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Case Report

Sedative Effects of Xylazine for Premedication in Sheep

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Abstract

Background: Europe is facing urgent shortcomings in terms of animal welfare. Science and good animal welfare go hand in hand. If an animal is suffering stress or pain it could affect the results of the research. The guiding principles underpinning the humane use of animals in scientific research are called the three Rs: reduction, replacement and refinement. Refinement include, using appropriate anesthesia and analgesia. The present study was aimed to compare dose of xylazine used for premedication in three different sheep weight groups.

Goal: The main goal is to reduce duration of stress for the animal during premedication. Our anesthetic protocol is three stages: premedication, induction and deep general anesthesia with inhalation anesthesia. Fifteen healthy adult Romanov`s breed female sheep of weighing (10-15kg; 15-20kg; 20-25kg) and aged (5, 6 and 8 months) were used and divided into three groups. Animals were accommodated in the same environmental conditions. Xylazine was given 1mg/kg BW by IM route.

Conclusion: Sedation on lateral recumbency or 9th of sedation score after xylazine (1mg/kg) injection IM were reached significantly faster for bigger weight sheep ($p<0.05$). The results illustrate the need of consideration to the next studies for appropriate xylazine dose for smaller weight sheep in research.

Keywords: Sheep anesthesia; Xylazine anesthesia; Sheep

Background

Europe is facing urgent shortcomings in terms of animal welfare, whether it be long distance transportation, routine livestock mutilations, the booming trade and trafficking of pets, equines and wild animals, increased use of animals for testing and research, cruel slaughter practices or the intensification of farming systems and animal sentience as recognized in the Treaty is being disregarded [1]. The term "animal welfare" in research includes the following: animal's health, feeding, and housing in best environment; animals should be relatively free from negative conditions, such as pain, fear and distress, and capable of enjoying life behave in a way that is typical of their species [2].

The three Rs (3Rs) in relation to science are guiding principles for more ethical use of animals in testing. The 3Rs are: replacement: methods which avoid or replace the use of animals in research. Reduction: use of methods that enable researchers to obtain comparable levels of information from fewer animals, or to obtain more information from the same number of animals. Refinement: use of methods that alleviate or minimize potential pain, suffering or distress, and enhance animal welfare for the animals used [3]. "Refinement alternatives" refers to the modification of husbandry or experimental procedures to minimize pain and distress, and to enhance the welfare of an animal used in science from the time it is born until its death [4]. Examples of refinement include, using appropriate anesthetics and analgesics [5].

Research animals are valuable tools for understanding the patho physiology and in developing therapeutic interventions for a disease [6]. Proper selection of the animal model in the protocol development will allow justification for animal use and maximize the chances for a successful research outcome. Correspondingly, the animal model will continue to be important for testing these new therapies before they are applied in clinical studies.

Both large and small animal models have been developed for the study of myocardial ischemia. The advantage of large animal models relates primarily to their similarity in physiology to humans and ease of instrumentation [7]. Depending on the cardiovascular process being studied, the choice of animal model needs to be considered carefully since it affects experimental outcomes and whether findings of the study can be reasonably translated to humans. As a simple rule, the closer the heart or body weight of the animal model to human heart or body weight, the more

similar are the hearts [8]. Because of its similarity to humans in important respects, sheep (Ovis aries) are a common animal model for translational research in cardiovascular surgery [9]. There are several reasons why sheep make excellent experimental subjects for physiological studies. Their body weight and size approximates to that of a human, and they adapt rapidly and extremely well to a laboratory environment [10].

According to EU requirements: Member States shall ensure that, unless it is inappropriate, procedures are carried out under general or local anesthesia, and that analgesia or another appropriate method is used to ensure that pain, suffering and distress are kept to a minimum. Procedures that involve serious injuries that may cause severe pain shall not be carried out without anesthesia. Moderate procedures include surgery under general anesthesia and appropriate analgesia, associated with postsurgical pain, suffering or impairment of general condition. Examples include: thoracotomy etc [11].

There are some disadvantages in ruminant anesthesia, special consideration needed because of bloat/rumen distension, regurgitation/aspiration of rumen content, salivation, difficult intubation, cardiovascular and respiratory distress such as hypoxemia, hypoventilation, hypotension/poor perfusion, hypothermia. But in general, ruminants can be anesthetized successfully by general anesthesia. Sheep respond well to and recover quickly from general anesthesia. The inhalation anesthesia which is the best type of anesthesia, not always available in the field, and the use of the injectable anesthetics is mandatory [12,13].

In some studies there is proved intramuscular administration of xylazine for premedication in sheep provided the best route of administration for onset, duration, and total analgesic response in compare with IV and subcutaneous routes. The intramuscular administration of xylazine gives no significant changes on heart rate, mean arterial blood pressure, cardiac output, or arterial carbon dioxide tension; also the arterial hypoxemia is reduced as a result of intramuscular administration [13].

Case presentation

All procedures involving animals conformed to the European Community guiding principles and were approved by the State Food and Veterinary Service of the Republic of Lithuania and the Ethics Committee of the Lithuanian University of Health Sciences. Animals used for this study were presented to Lithuanian University of Health Sciences Animal Research Center in May 2017. Animals were used for open thorax cardio surgery – ischemia model and also were used for this study. The study was performed on 15 healthy adult local breed female sheep. All animals accommodated in the same environmental conditions, and were divided into three weight groups they got same anesthetic protocol, same xylazine dose by IM route.

Premedication were performed for selected sheep, carried out by one person into the small, quiet and calm capturing the animal and under sterile conditions performing intramuscular injection to administer medicines for premedication: xylazine (1mg/kg IM) approximately after 5 to 10 minutes sheep lies down, it depends on sheep weight and age, then sheep is moved to the shaving table and then gets injection of butorphanol (0.2mg/kg IM), without additional fixation, suffering and fare. Butorphanol were repeated after 1 hour during operation for pain management. The anesthesia protocol includes premedication, induction, following tracheal intubation; each patient is connected to a standard circle anesthetic circuit. Sevoflurane oxygen was supplied by use of an out-of-circuit precision Sevoflurane vaporizer and artificial ventilation Dräger apparatus.

Statistical Analysis

Data were analyzed using MS Office Excel 2010 (MS Windows, USA). Normally distributed data were analyzed using analysis of variance (anova) single factor; F-test was used to test the null hypothesis that the variances of two populations are equal. Anova and F-test were used to compare data between groups. For all analyses, a p-value of <0.05 was considered to indicate significance.

Results

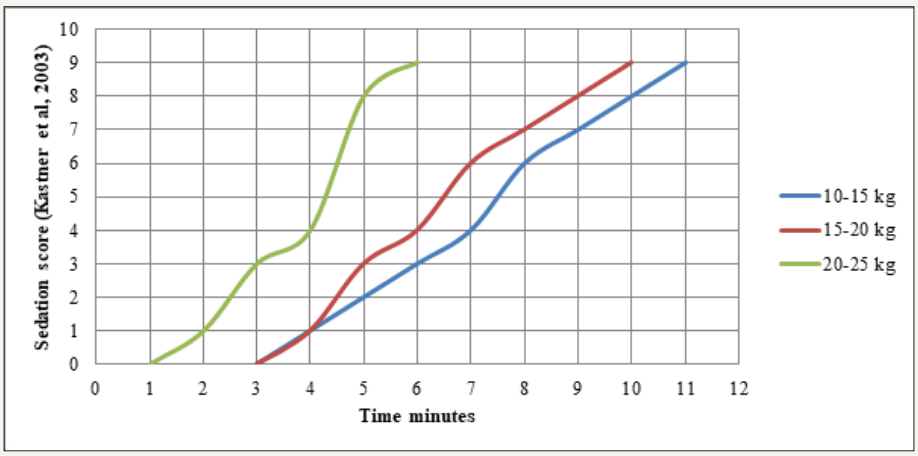

Figure 1: Sedation scores in fifteen sheep different weight groups (10-15kg n=4; 15-20kg n=3; 20-25kg n=8), after intramuscular administration of xylazine (1mg/kg).

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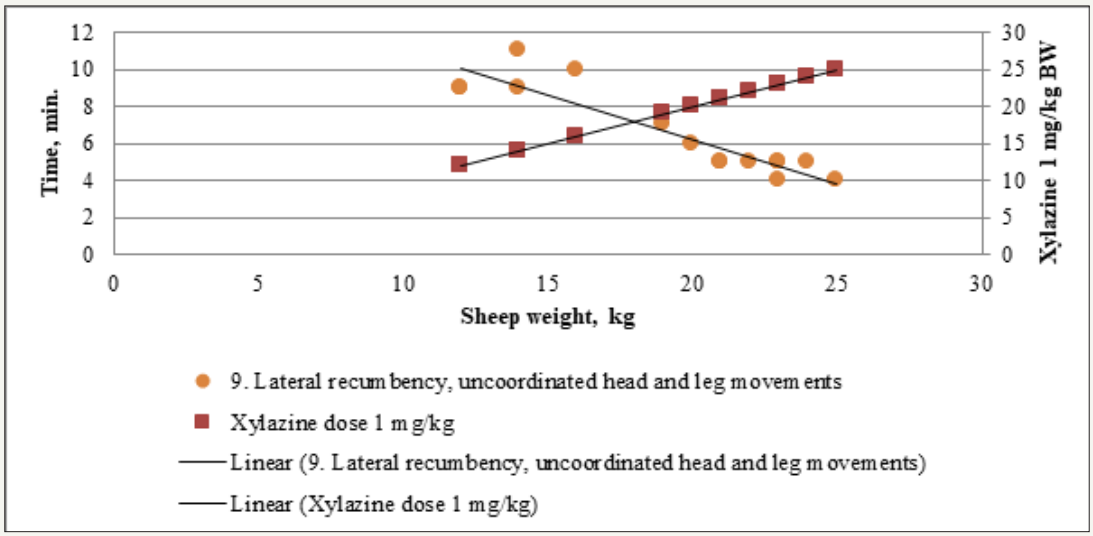

Figure 2: Sedation or 9th stage of sedation score Kästner et al. [14] after xylazine (1mg/kg) injection IM were reached significantly faster for bigger weight sheep ($p<0.05$). Dots in graph represent round numbers. Minimum weighing sheep (12kg) 9th sedation stage reached in 10min., the maximum weighted sheep (25kg) reached the same stage in 4 minutes, all with the same dose of xylazine 1mg perkg BW.

Fifteen animals were included in the study and all completed premedication period without side effects or complications. Behavioral effects like sedation scores were noted Kästner et al. [14] in time scale (Figure 1 & 2). Sedation scores from=0 indicates standing, alert, normal behavior to sedation score then 10 indicates lateral recumbency, no movement. In this study the xylazine alone never caused sedation score 10. Highest score was 9=lateral recumbency, uncoordinated head and leg movements Lines indicate averages scores. *Significantly different from each group within the same dose of xylazine ($p<0.05$). After xylazine IM injection sedation scores of three different sheep weight groups were noted on time scale. Sedation score on time scale were compared between groups, those in I group (10-15kg) reached sedation 9th score lateral recumbency, uncoordinated head and leg movements at 9.5±2 minutes were significantly slower compared with II (15-20kg) and III 20-15kg) groups ($p<0.05$).

Discussion and Conclusion

Xylazine was initially developed in 1962 by Bayer (Leverkusen, Germany) as an antihypertensive drug. However, it was limited for human use by its potent sedative side effects. Later xylazine became an effective sedative drug for animal use [15]. Xylazine is 10-20 times more potent in ruminants than in other species. In sheep, it has a short elimination half-life and is rapidly cleared from plasma after intramuscular (IM) and intravenous (IV) administration. The peak level of drug concentration in the plasma is reached after 12-14min in all the species studied following intramuscular administration of Xylazine [16]. Recommended doses of xylazine for IV administration to sheep vary markedly [13], were found that 0.05mg kg of xylazine IM resulted in poor sedation, whereas administration of 0.1mg kg xylazine IM resulted in obvious signs of sedation, but the animals remained standing [17]. Doses of drugs used for sedation, analgesia, and anesthesia vary greatly depending on the anesthetic protocol, the physical condition of the animal, the route of administration, and the particular indication [12]. The IM route is seen more reliable than the IV in sheep, it is easy to give, with less excitement to the patient, further to that it increase the duration of anesthesia, and analgesia with less adverse effect on respiration, heart rate, and other vital signs of animal [13]. Xylazine can cause dose-dependent cardiovascular depression, although this is less after IM injection. Rapid IV injection of α_2-agonists without supplementary oxygen should be avoided whenever hypoxemia may be critical [18].

Table 1: Numerical rating scale for assessment of sedation in sheep Kästner et al. [14].

Score	Behavior
0	Standing, alert, normal behavior
1	Standing, alert, reduced head and ear movements
2	Standing, slight head drop
3	Standing, moderate head drop
4	Standing, severe head drop and ataxia
5	Standing, severe head drop and severe ataxia
6	Sternal recumbency, head up
7	Sternal recumbency, unable to support head
8	Lateral recumbency, occasional attempts to attain sternal recumbency
9	Lateral recumbency, uncoordinated head and leg movements
10	Lateral recumbency, no movements

In our study for premedication were chosen higher Xylazine dose 1mg per kg BW by intramuscular route in order to avoid animal suffering, pain and fare caused by animal capturing, fixation etc. In first protocol was injected Xylazine, then waited 5 minutes after that injected Butorphanol, but then longer time of sheep lateral

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recumbency between different weights were noted. Fifteen animals were included in the study and all completed premedication period without side effects or complications, operation i.e. thoracotomy were proceeded after induction, intubation and on general and local anesthesia Table 1.

I group (10-15kg) reached sedation 9th score=lateral recumbency, uncoordinated head and leg movements at 9.5±2 minutes and were significantly slower compared with II (15-20kg) and III 20-15kg) groups ($p<0.05$). Minimum weighing sheep (12kg) 9th sedation stage reached in 10min., the maximum weighted sheep (25kg) reached the same stage in 4 minutes, all with the same dose of xylazine 1mg per kg BW. The results illustrate the need of consideration to the next studies for appropriate xylazine dose for smaller weight sheep in research in order to reduce animal suffering, pain and fare. Further studies are needed to show is it safe to use higher doses of xylazine for premedication in less weighing animals.

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