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results suggest that metoclopramide can be used as an adjuvant to improve acupuncture analgesia with an unclear mechanism (21). In 1992 Ganta et al, reported the equal analgesic effects of lidocaine and metoclopramide in prevention of pain caused by the injection of propofol (5).

It is concluded that Metoclopramide, a frequently prescribed antiemetic, can extend the duration of epidural analgesia induced by lidocaine in comparison to lidocaine alone. Nevertheless no evidence was found to indicate its addition to lidocaine can also speeds up the onset time of analgesia or prolong the duration of flaccid paresis. The combination of lidocaine and metoclopramide can be recommended in case of no available opioid drugs to enhance the efficacy of epidural analgesia induced by lidocaine. Authors would like to sincere thank to the Faculty of Veterinary Medicine and The Young Researcher Club of Islamic Azad University, Garmsar Branch for their kind collaboration and support to conduct the experiment.

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Results

None of the animals during the study experienced complication. Statistical analysis indicated that there were not significant differences among means of onset time of analgesia (OT), duration of flaccid paresis (DFP) and duration of analgesia (DA) in first, second and third injection within groups ($p>0.05$). Statistical analysis showed that mean of onset time of analgesia (OT) in group A (68.6±15.5 sec) was not significantly different in comparison to group B (45.8±17.1 sec) ($p>0.05$). Although mean of duration of flaccid paresis (DFP) was higher in group B (29.2±11.5 min) compared to A (18.3±5.2 min) it was not significantly different between groups ($p>0.05$). Mean of duration of analgesia (DA) was significantly higher in group B (39.1±16.2 min) compared to group A (23.6±5.5 min) ($p=0.018$). Results are illustrated in table 1.

Table 1. Mean and standard deviation of the measured variables after administration of drugs to induce epidural analgesia

	Group A 2% Lidocaine	Group B Combination of 2% lidocaine and metoclopramide
Onset time (sec)	68.6±15.5[a]	45.8±17.1[a]
Duration of flaccid paresis (min)	18.3±5.2[b]	29.2±11.5[b]
Duration of analgesia (min)	23.6±5.5	39.1±16.2

The measured variables in groups with the common superscripts were not significantly different from each other at the 0.05 significance level.

Discussion

Epidural analgesia can be performed in several surgical and painful procedures in addition of the ability to produce postoperative analgesia and continuous pain relief in patients with chronic pain such as patients with advanced stage of cancers, intervertebral disk or neurologic problems. Rabbit was used in the present experiment because reports showed that rabbit is a suitable model for inducing epidural block and evaluating sensory and motor loss under standardized experimental conditions (10,15). The procedure for lumbosacral epidural puncture in ferrets and rabbits is similar to that described in literature for dogs and cats, except that there is rarely a definitive popping sensation when the intervertebral ligaments are punctured at the time of entry into the epidural space (6). We did not encounter a problem during performing epidural analgesia, since the method was examined before and the injection site was carefully detected in cadaver.

Although mean onset time of analgesia was higher in the combination of metoclopramide and 2% lidocaine in group B (45.8±17.1sec) it was not significantly different from the one of 2% lidocaine alone ($p>0.05$). There are reports that have mentioned other combinations with lidocaine which can improve its motor block activities. Komoda et al reported 60 % extension of duration of flaccid paresis by addition of deoxaconitine, a traditional opioid agonist to alleviate pain, to lidocaine in comparison to lidocaine alone (11). Doherty, et al, reported that ionic complexes of local anesthetics such as lidocaine with medium molecular weight hyaluronic acid formulations can prolong loss of weight bearing twofold in local anesthesia in rabbit (4).

Mean of duration of analgesia was significantly increased when metoclopramide ($p=0.018$) was added to lidocaine in group B. This highlights the facts that metoclopramide has analgesic effects. Although the analgesic properties of the popular antiemetic, metoclopramide, have been demonstrated since several years ago, it's mechanism of action is still controversial (2, 17). There are some reports that show its analgesic effect was reduced by naloxone suggesting an opioid involvement of metoclopramide (17). In contrast that it did not alter the antinociceptive effects of morphine that suggests a lack of interaction between opioids and metoclopramide (20). Also there are reports of a relationship between serum levels of prolactin and analgesia produced by metoclopramide (12,13). Synergism between metoclopramide and electro acupuncture analgesia was described by Xu et al. He declared that patients having taken metoclopramide reported better analgesic effect during thyroidectomy under acupuncture anesthesia. The

Introduction

Epidural block, a form of regional anesthesia, is probably the most useful method to control postoperative pain after many surgical and painful procedures specially in abdominal surgeries (7). It's efficacy in producing loss of pain and sensation have been demonstrated in 1912 by a German physician by injecting drugs into the epidural space. After lidocaine was introduced in veterinary practice in 1944, it became a popular drug to induce epidural analgesia. Since then variety of drugs and their combinations have been reported in human and veterinary literature to induce epidural analgesia alone or adjunct to other methods of anesthesia for abdominal and perineal surgeries, obstetric manipulations and cesarean section, tail amputation and rear limb surgeries. It is also used to produce postoperative analgesia and relieve pain in patients with chronic pain. In spite of described advantages of epidural analgesia, it is not widely used in small animal practice. This may due to the fact that some surgeons are not fully familiar with the technique or they prefer one venous puncture to induce analgesia (8,10).

In clinical studies, successful epidural analgesia by administration of other non-opioid drugs like ketamine, deroperidol, clonidine, xylazine and metoclopramide have been stated (1,7,16,19). There are many reports describing analgesic effects of metoclopramide, a potent dopamine receptor antagonist, that is primarily used to treat nausea and vomiting. Significant analgesic properties of metoclopramide have been demonstrated by many authors since 19867. Also its analgesic effects have been described in specific surgeries like prosthetic hip surgery, knee arthroscopy (2,13,14,17,18). Derbent in 2005 showed that preoperative administration of metoclopramide provided postoperative analgesia in patients undergoing elective laminectomy (3). Although hypotheses have been launched for analgesic properties of metoclopramide its mechanism of action has not been determined yet (9,12). At present, there is no ideal drug or combination of drugs for postoperative epidural analgesia (7).

Since limitations exist for prescribing opioids in Iran, for veterinarian practitioners especially for those in private practice and when opioid drugs are not easily accessible, introduction of other analgesic drugs seems valuable. Therefore the present experimental animal modeling was conducted to study effects of metoclopramide on epidural analgesia induced by lidocaine in rabbits.

Materials and method

Fifteen adult and healthy New Zealand White rabbits weighting 3-3.5 kg of both genders randomly were divided into three groups. All experimental procedures were performed after approval was received by the University Research Committee in accordance with the guidelines of its Institutional Animal Experimentation Ethics Committee. After aseptic preparation of dorsal caudal area, epidural injection was performed thorough the deepest area in lumbosacral (L-S) junction via a 50 mm, 20 gauge epidural needle. The hind legs of the rabbits were flexed which allows maximal opening of the lumbosacral space. The procedure for lumbosacral epidural puncture in rabbits is similar to the described procedure in literature for dogs and cats (6). Hanging drop technique was used to realize that the needle is located into the epidural space. However before starting the project, the exact site of epidural injection was observed in a cadaver. In group A, 2 % lidocaine (1.5 ml) was used to induce epidural analgesia. While in group B the combination of 2 % lidocaine (1.5 ml) and metoclopramide HCl (0.5 ml) was used to induce epidural analgesia. The same procedure was performed 48 hours and a week later in all rabbits. The onset time of analgesia (OT), duration of flaccid paresis (DFP) and duration of analgesia (DA) was measured in all treatments in group A and B. Mean of the measured variables were compared among groups and between injections using between-groups and within groups (repeated measure) analysis of variances (ANOVA). Then Banferroni test was performed for pair wise comparison between means. The P values less than 0.05 were considered statistically significant.

Enhancement of Lido caine Analgesic Effects in Epidural Analgesia by Metoclopramide in Rabbits

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Abstract

Epidural analgesia is a type of regional block, commonly used in human and veterinary practice to alleviate pain solelyor auxiliary to other methods of anesthesia. This method of analgesia is widely used in abdominal, perineal, tail and rear limb surgeries and procedures. It is also widely common to relieve pain after operations and in patients with chronic pain. Many reports are available about analgesic properties of metoclopramide which is primarily used as antiemetic; meanwhile, Lidocaine was used to induce analgesia in different species of animal from long time ago. Since narcotics have limitation in prescribing by physicians and clinicians, promoting other types of drugs with analgesic effects seem worthwhile. The present prospective experiment was designed to study effects of metoclopramide on epidural analgesia induced by lidocaine in rabbits. Twelve healthy New Zealand white rabbits weighing 3-3.5 kg were divided randomly into two groups. In group A, 2 % lidocaine (1.5 ml) and in group B the combination of 2 % lidocaine (1.5 ml) and metoclopramide HCl (0.5 ml) was used to induce epidural analgesia. Two more injections with 48 hours and one week intervals were performed in the same manner. The onset time of analgesia (OT), duration of flaccid paresis (DFP) and duration of analgesia (DA) was determined in all treatments. Repeated measure ANOVA and Banferroni test were used to compare mean and variances within and between groups. Statistical analysis showed that there were no significant difference in mean of OT and DFP between groups ($p>0.05$). Whereas mean of duration of analgesia was significantly higher in group B (39.1±16.2 min) compared to group A (23.6±5.5 min) ($p=0.018$). In conclusion the addition of metoclopramide to lidocaine is effective in prolongation of epidural analgesia in rabbit. ***Islamic.Azad.Univ., Garmsar Branch. 5,1:73-77, 2009.***

Keywords: Epidural analgesia, Lidocaine, Metoclopramide, Rabbit.

مقایسه القای بی دردی به وسیله لیدوکایین و ادغام دارویی لیدوکایین، متوکلوپرآمید در روش بی دردی اپیدورال در خرگوش

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چکیده

بی حسی اپیدورال از انواع روش‌های بی دردی موضعی است که در القای بی دردی به تنهایی یا به صورت کمکی همراه باسایر تکنیک‌های بیهوشی در طب انسانی و دامپزشکی رایج است. این روش بی دردی در بسیاری از جراحی‌های محوطه شکمی، نواحی پرینه، دستکاری‌های مامایی، جراحی‌های دم واندام حرکتی خلفی و نیز کاهش درد بعد از عمل و در بیماران دارای دردهای مزمن کاربرد وسیعی دارد. گزارشات بسیاری نیزمبنی بر اثرات بی دردی داروی متوکلو پرامید که به صورت اولیه به عنوان ضد تهوع استفاده می‌شود موجود است. همچنین از داروی لیدوکایین از سال‌های بسیار دور جهت القای بی دردی اپیدورال در گونه‌های مختلف حیوانی استفاده می‌شود. ازآنجایی که داروهای مخدری دارای محدودیت در نسخه نویسی برای دامپزشکان و کلینیسین‌ها می‌باشند، ترویج کاربرد سایر داروها با اثرات ضد دردی با ارزش به نظر می‌رسد. دوازده خرگوش بالغ از هر دو جنس نر و ماده به وزن تقریبی ۳ تا ۳/۵ کیلوگرم به صورت تصادفی به دوگروه مساوی تقسیم‌شدند. درگروه شاهد، تحت مقیدسازی فیزیکی، درعمیق ترین نقطه قابل ملامسه در محل اتصال مهره‌های کمری-خاجی(Lumbosacral Junction) ۱.۵ میلی لیتر داروی لیدوکایین ۲درصد و درگروه‌آزمایش ادغام ۱.۵ میلی لیتر داروی لیدوکایین ۲درصد ونیم میلی لیتر داروی متوکلو پرآمید پس ازحصول اطمینان از ورود سوزن در فضای اپیدورال تزریق شد. به فاصله ۴۸ ساعت و یک هفته بعد از تزریق اول دو تزریق به ترتیب مشابه صورت‌گرفت. مدت زمان‌شروع اثربی دردی، طول مدت فلجی شلی پاها وطول مدت بی دردی درهردوگروه‌مورد بررسی قرارگرفت. میانگین‌شروع اثربی دردی و همچنین میانگین طول دوره فلجی شلی پاها درگروه‌آزمایش وشاهد بدون تفاوت معنی داری بود ($p>0.05$). در حالی‌که میانگین طول بی دردی در گروه آزمایش (39.1±16.2دقیقه) به صورت‌معنی داری بالا تر ازگروه‌شاهد (23.6±5.5دقیقه) بود($p=0.018$). بنابر این می توان نتیجه‌گرفت که داروی متوکلو پرآمید در طولانی ترنمودن دوره‌بی دردی دربی حسی اپیدورال القاشده بالیدوکایین دودرصد کاملاً موثر می‌باشد. مجله دانشکده دامپزشکی دانشگاه آزاد اسلامی‌واحد گرمسار، ۱۳۸۸، دوره ۵، شماره۱، ۷۷-۷۳.

واژه‌های کلیدی: بی دردی اپیدورال، لیدوکایین، متوکلوپرآمید، خرگوش.