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Original Article

Effects of Ketorolac, Xylazine, and Bupivacaine Multimodal Analgesia on Goats

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Abstract

The current study aimed to investigate the effect of some of the analgesic drugs, such as Xylazine, Ketorolac, and Bupivacaine alone/mixed, on analgesia scores in the local breed goats. This research was performed on 35 male and female local breed goats within the age range of 6-8 months with an average weight of 17±3 Kg. The animals were divided into seven groups (n=5). The first group received Xylazine at a dose of 0.1 mg/kg BW through intramuscular injection (IM), while the second group was administered Ketorolac at a dose of 2 mg/kg BW through IM. The third group was administered Bupivacaine at a dose of 2 mg/kg BW through subcutaneous injection (SC). The fourth group was administered ketorolac at a dose of 2 mg/kg BW through IM and after 1 h was administered xylazine at a dose of 0.1 mg/kg BW through IM. The fifth group was administered Bupivacaine at a dose of 2 mg/kg BW through SC and after 1 h was administered xylazine at a dose of 0.1 mg/kg BW through IM. The sixth group was administered a mixture of Bupivacaine and ketorolac at the dose of 2 mg/kg BW through SC and 2 mg/kg BW through IM, respectively. The seventh group was administered Bupivacaine at a dose of 2 mg/kg BW through SC and ketorolac at the dose of 2 mg/kg BW through IM simultaneously. After 1 h, the seventh group was administered xylazine at the dose of 0.1 mg/kg BW through IM. Analgesia scores were evaluated every 10 min from the starting point for 180 min to determine values, such as respiratory and heart rate as well as rectal temperature. Moreover, the analgesic degree was examined for the head, flanks, hind limb, forelimb, and tail every 10 min. The recorded data in the current study revealed that the seventh group had a higher analgesic effect, compared to the other groups depending on the analgesia of the head, tail, flank, forelimb, and hindlimb. In the end, the group that received the mixture or combination of Bupivacaine (2 mg/kg BW-SC) and ketorolac (2 mg/kg BW-IM) followed by the administration of xylazine at a dose of 0.1 mg/kg BW after 1 h had a short period of onset of analgesia and showed long analgesia time and more depth, compared to other groups and without ataxia.

Keywords: Bupivacaine, Goats, Ketorolac, Multimodal analgesia, Xylazine

1. Introduction

The domestic goat (*Capra hircus*) is one of the oldest domesticated species of animal initially domesticated from the wild goat *C. aegagrus* in the Zagros Mountains of Iraq and Iran 10,000 years ago (1). It should be mentioned that there are over 300 distinct breeds of goat. *Capra hircus* is a member of the animal family *Bovidae* and the subfamily *Caprinae*. Goats are the best example of a multipurpose species as they have been used for milk, meat, fur, and skins almost all over the world (2, 3). Moreover, they are widely used as models in biomedical research (4).

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage resulting in physiological and behavior changes (5). This undesirable feeling is accompanied by tissue damage and surgical operation. It is a complex process consisting of biopsychosocial

reactions between neurochemical systems and neuroanatomic systems with emotional and mental processes (6).

Like other animal species, small ruminants and goats experience pain after noxious stimuli that come from trauma or disease (7). Goats are evidently sensitive to pain and intolerant of painful procedures; hence, their reactions to pain often include extreme bleating, whining, and crying (8). The sudden deaths after the operation are attributed to ventricular fibrillation induced by catecholamine due to inadequate analgesia. Therefore, the analgesia should start before the operation using several techniques and analgesic agents that work on several pain pathways (9).

The α2-agonists were used as sedative agents; however, analgesic effects were revealed at below sedative doses (5). Xylazine is a sedative, analgesic, muscle relaxant, α2-agonists drug commonly used in veterinary practice (10, 11). It is 10 to 20 times more effective on ruminants, compared to other species and causes more profound sedation. Therefore, it is used as sedative, analgesics, and anesthetic adjuncts (11). The goats are more sensitive to xylazine, compared to the sheep, and it should be noted that xylazine has different analgesic effects among the sheep breeds.

The α2-agonists result in respiratory depression, hypercapnia, and significant hypoxemia in small ruminants (9, 12). The α2 agonists exert their analgesic effects on spinal and supra-spinal regions. The primary afferent terminals in peripheral and spinal nerve endings are the common locations in which the α2 receptors are placed, which are at the level of the superficial laminae of the dorsal horn of the spinal cord and centrally in the brainstem. Therefore, the analgesic actions are predictable when α2-agonists are administrated in any of these locations, which may also be synergistic with other groups of analgesic agents (13). The α2-agonists provide an intense but short duration of analgesia when given systemically. The I.M. administration of xylazine provides long analgesia, compared to I.V.; however, the peak effect duration was shorter (14).

Small Animal Veterinary Association advises using local anesthesia as part of multimodal analgesia in small animals (15). Bupivacaine is a local anesthetic drug providing analgesia for a long time in small ruminants. It is used as an anesthetic in the epidural space, causing sleepiness, tremors, and bloating, so it should be taken care of when used in the ruminants (16). Bupivacaine has no adverse effects on blood gases or hematological and biochemical parameters (17).

Ketorolac tromethamine (KT) is a nonsteroidal anti-inflammatory drug (NSAID) that is a derivative of heteroaryl acetic acid (18). It has high analgesic qualities and is mostly employed in the treatment of human discomfort. It is the first nonsteroidal anti-inflammatory drug (NSAID) to be licensed for parenteral usage and may be taken intravenously or intramuscularly. This analgesic medication is effective whether used alone or in conjunction with other agents as part of a multimodal analgesic strategy (19). It may also be administered orally to provide analgesic relief.

As a result of decreasing the production of prostaglandins, ketorolac has analgesic and anti-inflammatory properties. When administered to humans, ketorolac is quickly absorbed with a mean half-life for absorption of 3.8 min and a duration of action ranging within 6-8 h. It should be mentioned that the same is true for animals as well (20). After intravenous or intramuscular injection, the analgesic impact is felt within 30 min with the maximal effect occurring between 1 and 2 h with a duration of 4-6 h (21).

Little research has been performed regarding pharmacokinetics and their use in farm animals. A single dose pharmacokinetic profile of KT has been evaluated in sheep (22), calves (23), and goats (24). The KT in farm animals has extreme species differences in terms of pharmacokinetics. Its half-life was 4.5-10 h in dogs and humans (18). In goats and calves, the intravenous administration of the dose led to a short half-life, while the oral administration resulted in a long half-life (23, 24). The very rapid decline of

the ketorolac concentrations in plasma suggests that the drug should not be used as single analgesic therapy in sheep (22).

The practice of a combination of various analgesic medication classes or strategies to target distinct sites along the pain pathway is known as multimodal analgesia (25). The notion of multimodal analgesia was created on the basis of the understanding that postoperative pain is a complicated and multifaceted event that requires a variety of treatment options. As a result, it is probable that rather than relying on a single medicine or approach, a combination of analgesics from various classes operating on diverse target locations may give improved pain relief while reducing the likelihood of unwanted effects.

Multimodal analgesia can be defined as the administration of two or more medications that act through different mechanisms to provide analgesia, such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ketamine, 2-agonists, glucocorticoids, and duloxetine. It should be noted that each of these medications has a distinct mechanism of action for providing analgesia. This has the ability to lessen the unpleasant effects of opiates, such as nausea and vomiting, as well as respiratory depression which, in turn, reduces the likelihood of more severe problems. These medications may be delivered via the same route or through other methods.

The goal of multimodal analgesia is to increase pain management while decreasing the need for opioids and the harmful consequences associated with their use (26, 27). Multimodal analgesia aims to block the pain pathways at various places at the same time by using drugs with diverse modes of action, resulting in more effective pain management with lower dosages and a lower prevalence or severity of toxic side effects. Transduction and peripheral sensitization may be inhibited using drugs. They can also be used to block the transmission of sensory impulses, alter the spinal pathways involved in central sensitization and block the perception of an unpleasant stimulus in the brain (28).

The present study aimed to evaluate the use of ketorolac, xylazine, and bupivacaine combination as a multimodal analgesia protocol in goats.

2. Materials and Methods

2.1. Chemicals and Disposable Devices

Several materials were used in this study, such as a disposable syringe with different sizes of 5, 10, 20 ml (manufactured in China), Povidone 10% (manufactured in Turkey), Cotton, Hypodermic needles gauges with sizes of 23, 22,19, and 18) (manufactured by Pic, Italy), xylazine (manufactured by AstraZeneca, UK), ketorolac (manufactured by Huons, South Korea), and Bupivacaine (manufactured by Dutch, Germany).

2.2. Study Design

G1: Xylazine group: Xylazine administration at a dose of 0.1 mg/kg BW-IM (28)

G2: Ketorolac group: Ketorolac administration at a dose of 2 mg/kg BW-IM (22)

G3: Bupivacaine group: Bupivacaine administration at a dose of 2 mg/kg BW-SC (28)

G4: Xylazine ketorolac group: Ketorolac administration at a dose of 2 mg/kg BW-IM and after 1 h, administration of xylazine at a dose of 0.1 mg/kg BW-IM

G5: Xylazine Bupivacaine group: Bupivacaine administration at a dose of 2 mg/kg BW-SC and after 1 h, administration of xylazine at a dose of 0.1 mg/kg BW-IM

G6: Bupivacaine ketorolac group: Bupivacaine administration at a dose of 2 mg/kg BW-SC and simultaneous administration of ketorolac at a dose of 2 mg/kg BW-IM

G7: Xylazine Bupivacaine ketorolac group: Ketorolac administration at a dose of 2 mg/kg BW-IM and simultaneous administration of Bupivacaine at a dose of 2 mg/kg BW-SC, then after 1 h, administration of xylazine at a dose of 0.1 mg/kg BW-IM

2.3. Preparation of Animals

Animals were housed in an animal college station for 2 weeks before the experiment. They were dewormed

and kept for acclimatization on place and weather. Moreover, they did not receive food for 12 h and water for 2 h before the reception of analgesic drugs.

2.4. The Vital Signs

Vital signs of each animal, including the respiratory rate, heart rate, rectal temperature, degree of analgesia of the head, flank, forelimb, hindlimb, and tail were measured at a period of 180 min from the starting point of anesthesia (0-180). Furthermore, the time of injection, time of onset of analgesia, and recovery from analgesia were recorded.

2.5. Degree of Analgesia

Absence of pain (created by skin pinprick and pinching the digit of a goat), Mild degree of the analgesia +, Moderate analgesia ++, and Deep analgesia +++ (29).

2.6. Statistical Analysis

The obtained data were statistically analyzed using one way ANOVA test and Least Significant Difference to determine the significance between the groups after drug administration during the time of reading with a p-value of less than 0.05 (SPSS, 2008).

3. Results

3.1. Respiratory Rate

In general, the differences in the respiratory rates of the different groups underwent an insignificant (P<0.05) decrease from the reading of time zero, except for the G6 which showed a significant increase at the beginning of anesthesia for a short period followed by a decreasing trend. The findings are shown in figure 1.

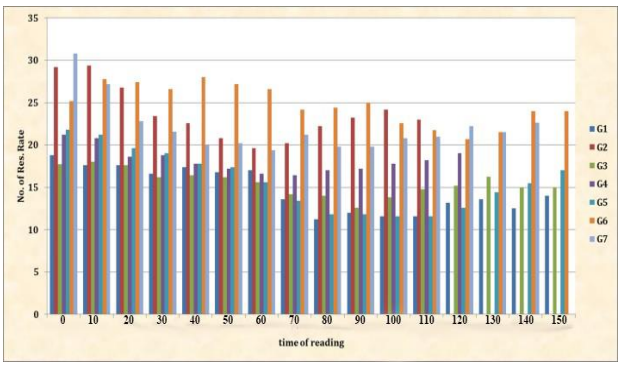

Figure 1. Respiratory rate trends after starting anesthesia in different groups

3.2. Heart Rate

Generally, all groups initially showed a slow decrease in HR followed by a slow increase till the end of the reading, except for G3 which underwent an increase at 10 min followed by a slow decrease till the end of the reading. It should be noted that these readings are insignificant at the level of P<0.05 as shown in figure 2.

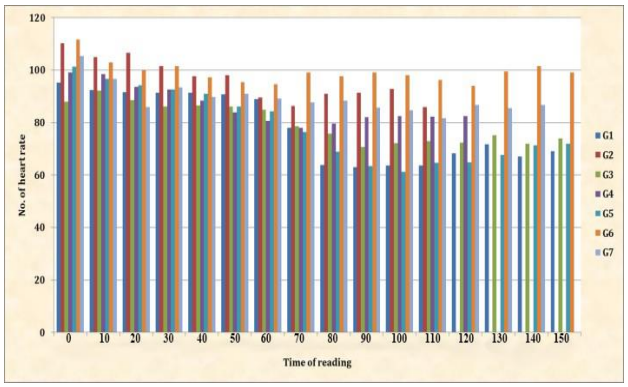

Figure 2. Heart rate trends after starting anesthesia in different groups

3.3. Rectal Temperature

Generally, there was a slight decrease in rectal temperature in different groups. These readings were non-significant at the level of P<0.05 as shown in figure 3.

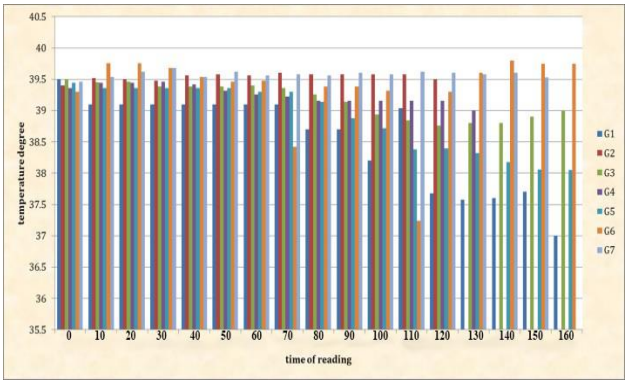

Figure 3. Rectal temperature trends after starting anesthesia in different groups

3.4. Level of Analgesia in Different Body Parts of the Animals

The recorded data in G1 showed a deep level of analgesia at 20 min from the zero time and stayed at the same level to the end of 40 min. Afterward, it underwent a gradual decrease and reached the moderate level in 90 min and then disappeared until the end.

The recorded data in G2 showed that a mild level of analgesia started at the min 50 and stayed at the same level until the min 80 and then disappeared until the end. The results from the G3 showed that a mild level of analgesia started at the min 60 and stayed at the same level to the min 80, then decreased until it disappeared by the end. The recorded data in G4 showed that a mild level of analgesia started after 50 min which increased to the moderate level at the min 60, but decreased to the mild level at the min 70, and continued decreasing until the min 80 and 90 and finally disappeared by the end.

The obtained results from G5 showed the mild effect of analgesia at the min 50 which became deep at the min 60 and stayed deep till the min 100 but decreased after that till the end. The recorded data in G6 showed mild analgesia at the min 50 which increased gradually to a moderate level at the min 80 and stayed at the same level until the min 100 but decreased gradually till the end. In G7, the results showed mild analgesia at the min 40 which increased to the moderate level at the min 50 and reached the deep level at the min 70 and stayed at the same level till the min 120, then decreased gradually till the end.

Statistically, the analgesia in G2, G3, G4, G5, and G6 groups 10, 20, and 30 min after the beginning points showed significant (P<0.05) differences with the first group. The level of analgesia 40 min after the starting point of the experiment showed significant differences between the first and the sixth group. The level of analgesia 50 min after the starting point of the experiment showed that there was no significant difference among the G2, G4, G5, and G6 groups; however, this set showed significant differences with G1, G3, and G7 groups.

The level of analgesia 60 min after the starting point of the experiment showed that there were no significant differences among G2, G3, and G6 groups. Moreover, there were no significant differences between G4, G5, and G7 groups, and these sets showed significant differences with the first group. The level of analgesia 70 min after the starting point of the experiment showed that there were no significant differences among G2, G3, and G4 groups or among G5 and G6 groups. Moreover, G2, G3, G4, G5, and G6 groups had significant differences from G1 and G7 groups.

The level of analgesia 80 min after the starting point of the experiment showed that there were no significant differences between G2, G3, and G4 groups. Moreover, the level of analgesia 80 min after the starting point of the experiment showed that there were no significant differences between the G1, G6, and G7 groups, while these sets showed significant differences with the G5 group. The level of analgesia at the min 90 was not significantly different among the G1, G2, and G4 groups.

The level of analgesia 100 min after the starting point of the experiment showed that there were no significant differences among G2, G3, and G4 groups or between G6 and G7 groups. However, the rest of the experimental groups had significant differences with each other and with the above-mentioned sets. Furthermore, the level of analgesia 110 min after the starting point of the experiment showed that there were no significant differences among G2, G3, and G4 groups or between G6 and G7 groups. However, the rest of the experimental groups showed significant differences with the mentioned sets of groups (G2-G4, G6, and G7).

The level of analgesia 120 min after the starting point of the experiment was not significantly different among G2, G3, and G4 groups or between G4 and G7 groups. Nevertheless, the rest of the experimental groups showed significant differences from the aforementioned sets of groups. The level of analgesia 130 min after starting point of the experiment was not significantly different among G1, G2, G3, G4, and G6 groups, while the rest of the experimental groups showed significant differences with the aforementioned sets of groups (G1-4 and G6). The level of analgesia 140 min after the starting point was not significantly different among the G1, G4, and G6 groups, while the

rest of the experimental groups had significant differences with each other in this regard. The level of analgesia 150 min after the starting point was not significantly different between G1 and G6 groups, while the G7 group showed significant differences with the previous set. The level of analgesia 160 min after the starting point was not significantly different between G1 and G6 groups, while the G7 group had significant differences with them in this regard.

4. Discussion

A combination of medications from different classes offers effective analgesia with fewer doses of individual agents, which may reduce the severity of dose-related adverse events. Each medication has a special target pain mechanism and the combination of different medications with different mechanisms of action expand the area of analgesia. This approach offers increased efficacy due to additive or synergistic effects without increasing the dose (9).

A multimodal analgesic approach should be used for the treatment of postoperative pain as it can potentially reduce side effects and provide the benefit of treating pain through different cellular pathways (26). In general, the respiratory rate in all groups decreased, compared to the reading of time zero, except for G6, which first increased and then decreased. In addition, xylazine has been linked to reduced lung amenability, tachypnea, pulmonary edema, and hypoxia in goats, among other things.

It is possible that small ruminants are more susceptible to the effects of alpha2 agonists on respiratory function than cattle (30). The administration of xylazine to goats results in bradycardia and a decrease in cardiac output (31). In sheep, xylazine causes decreased thermoregulation, resulting in hypothermia (32). A comparison was made between the length of the anesthetic produced by bupivacaine, with or without epinephrine, and that produced by lidocaine, with or without epinephrine. Based on the results of this comparison, bupivacaine is recommended for extended flank surgery (29).

Twelve healthy small East African goats of both genders were administered 2% lidocaine and 2% xylazine, and both medications elicited analgesia within 5 min in both groups. Within 5-7 min of administering epidural xylazine, signs of drowsiness, cardiovascular alterations, and lateral recumbency appeared on their faces. Approximately 3 min after lidocaine was administered epidurally, tail flaccidity and hind limb paralysis ensued. The analgesic effect of xylazine was sufficient, spreading from the flank to the head and forelimbs (33).

In addition to being an anti-inflammatory agent, ketorolac is an analgesic drug that may be used in conjunction with other medications to manage acute pain in the limbs and head. Ketorolac may be injected intravenously or intramuscularly and has been shown to be an effective analgesic agent whether used alone or in combination with other drugs as part of a multimodal approach to analgesia (Figure 1) (19).

In conclusion, the combination of Ketorolac, Bupivacaine, and xylazine results in higher and longer analgesia in goats, compared to the other groups.

1. Addition of xylazine to the other analgesic drugs makes the analgesia start early in goats.
2. Usage of ketorolac alone in goats in the dose used in this experiment gives short and mild analgesia, while its use in combination leads to a synergistic effect, and enhances the effect of multimodal effect of analgesia.

Recommendations

1. Usage of this combination (ketorolac xylazine and Bupivacaine) in another protocol (doses) for pre- and post-operation analgesia.
2. Conduction of more trials and studies about this topic, and studying the possibility of its application on other animals.

Authors' Contribution

Study concept and design: A. F. S.
Acquisition of data: A. F. S.
Analysis and interpretation of data: T. A. A.
Drafting of the manuscript: T. A. A.

Critical revision of the manuscript for important intellectual content: A. F. S.
Statistical analysis: A. F. S.
Administrative, technical, and material support: A. F. S. and T. A. A.

Ethics

The study protocol was approved by the ethics committee at the University of Al-Qadisiyah, Al Diwaniyah, Iraq.

Conflict of Interest

The authors declare that they have no conflict of interest.

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