IV metoclopramide prior to surgery that elicited analgesia and was seemingly sufficient to manage post operative pain after ovariohysterectomy. However, further studies are needed to determine the optimal dose of metoclopramide for minimizing such pain.

Controversies exist regarding analgesic actions of metoclopramide. It is reported that metoclopramide produced a significant analgesic effect when tested by both acetic acid induced writhing and hot plate test.⁸ The pain reducing property of metoclopramide was compared with that of a narcotic combination drug in patients suffering from ureteric colic. The results supported the analgesic actions of metoclopramide.¹² Also metoclopramide was administered preoperatively in patients undergoing hip surgery. The pain free period was significantly longer in patients receiving pre-operative metoclopramide.²⁵ Local analgesic effects of metoclopramide following intradermal injection of the drug have confirmed by Pang et al in 1998.²⁶ In contrast there are existed reports in literature indicating that the drug does not have either clinically relevant analgesic action or supplement analgesia in post operative pain.^{15, 27} Ceccherelli in a very recent published study that aimed to verify whether the administration of metoclopramide potentiates the analgesic efficacy of manual and electro-acupuncture in the rats, demonstrated that metoclopramide possesses analgesic actions. He also reported that it can potentiate the effect of electro-acupuncture.¹⁷ Our results are in agreement with those demonstrated pain reducing properties of metoclopramide.

In conclusion, a pretreatment with single dose intravenous administration of metoclopramide is effective in reducing postoperative pain in dogs undergoing ovariohysterectomy and this drug seems to be an appropriate alternative analgesic for controlling mild to moderate pain, in limited circumstances for prescription of opioid drugs.

References

1. Wall PD. Defining pain in animals. In: Short CE, van Poznak A. eds, *Animal Pain*. 2nd ed. New York: Churchill-Livingstone Co, 1991: 63–79
2. Colantonio D, Evaluation of postoperative pain in dogs. Available at: <http://www.vip.vetsci.usyd>. Accessed Aug 2000.
3. Taylor R. Lecture notes in physiology V3008 Department of Physiology, University of Sydney, 2000
4. Johnson JM, The Veterinarians responsibility: assessing acute pain in dogs and cats part1, *Compend Contin Educ Pract Vet*. 1991;13:804-7.
5. Connolly G. Companion animal analgesics: Assessment of pain. <http://www.fda.gov/AnimalVeterinary/NewsEvents/FDAVeterinarianNewsletter/ucm133880.htm>. *FDA Veterinarian Newsletter September/October 2000 Volume XV, No. V*. Accessed Apr 2009.
6. Kurt K, Sladky A. Evaluation of epidural morphine for postoperative analgesia in ferrets. *Am Assoc Lab Anim Sci* 2000; 6:33-38.
7. Tavakoli A, et al. Enhancement of lidocaine analgesic effects in epidural analgesia by metoclopramide in rabbit. *Vet J of Islam Azad Univ, Germsar Branch*, 2009; 5: 73-7.
8. Ramswamy S, Bapna JS. Analgesic effect of metoclopramide and its mechanism. *Life Sci* 1986; 38:1289-92.
9. Derbent A, UyarM, Demirag K, et al. Can antiemetics really relieve pain? *Advances in Therapy* 2005; 22: 307-12.
10. Fujii Y, NakayamaM. A lidocaine/metoclopramide combination decreases pain on injection of propofol. *Can J Anesth* 2005; 52: 474–477
11. Genta R, Fee JPH. Pain on injection of propofol: comparison of lidocaine with metoclopramide. *Br J Anaesth* 1992; 69: 316-7.
12. Hedenbro JL, Olsson AM, Metoclopramide and uretric colic. *Acta Chir Scand* 1988; 154:439-40.
13. Majedi H, et al. A comparison of Metoclopramide and Lidocaine for Preventing Pain on Injection of Diazepam. *Anesth Analg* 2002; 95:1297–9.
14. Liaw WJ, Pang WW, Chang DP, et al. Pain on injection of propofol: the mitigating influence of metoclopramide using different technique. *Acta Anesthesiol Scand* 1999; 70: 631-633
15. Lisander B. Evaluation of the analgesic effect of metoclopramide after opioid-free analgesia, *Br J Anesth* 1993; 70: 631-3.
16. Kurtipek O. Histopathologic changes after repetitive peridural administration of metoclopramide. *Anesth Analg* 1999; 88: 100-2.
17. Ceccherelli F, Gagliardi G, Roveri A. et al. Evaluation of the effect of metoclopramide on acupuncture and electro-acupuncture analgesia- A blind and controlled study in rats. *Dt Ztschr F Akup*. 2010; 53: 11-16
18. Lisander B, Kandler B. Analgesic action of metoclopramide in prosthetic hip surgery. *Acta Anesthesiol Scand* 1993; 37: 49-53.
19. Firth AM, Haldane SL. Development of a scale to evaluate post- operative pain in dogs. *J Am Vet Assoc* 1999; 214: 651-59.
20. Rosenblatt WH, Coffi AM, Sinarta R, et al. Metoclopramide: an analgesic adjunct to patient-controlled analgesia. *Anesth Analg* 1991; 73:553-5.

21. Bishop Y. In: The veterinary formulary, 6th edition, Pharmaceutical press, Chicago, USA, 2005:263.
22. De Sousa S, Dickinson R, William R. et al. Contrasting Synaptic Actions of the Inhalational General Anesthetics Isoflurane and Xenon. *Anesthesiol* 2000; 92 :1055-1066).
23. Carpenter RE, Wilson DV, Evans AT. Evaluation of intraperitoneal and incisional lidocaine or bupivacaine for analgesia following ovariohysterectomy in the dog. *Vet Anaesth Analg* 2004; 31:46-52.
24. Hansen B. Assessment of pain in dogs: Veterinary clinical studies. *ILAR Journal*, 2003; 3:197-205.
25. Kandler D, Lisander B. Analgesic action of metoclopramide in prosthetic hip surgery. *Acta Anesthesiol Scand* 1993; 37: 49-53
26. Pang WW, Mok MS, Chang DP, et al. Local anesthetic effect of tramadol, metoclopramide, and lidocaine following intradermal injection. *Reg Anes & Pain Med* 1998; 23: 580-583
27. Danzer BL, Birnbach DJ, Stein DJ, et al. Does metoclopramide supplement postoperative analgesia using patient controlled analgesia with morphine in patients undergoing elective cesarean delivery? *Reg Anest & Pain Med* 1997; 22: 424-427

بررسی اثرات بی‌دردی متوکلوپرامید پس از جراحی اوریهیسترکتومی در سگ

آذین توکلی^۱، حسین کاظمی مهرجردی^۲، آرمان حقیقی^۱

^۱گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه آزاد اسلامی واحد گرمسار، گرمسار، ایران.
^۲گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه فردوسی مشهد، مشهد، ایران.

هدف- بررسی اثرات ضد‌دردی داروی ضدتهوع متوکلوپرامید در کنترل درد پس از جراحی معمول برداشت رحم و تخمدان در سگ.

طرح- مطالعه تجربی انتخابی

حیوانات- شانزده سگ ماده عقیم نشده با میانگین وزنی 15 ± 2 کیلوگرم

روش کار- ۱۶ قلاده سگ ماده به صورت تصادفی در دو گروه مساوی A (مورد) و B (شاهد) قرار گرفتند. در سگهای گروه مورد پیش از انجام جراحی به میزان ۰/۵ میلی گرم به ازای هر کیلوگرم وزن بدن به صورت داخل وریدی داروی متوکلوپرامید و در سگهای گروه شاهد هم حجم آن به صورت داخل وریدی نرمال سالین تزریق شد. داروی اسپرومازین به میزان ۰/۱ میلی گرم به ازای هر کیلوگرم وزن بدن به عنوان پیش بیهوشی، داروی تیوپنتال سدیم به میزان ۸ میلی گرم به ازای هر کیلوگرم برای القای بیهوشی و تداوم بیهوشی با استفاده از داروی استنشاقی ایزوفلوران صورت گرفت. کلیه سگها تحت جراحی معمول برداشت رحم و تخمدان از خط وسط قرار گرفتند. سپس پیش از جراحی (زمان صفر) و ۰/۵، ۱، ۳، ۶ و ۲۴ ساعت پس از جراحی، تست ارزیابی درد با روش دانشگاه ملیورن (UMPS) صورت گرفت. زمان به طول انجامیدن عمل جراحی و زمان بازگشت از بیهوشی ثبت شده و در پایان داده ها با استفاده از آزمونهای آماری T-test، Wilcoxon و Mann-Whitney در سطح معنی داری $P < 0/05$ مورد تجزیه و تحلیل آماری قرار گرفتند.

نتایج- میانگین زمان بازگشت از بیهوشی در گروه شاهد $2/3 \pm 18/6$ به صورت معنی داری از گروه مورد $2/3 \pm 11/4$ بالاتر بود ($P=0/001$). میزان درد در ساعات ۰/۵، ۱، ۳ و ۶ ساعت پس از جراحی به صورت معنی داری در گروه مورد نسبت به گروه شاهد بالاتر بود ($p < 0/05$) اما در زمان ۲۴ اختلاف معنی داری در بین دو گروه مشاهده نشد ($p=0/6$). بین زمانهای صفر و ۲۴ در هیچ یک از دو گروه اختلاف معنی داری در میزان درد وجود نداشت اما در زمانهای ۰/۵، ۱، ۳ و ۶ ساعت پس از جراحی میزان درد در هر دو گروه به صورت معنی داری از زمان صفر بیشتر بود ($p < 0/05$).

نتیجه گیری: نتایج این پژوهش نشان می دهد که داروی متوکلوپرامید دارای اثرات ضد‌دردی بوده و موجب کاهش درد پس از عمل جراحی برداشت رحم و تخمدان در ۶ ساعات اولیه پس از جراحی می شود. همچنین طول زمان بازگشت از بیهوشی به صورت معنی داری با به کار بردن این دارو کاهش می یابد.

کلید واژگان- برداشت رحم و تخمدان، درد پس از عمل جراحی، متوکلوپرامید، سگ.