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# Comparison the Analgesic Effects of Lidocaine, Xylazine and their Combination Used into the Epidural Space in Rabbits

**Mehdi Marjani*[1], Azin Tavakoli[2], Jafar Tavakoli[1]**

## Abstract

**Objective-** Addition of the drugs to lidocaine to induce epidural analgesia in order to elongate and enhance the analgesia has been investigated previously. The objective of this study was to compare the effects of epidurally administered xylazine either in combination of lidocaine or alone in rabbits.
**Design-** Experimental study
**Animals-** Twelve healthy and adult male New Zealand white strain rabbits weighting 2.2±0.3 kg were used in this study.
**Procedures -** Following the epidural catheterization of all rabbits under general anesthesia they were randomly assigned to three equal groups of A, B and C. The next day administration of 4 mg/kg of 2% lidocaine, 3 mg/kg of 2% xylazine and 2 mg/kg of 2% lidocaine-1.5 mg/kg of 2% xylazine mixture was performed in group A, B and C respectively through the epidural catheter. The motor activity, the onset time of blockade, the duration of blockade, heart rate, respiratory rate and rectal temperature were recorded prior and during analgesia.
**Results-** Values were not significantly different among the three groups (P>0.05) and no complication occurred during a week after induction of epidural analgesia. Either of the alone drugs or their combination is safe to be used into the epidural space in rabbits.
**Conclusions and Clinical Relevance-** By considering the reduced dose of xylazine, the combination of xylazine and lidocaine seems superior to induce epidural analgesia in rabbits.
**Key words-** xylazine, lidocaine, epidural, rabbit.
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## Introduction

Epidural administration of local anesthetic is considered a relatively safe and effective method for providing anesthesia and postoperative analgesia. Different drugs and their combinations have been used to induce epidural analgesia. After 1944 that lidocaine was introduced in veterinary practice, it has been widely used in all species because of its excellent diffusing and penetrating properties as well as rapid onset of surgical analgesia[12, 13, 14]. However, its action is too short-lived to be used for major procedures[1, 2, 5].Therefore its combination with other drugs in order to increase the duration of nerve block in epidural analgesia is concerned. The ideal epidural anesthetic should produce rapid onset of action, long duration of analgesia and muscle relaxation. The rapid reversal of the block at the end of the procedure should be provided[9] .At present, there is no ideal drug or combination of drugs for postoperative epidural analgesia[4, 23].

Xylazine is an alpha-2 agonist that has been used widely to induce epidural analgesia in human beings as well as animals. Its epidural administration found to be safe and effective in horses[11, 16], ponies[8], cattle[6], goats[3, 7]and dogs[10]. It has been shown that the addition of xylazine to lidocaine used for the epidural analgesia speeds up the action of lidocaine and provides a longer duration of analgesia as well[15, 21].

Rabbits are routinely used for experimental studies and frequently need to be anesthetized. Also rabbits are shown to be an appropriate species for evaluating the sensory and motor loss in epidural analgesia during animal model and experimental studies[13, 18]. However to the authors' knowledge no published information appears to be available regarding epidural administration of xylazine in rabbits.

[1]Faculty of Veterinary Medicine, Islamic Azad University, Karaj branch, Karaj, Iran.
[2]Faculty of Veterinary Medicine, Islamic Azad University, Garmsar branch, Garmsar, Iran.
Address all correspondence to Dr. Mehdi Marjani (DVM, DVSc), E-mail: mzmarjani@gmail.com

This study was designed to compare the analgesic effects of epidurally administered xylazine either in combination of lidocaine or alone in rabbits. Also the associated changes in heart rates (HR), respiratory rates (RR) and rectal temperature (RT) were evaluated.

## Materials and methods

*Animals*

Twelve healthy and adult male New Zealand white strain rabbits weighting 1.8 to 2.5 kg (mean weight 2.2±0.3) were used in this study. The experimental protocol used was reviewed and approved by Karaj Institutional Animal Care and Use Committee. All animals had free access to food and water and were individually housed in a 12-h light dark cycle. Following the epidural catheterization of all rabbits they were randomly assigned to three equal groups of A, B and C.

*Technique*

The intramuscular injection of the combination of 5mg/ kg xylazine (Rampon®, 2% Bayer, Germany) and 40 mg/kg ketamine (Ketalar®, 10%, Alfasan, Woerden, Holland) was used to induce general anesthesia in all rabbits.
The aseptic preparation of the dorsal to caudal area in rabbits was performed prior to placement of epidural catheter. The proper site of epidural catheter placement was evaluated in cadavers before the study started. After cutaneous incision of the tail, interspace between two caudal vertebrae was incised and a 23-gauge catheter (Periquick®, Gamida Lab., Eaubonne, France) was gently slided 15 cm cephalad into the epidural space in order to set the tip of the catheter at the L2 level. The proper position of the catheter was examined by epidural injection of 2 ml of 2% lidocaine allowing a complete motor and sensory blockade of the distal limb and tail. The system was tunneled and secured, and implanted subcutaneously on the back of the rabbit. The rabbits were neurologically examined after full recovery from general anesthesia. Either a rabbit that showed any signs of abnormal sensory or motor functions were excluded from the study.
A day following the epidural catheterization, the rabbits with correct location of epidural catheter were examined to ensure no neurological abnormalities and their epidural catheters were re-examined with normal saline 0.2 ml injection to ensure no occlusions. Finally, 12 successfully catheterized rabbits were randomly assigned to three groups in the following order:
Group A: epidural administration of 4mg/kg of 2% lidocaine (Lurocaine, Vetoquinol, France)
Group B: epidural administration of 3 mg/kg of 2% xylazine (Xylazine, Alfasan, Holland) Group C: epidural administration of 2 mg/kg of 2% lidocaine-1.5 mg/kg of 2% xylazine mixture.
All experimental drugs were diluted to 1 ml total volume by normal saline. After epidural injection of the drugs, the epidural catheter was removed and animals were released on the floor.

*Evaluated parameters*

The animal's sensory blockade by seeking an aversive response to pinprick stimulation with a 22-gauge needle progressing from the sacral to thoracic dermatomes at 1, 2, 3, 4, 5 min after epidural injection and then every 5 minutes until sensory blockade disappeared was recorded.
We rated each testing site as follows: the foot = -2, the knee = -1, the epigastrium = +1, the chest= +2 and the hand = +3
Motor activity was evaluated using a modified Langerman's scale used in similar studies[20]. Rabbits were observed continuously and tested every 30 s until the peak intensity of motor blockade was reached. Evaluations of spontaneous motor activity were then made every 5 min until symptoms disappeared. Motor function was scored as follows: 0, free movements of the animal using hind limbs needed without limitation or loss of balance; 1, limited or asymmetrical movements of the hind limbs needed to support the body and walk; 2, inability to support the back of the body on the hind limbs, despite existing ability to move the limbs and to respond to a painful stimulus; and 3, total paralysis of the hind limbs**.**
Also the onset time of blockade (referred to the time needed between the drug administration and the start of any degree of blockade), duration of blockade (the time during which the rabbit presents any degree of blockade), time to maximum blockade (time needed between drug administration and maximum sensory blockade level or motor blockade degree achieved) and maximum degree of blockade (the highest score during motor blockade period) were measured.
In addition, the rabbit's heart rate/min (HR), respiratory rate/min (RR) and rectal temperature (º C) were recorded ten minutes before epidural injection (time -10), ten minutes after epidural injection (time 10) and subsequently at 10-min interval over a period of 90-min.

*Statistical Analysis*

The data are expressed as mean ± SD of 4 rabbits in each group. Mean of the measured variables were compared among groups and within group 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.

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## Results

None of the rabbits in the three groups died or showed any sign of long-term neurological deficits during a 1-week observation period. Opisthotonus was exhibited by some rabbits only in group A. The onset of motor blockade stages and onset of sensory blockade sites in all groups are showed in table 1, however values were not significantly different among the three groups (P.0.05).

None of the rabbits in these three groups showed sensory blockade in site +3(hand). All the rabbits in these groups showed motor blockade 3 (total paralysis) during the observation period. Mean duration of maximum motor blockade was 25.1 min in group A, 29 min in group B and 26.5 min in group C that were not significantly different between the groups.

Mean heart rate/min was decreased in group A and B and increased in group C. However the differences were not significant (P>0.05). Although mean respiratory rate/min was decreased in all groups, the respiratory depression was more evident in group B. The lowering of the respiratory rate was significant in group B compared to group A and C (P<0.05). Mean rectal temperature was decreased in all the groups without significant differences among them (P>0.05). Data are illustrated in table 2.

**Table 1.** The blockade onset times and durations after epidural administration of the drugs.

| Parameter | Group A | Group B | Group C |
|---|---|---|---|
| **Sensory blockade onset (min)** | 1.4± 0.1 | 1.2 ± 0.7 | 1.0± 0.2 |
| **Time to maximum sensory blockade (min)** | 3.9±1.5 | 3.6± 0.9 | 3.7± 1.6 |
| **Duration of maximum sensory blockade (min)** | 21.5 ±0.9 | 22± 0.5 | 23.4± 0.5 |
| **Duration of sensory blockade (min)** | 54± 9 | 51± 13 | 50± 8 |
| **Motor blockade onset (min)** | 1.9 ±0.3 | 1.8± 0.5 | 1.1± 0.7 |
| **Time to maximum motor blockade (min)** | 3.9 ±1.1 | 5.5± 0.9 | 4.9± 0.5 |
| **Duration of maximum motor blockade(min)** | 25.1±8.1 | 29± 7.7 | 26.5 |
| **Duration of motor blockade (min)** | 33±11 | 32± 12.1 | 30±10 |

Data presented are the mean ± S.D., P<0.05, n=12 rabbits

**Table 2-** Mean ± SD of heart rate/min, Respiratory rate/min and rectal temperature (º C) measured at different times prior and after the procedure.

| Time | Heart rate/min | | | Respiratory rate/min | | | Rectal temperature | | |
|---|---|---|---|---|---|---|---|---|---|
| | Group A | Group B | Group C | Group A | Group B | Group C | Group A | Group B | Group C |
| **- 10** | 217.0 | 214.0 | 215.0 | 133.5 | 128.0 | 155.0 | 39.8 | 39.5 | 38.7 |
| **10** | 202.5 | 189.0 | 199.0 | 132.0 | 100.0 | 118.0 | 38.5 | 39.2 | 37.8 |
| **20** | 201.0 | 181.0 | 200.0 | 121.5 | 86.2 | 119.0 | 37.8 | 38.5 | 37.3 |
| **30** | 198.0 | 197.0 | 198.5 | 109/0 | 72.0 | 106.0 | 38.3 | 38.2 | 37.2 |
| **40** | 200.5 | 174.5 | 199.0 | 126.0 | 91.1 | 108.0 | 39.0 | 38.0 | 36.9 |
| **50** | 208.0 | 180.0 | 195.0 | 120.0 | 70.0 | 95.0 | 38.3 | 38.2 | 36.8 |
| **60** | 212.0 | 188.0 | 202.0 | 135.0 | 86.2 | 90.7 | 38.5 | 38.1 | 36.9 |
| **70** | 225.5 | 174.6 | 212.0 | 142.0 | 92.0 | 97.0 | 38.5 | 38.2 | 37.1 |
| **80** | 244.6 | 175.5 | 206.5 | 139.0 | 83.0 | 80.0 | 38.7 | 38.4 | 36.7 |
| **90** | 245.0 | 203.0 | 210.0 | 145.5 | 76.0 | 100.0 | 38.9 | 38.6 | 37.4 |

Data presented are the mean, P<0.05, n=12 rabbits

## Discussion

In the present study we aimed to compare the analgesic effects of xylazine and its combination with lidocaine in epidural analgesia in rabbits. Many factors involve providing successful epidural analgesia including surgical site, direction and rate of injection of the local anesthetic, the type and volume of the anesthetic agent, nerve root size and patient posture.

None of the measured parameters were significantly different among the groups at different times. The addition of xyalzine did not increase the duration of sensory or motor loss induced by lidocaine. Reports are available in the literature regarding the use of combination of xylazine and lidocaine in to the epidural space. Lee et al. induced epidural analgesia with either xylazine or lidocaine in bovine and reported that the number of spinal segments involved in the area of analgesia when the anesthetic contained xylazine was significantly greater than with lidocaine alone.[17]Also Grubb et al. reported that the combination of xylazine and lidocaine produced the quicker and longer analgesia

than that of the either of the drugs alone in cows.[11] DeRossi showed that the degree of analgesia was more profound and the duration was longer whenepidural administration of the combination of xylazine and lidocaine was used than that the drug used alone in goats. However longer motor loss was resulted when the combination of the drugs was used which would be a disadvantage when early ambulation after the procedure is considered.[7]We did not observe any significant difference in different measured parameters in this study. We believe by increasing number of the patients the evaluation of the degree and duration of analgesia will be improved. However number of the subjects in similar studies is approximately equivalent to the number we used. None of the rabbits showed an abnormal consciousness after the epidural drug administration. None of the rabbits showed any long-term neurological deficits during a 2 -week observation.

In addition to clinical demonstration of epidural use of the drugs, changes in physiologic parameters like heart rate, respiratory rate and rectal temperature was recorded in this study. When Xylazine used alone, more disturbances were noted in physiologic parameters. This finding is in agreement with similar reports.[7, 17, 22] We did not observe any significant difference regarding the epidural use of xylazine, lidocaine or their combination in rabbits. To the authors knowledge this is the first report of the work with detailed explanation of the technique in inducing epidural analgesia in rabbits. By reviewing the literature results revealed that the use of xylazine in combination to the other drugs to induce epidural analgesia can decrease the side effects as well as to increase the duration and degree of produced sedation. It is hypothesized that the increase in duration and degree of analgesia might be due to the vasoconstriction produced by xylazine that allows a prolonged presence of both drugs in the spinal effect.[7,19] Also it is reported that the decrease in heart rate and blood pressure are less when the combination of lidocaine and xylazine was used.[3, 7, 22] This results from the lower dose of the administered xylazine when its combination with lidocaine is considered.

As conclusion either of the alone drugs or their combination are safe to be used into the epidural space in rabbits. Although no significant differences were observed in this study, the combination treatment of xylazine and lidocaine seems superior to induce the epidural analgesia in rabbits due to reduction in the dosage of the drugs. Further studies with increased number of the subjects are recommended to evaluate the specific changes in duration and degree of analgesia. The methodology of inducing epidural analgesia explained in this study was elaborated so that the other works can duplicate the method easily.

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## چکیده

# مقایسه اثرات بی دردی لیدوکایین، زایلازین و ادغام لیدوکایین و زایلازین در بی‌حسی اپیدورال در خرگوش

مهدی مرجانی*[۱]، آذین توکلی[۲]، جعفر توکلی[۱]

[۱]دانشکده دامپزشکی دانشگاه آزاد اسلامی واحد کرج، کرج، ایران.
[۲]دانشکده دامپزشکی دانشگاه آزاد اسلامی واحد گرمسار، گرمسار، ایران.

**هدف**- پیشتر، افزودن داروهای مختلف به لیدوکایین و تجویز اپیدورال آن جهت طولانی نمودن و افزایش اثرات بی‌دردی در بی‌حسی اپیدورال مطالعه شده است، اما گزارشی از تجویز زایلازین به صورت اپیدورال در خرگوشها وجود ندارد. هدف از این مطالعه مقایسه طول و میزان بی‌دردی در تجویز اپیدورال زایلازین به تنهایی یا در ادغام با لیدوکایین در خرگوش می‌باشد.

**طرح**- مطالعه تجربی

**حیوانات**- ۱۲ خرگوش نر، بالغ از نژاد سفید نیوزلندی با میانگین وزنی ۰/۳±۲/۲ کیلوگرم

**روش کار**- تحت بیهوشی عمومی، کاتتر اپیدورال در فضای اپیدورال کلیه خرگوشها کار گذاشته شد و به صورت تصادفی خرگوشها به سه گروه مساوی تقسیم شدند. روز بعد به ترتیب ۴ میلی‌گرم به ازای هر کیلوگرم وزن بدن لیدوکایین ۲٪، ۳ میلی‌گرم به ازای هر کیلوگرم وزن زایلازین ۲ ٪ و ادغام ۲ میلی گرم به ازای هر کیلوگرم وزن بدن لیدوکایین ۲٪ و ۱/۵ میلی گرم به ازای هر کیلوگرم وزن بدن زایلازین ۲٪ در گروههای A، B و C از طریق کاتتر اپیدورال تجویز شد. میزان فعایت حرکتی، شروع اثر بی دردی و مدت زمان بی‌دردی به همراه تعداد ضربان قلب، تنفس و دمای بدن در هر سه گروه پیش و در طول بی حسی اپیدورال ثبت شد.

**نتایج**- نتایج هیچ اختلاف معنی‌داری را در تمامی مقاطع زمانی در پارمترهای مختلف اندازه گیری شده نشان ندادند ($P>0.05$). همچنین هیچگونه عارضه حرکتی یا بالینی در خرگوشها تا یک هفته پس از تجویز داروها دیده نشد.

**نتیجه گیری و کاربرد بالینی** – بدین ترتیب زایلازین به تنهایی و یا در ادغام با لیدوکایین به صورت مطمئنی در فضای اپیدورال در خرگوش قابل تجویز می‌باشد. با در نظر گرفتن کاهش دوز داروها در ادغام دارویی، به نظر می‌رسد ادغام دارویی زایلازین و لیدوکایین در بی‌حسی اپیدورال در خرگوش ارجحیت دارد.

**کلمات کلیدی**- زایلازین، لیدوکایین، اپیدورال، خرگوش