

Comparison of the anesthetic effect of paracetamol, tramadol, ketamine, xylazine, combination in three anesthetic protocols by using two different administration routes in sheep

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Abstract

The present study was aimed to compare the efficacy of using three anesthetics protocols of sheep anesthesia by combination of Ketamine (K), Paracetamol (P), Tramadol (T), and Xylazine (X), giving by IV or IM routes. Fifteen healthy adult local breed sheep of both sexes weighing (27.4 ± 2.46) kg and aged (12-14 months) were used and divided into three equal groups. Animals were accommodated in the same environmental conditions. G1 was giving $K_4 T_2 P_{10} X_{0.05}$ by IV route, G2 giving $K_{10} T_2 P_{10} X_1$ mg/kg by IM route and G3 giving $K_{20} T_4 P_{10} X_{2.5}$ mg/kg by IM route. The HR, RR, RT, muscle relaxation, limb, and flank analgesia, and rumen movement were taken before administration of anesthesia and consider as the control reading, then were taken at 5, 10, 15, 20, 30, 45 and 60 minutes or till the end of anesthesia. In G1 the induction time, the surgical anesthesia, and the total recovery time were become 50.6 s, 23 m, and 9.4 m respectively. The HR, RR, and RT were increased, the muscle relaxation, and analgesia were moderate. In G2 the induction time, the surgical anesthesia, and the total recovery time were 5, 36, and 5.6 m, respectively. The HR and RR were decreased, and the RT was increased. The muscle relaxation was deep, analgesia was moderate for 10 minutes. In G3 the induction time, the surgical anesthesia, and the total recovery time were 3.6, 73.4, and 7 m respectively. The HR started stable, then after 15 minutes decreased sharply, The RR was irregular, with apnea, the RT was increased, the muscle relaxation was deep for 35 minutes, and the analgesia was deep for 45 minutes.

In conclusion; The (K), (P), (T), and (X) combination as anesthetic protocol is seen suitable for sheep anesthesia. The surgical anesthesia, and the depth of analgesia are increased with the increase of ketamine and xylazine doses, and the addition of tramadol, and paracetamol, enhance the quality of anesthesia and make the induction and recovery are good. The protocol of G2 is seen the best between the three protocols used in this experiment. The protocol of G3 is seen superior in analgesia and duration of surgical anesthesia but with respiratory depression.

Key words: Paracetamol, tramadol, ketamine, xylazine, anesthesia, sheep.

مقارنة تأثير خليط الباراسيتامول والترامادول والكيثامين والزيلازين في ثلاثة برامج تخدير للأغنام باستخدام طرق اعطاء وجرعات مختلفة

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الخلاصة

هدفت الدراسة الى مقارنة فعالية استعمال ثلاثة برامج تخدير لخليط الكيثامين والباراسيتامول والترامادول والزيلازين في الاغنام اعطيت عن طريق الوريد او العضلة . خمسة عشر من الاغنام المحلية البالغة من كلا الجنسين كان معدل اوزانها (27.4 ± 2.46) كغم وعمرها 12-14 شهر قسمت الى ثلاثة مجاميع متساوية . المجموعة الاولى اعطيت كيثامين 4 ملغم/كغم والترامادول 2 ملغم/كغم والباراسيتامول 10 ملغم/كغم والزيلازين 0.05 ملغم/كغم عن طريق الوريد ،

والمجموعة الثانية اعطيت كيتامين 10 ملغم\كغم والترامادول 2 ملغم\كغم والباراسيتامول 10 ملغم\كغم والزيلازين 1 ملغم\كغم عن طريق العضلة ، والمجموعة الثالثة اعطيت كيتامين 20 ملغم\كغم والترامادول 4 ملغم\كغم والباراسيتامول 10 ملغم\كغم والزيلازين 2.5 ملغم\كغم عن طريق العضلة . تم اخذ معدل ضربات القلب ومعدل التنفس ودرجة حرارة المستقيم والاسترخاء العضلي والتسكين للأطراف والخاصرة وحركة الكرش قبل اعطاء التخدير واعتبرت قراءة السيطرة لذلك الحيوان ، ثم اعيدت القراءات في الاوقات 5 و 10 و 15 و 20 و 30 و 45 و 60 دقيقة أو حتى نهاية فترة التخدير . في المجموعة الاولى كان وقت احداث التخدير والتخدير الجراحي ووقت الافاقة هو 50.6 ثانية و 23 و 9.4 دقيقة على التوالي ، كما وازداد كل من معدل التنفس ومعدل ضربات القلب ومعدل درجة الحرارة بينما كان التسكين وارتداء العضلات متوسطا . في المجموعة الثانية كان وقت احداث التخدير والتخدير الجراحي ووقت الافاقة هو 5 و 36 و 5.6 دقيقة على التوالي ، وكان معدل التنفس ومعدل ضربات القلب قد تناقص ومعدل درجة الحرارة قد ازداد و كان ارتداء العضلات عميقا والتسكين متوسطا لمدة 10 دقائق . و في المجموعة الثالثة كان وقت احداث التخدير والتخدير الجراحي ووقت الافاقة هو 3.6 و 73.4 و 7 دقيقة على التوالي ، وكان معدل ضربات القلب قد بدء مستقرا وبعد 15 دقيقة قد تناقص بشدة وكان معدل التنفس غير مستقرا وكان مصحوبا بتوقف التنفس ، ومعدل درجة الحرارة قد ازداد و كان ارتداء العضلات عميقا لمدة 35 دقيقة والتسكين عميقا لمدة 45 دقيقة . نستنتج ان خليط الكيتامين والباراسيتامول والترامادول والزيلازين كان مناسباً كبرنامج تخدير للأغنام ، وكان التخدير الجراحي وعمق التسكين يزدادان طردياً مع زيادة جرعة الكيتامين والزيلازين ، وان اضافة الباراسيتامول والترامادول قد عززت نوعية التخدير وجعلت من احداث التخدير والافاقة جيدتان . كما ان برنامج التخدير في المجموعة الثانية كان هو الافضل من بين برامج التخدير الثلاثة المستخدمة في هذه الدراسة . و ان برنامج التخدير في المجموعة الثالثة كان متوقفاً في التسكين وطول فترة التخدير الجراحي مع انخفاض واضح في معدل التنفس .

الكلمات المفتاحية: الباراسيتامول ، الترامادول ، الكيتامين ، الزيلازين ، التخدير في الأغنام

Introduction

Ruminants in general can be anesthetized successfully by general anesthesia, but with special considerations that may affect anesthesia, like regurgitation, ruminal tympany, salivation, and cardiovascular and respiratory distress. Sheep is one species of ruminants frequently need to anesthetized with the surgical operations, and also frequently used as a model of anesthesia of ruminants. 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. Not all the anesthetic or the analgesic drugs are effective in all species of animals. The economic considerations and limited number of anesthetics and analgesics used in small ruminants may direct the use of drug and technique (1).

The ketamine, barbiturate, and propofol, are the most injectable anesthetic drugs used in the world. Ketamine a dissociative anesthetic agent can be used singly or in combination for induction, maintenance of anesthesia, and balanced anesthetic applications. It is commonly used in small ruminants for induction and maintenance of anesthesia. Ketamine alone may have many objectionable side effects, like rigidity of voluntary muscles, poor muscle relaxation, and convulsions. To subside these adverse

effects the using of sedative preanesthetic combining drugs like diazepam, and xylazine are advisable, and use of analgesics, and muscle relaxant drugs which so called balanced anesthesia that's expansion the area of ketamine usage. (2,3,4,5,6)

Tramadol is potent analgesic widely used in humans for many years, and recently introduce in veterinary analgesia (7,8,9). It is a centrally acting analgesic structurally related to codeine and morphine. It contributes the analgesic activity by serotonin, and norepinephrine reuptake inhibition (10). Thus tramadol enhances inhibitory effects on pain transmission both by opioid and monoaminergic mechanisms (11).

Paracetamol (acetaminophen) in human medicine is the most popular analgesic, antipyretic used in the world (12). While in veterinary medicine has no, or restricted use as in pigs and dogs. It acts through the cyclooxygenase (COX) pathway by inhibition of prostaglandin synthesis, also it has central analgesic effect that is mediated through the activation of descending serotonergic pathways (interferes with serotonergic descending pain pathways) (13,14,15,16). Introduce of IV injectable paracetamol formula (17,18,19,20,21,22,23, 24) in the analgesic field of human beings,

embolden us to use this drug in animals. Paracetamol tramadol combination in human beings brings together different but complementary mechanisms of analgesic action. These agents interact to produce synergistic analgesia (25,26).

Xylazine is a potent and effective α_2 -agonist sedative and analgesic drug in sheep. It has been widely used in veterinary medicine for long time as a sedative, or for control of pain alone or in combining with other drugs. Ruminants are more sensitive (10-20 time) to xylazine than other species of animals (27). Xylazine ketamine combination is frequently used for induction and maintenance of anesthesia in most species of animals. In sheep the ketamine and α_2 -adrenoceptor agonists combination increase the degree of analgesia, and prolong anesthesia, but it increase the respiratory depression till it may need oxygen supplementation.

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. Lower doses should be administered when combinations of drugs are used or high-risk animals are involved (1).

For the earlier advantages of use of each drug alone (ketamine, Tramadol, Paracetamol, and Xylazine), or in combination between them, to gain the synergistic effect of this cocktail, the study was designed to evaluate the anesthetic effect of paracetamol, tramadol, ketamine, xylazine, combination in three anesthetic protocols by using two different administration routes in sheep.

Materials and methods

The study was performed on 15 healthy adult local breed sheep of both sexes weighing (27.4 ± 2.46) kg and aged between (12-14 months). All Animals accommodated in the same environmental conditions, and were divided into three equal groups (n=5) they were giving different anesthetic protocol by two route of administration. G1(K4 T2 P10X0.05) giving IV injection of Tramadol (mepha) 2mg/kg, Ketamine (Astrapin) 4mg/kg, Paracetamol (Ajanta pharma) 10mg/kg,

and Xylazine (Bayer) 0.05mg/kg B.W., G2(K10 T2 P10 X1) giving IM injection of Ketamine 10mg/kg, Tramadol 2mg/kg, Paracetamol 10mg/kg, and Xylazine 1mg/kg B.W, and G3(K20 T4 P10 X2.5) giving IM injection of Ketamine 20mg/kg, Tramadol 4mg/kg, Paracetamol 10mg/kg, and Xylazine 2.5mg/kg B.W. (28). Animals were fasting 24 hrs. and water withheld 12hrs before giving anesthesia. The four limbs of the animal were tied (29), and the animal was cast in lateral recumbency for at least 30 minutes before taking the time zero reading (reading before giving anesthesia) of the vital signs (The heart rate (HR), respiratory rate (RR), rectal temperature (RT), and the rumen movement) (30) to minimize the effect of animal movements on the vital signs. The tie was released after giving the drugs. The baseline recordings of the RR, HR, and RT and other vital signs were recorded before administration of the drugs (reading before anesthesia) and considered as the control reading in the same animal. Then the readings were repeated at 5, 10, 15, 20, 30, 45 and 60 minutes after drug administration (or, till the recovery of animal). The induction time, duration of anesthesia, duration of surgical anesthesia, degree of limb and flank analgesia creating by skin pinprick (Scoring into Mild +1, Moderate +2, and Deep+3) (31), degree of muscle relaxation (creating by flexion and extension of the limbs, and graded to, no muscle relaxation = 0 (when the animal conscious), minimal +1, moderate +2, and marked +3 muscle relaxation (32), and recovery time were recorded also for each animal. The data were statistically analyzed using one way ANOVA test to find the significance between the times before and after drug administration and between the groups by using of SPSS program at the $P < 0.05$ (33).

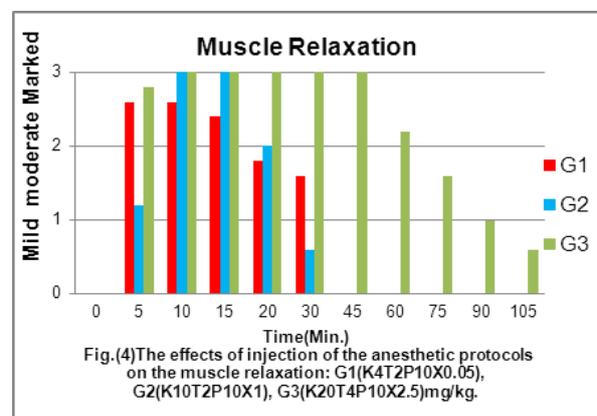
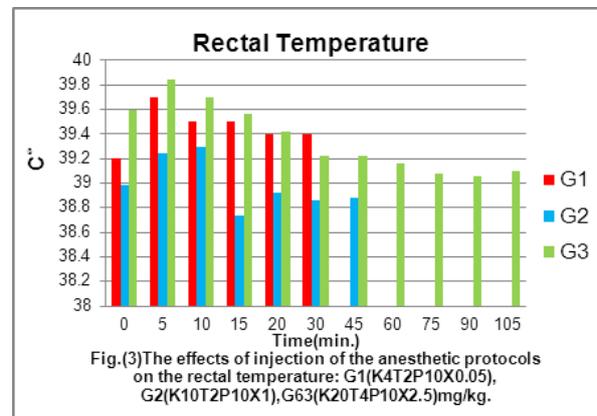
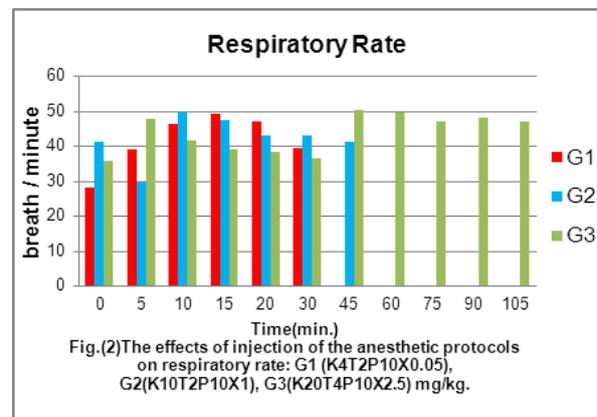
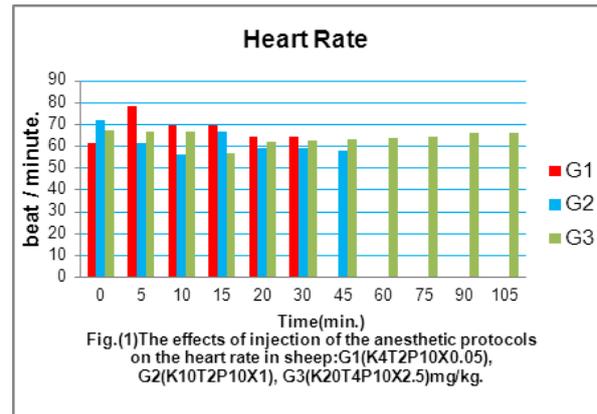
Results

The HR in G1 was increased highly and significantly at 5 minutes time of reading in compare with zero time reading. The rise was decreased slowly till the end of observation at 30 minutes where the anesthesia was ended in this group but not return to the base line (Fig.1). The RR was increased sharply at

the 5 minutes time of reading and reached a high reading 49.4 ± 18.01 breath/minute at 15 minutes of the period of anesthesia, and then reduced slowly to reach 39.6 ± 13.10 breath/minute at 30 minutes, but remain higher than the control reading (Fig.2). The RT was increased at the first 5 minutes of time reading then return to the base line reading between 10 and 15 minutes of the time of anesthesia, and then decreased below the normal till the end of observation (Fig.3). The muscle relaxation, and the limb, and the flank analgesia were moderate between 5-15 minutes then decreased below the moderate till the end of anesthesia (Fig.4, 5, 6). The rumen movement was decreased more than the control reading and the decrease was significant at 10 and 15 minutes (Fig.7). The time of induction, the surgical anesthesia, and the total time of recovery were 50.6 ± 4.93 seconds, 23 ± 3.74 minutes, and 9.4 ± 2.71 minutes respectively (Fig.8).

In G2 the HR was sharply significantly decreased at the 5 and 10 minutes time reading, where it reached the least reading 56.4 ± 2.4 beat/minute at 10 minutes in compare to the control reading. Then it again rose sharply 66.6 ± 4.7 beat/minute at 15 minutes time of reading, following by slowly decrease to reach 58.2 ± 2.57 at the end of anesthesia at 45 minutes (Fig.1). The RR was significantly decreased sharply, 29.8 ± 6.10 breath /minute at 5 minutes time of reading in compare to the control reading 41.2 ± 6.82 . The decrease followed by sharp and high increase 49.8 ± 8.25 breath /minute at 10 minutes time of reading followed by slowly decrease till the end of anesthesia at 45 minutes where it became normal. The respiration was interrupted by many episodes of apnea; each one last for more than 20 seconds, with an irregular respiratory rhythm (Fig. 2). The RT was increased during the first 10 minutes of observation in compare to the control reading, then at the 15 minutes of anesthesia decreased and remains less than the reading of before anesthesia till the end of observations at 45 minutes (Fig.3). The muscle relaxation become deep for 10 minutes only (at 10 and 15 minutes of observation) then become moderate at 20 minutes and less than mild at 30 minutes

(Fig. 4). The limb analgesia started mild at 5 minutes then become moderate from 10 to 20

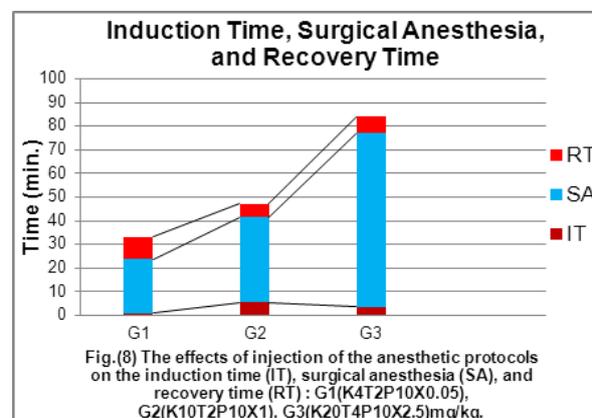
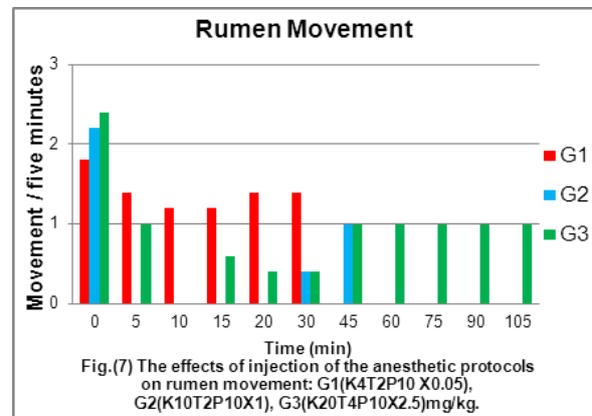
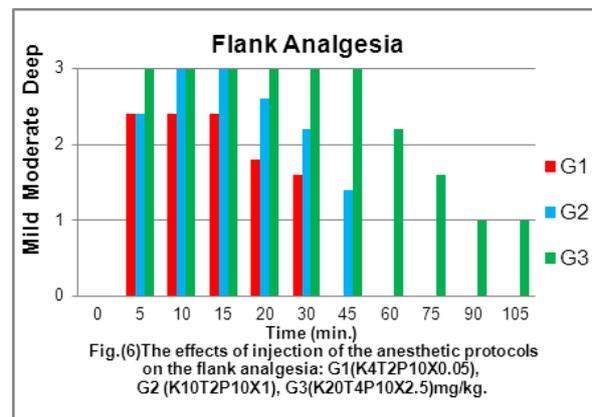
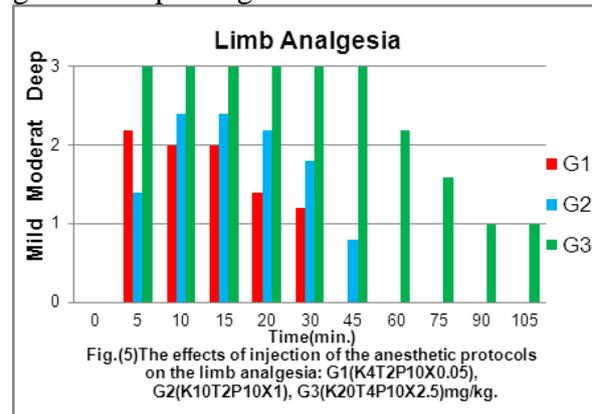


minutes, then reduced at 30 and 45 minutes (Fig.5). Flank analgesia started moderate at 5

minutes. Deep flank analgesia was gained for ten minutes (at 10 to 15 minutes time of reading), then reduced again to moderate and become mild at 45 minutes of observation (Fig.6). The cessation of rumen movement was gained from 5 to 20 minutes of anesthesia then regain at 30 minutes and 45 minutes but not reach to the reading before anesthesia (Fig. 7). The time of induction of this IM route of injection anesthetic protocols was 5.6 ± 1.02 minutes, and the surgical anesthesia was 36 ± 3.96 minutes, while the total time of recovery was seen very short, taking only 5.6 ± 1.16 minutes (Fig.8).

In G3 The HR was little stable near the readings before anesthesia at the first 10 minutes of anesthesia, then decrease sharply and significantly at the 15 minutes followed by slowly increased till the end of anesthesia after 105 minutes where it become 66 ± 4.42 beat /minute (Fig.1). The RR was irregular. There was significant sharp increase 48 ± 4.14 breath/minute at 5 minutes in compare with 36 ± 3.20 breath/minute before anesthesia, then decreased and became around 40 breath/minute up to the 20 minutes time of anesthesia. At 30 minutes there was sharp significant decrease of RR where it reached the least reading 36.6 ± 6.16 breath/minute, followed by sharp significant increase where it reached the highest reading 50.4 ± 6.74 breath/minute at 45 minutes, succeeding by slow decrease in rate until it reach 47.2 ± 5.74 breath/minute at 105 minutes the end of anesthesia (Fig. 2). The respiration was significantly high most of the time of anesthesia. Many episodes of apnea each one lasted more than 20 seconds with high grunt sounds interpose the respiration during anesthesia. The RT was increased at the 5 and 10 minutes time of anesthesia, and then decreased near to the normal at the 15 minutes, afterward the RT continued in reducing slowly where it reached 39.1 ± 0.21 at the end of anesthesia in 105 minutes (Fig. 3). The muscle relaxation started moderate at the first 5 minutes of anesthesia, and then developed to deep relaxation extending between 10 to 45 minutes of anesthesia, where it reduced gradually to become moderate, then mild at 75 and 90 minutes of time of anesthesia (Fig. 4). The analgesia of

flank region and the analgesia of limbs gained deep analgesia for 45 minutes where



it converted to moderate and finally become mild at the end of anesthesia (Fig. 5, 6). The

rumen movements were decreased and reached the least reading at 20 and 30 minutes of anesthesia time and again rose slowly till the end of anesthesia but did not reach the reading before anesthesia (Fig.7). The induction time was taking short time 3.6 ± 1.60 minutes while the surgical anesthesia was 73.4 ± 10.71 minutes and the total recovery time was 7.0 ± 2 minutes (Fig. 8).

Discussion

The economic considerations and the limited number of anesthetic and analgesic drugs authorized to use in small ruminants anesthesia may directive the use of the drug and the technique. Inhalational anesthesia in the field is unpractical and uneconomic, except when the economic value of the animal is high. Injectable anesthesia is easy and relatively safe to perform and has advantages in improve quality of pain management. Injectable anesthetics are used for either induction or for maintenance of short-term anesthesia (1).

Balanced anesthesia is use of multiple drugs to minimize the dose and therefore the side-effects of any one of drug (34). It has been widely used for many years, this term also transferred to pain medicine, so called balanced analgesia (35,36). Combining drugs from different classes offers effective analgesia with fewer doses of individual agents, which may reduce the severity of dose related adverse events. Each drug has special target pain mechanism. Combination between different drugs with different mechanisms of action expanse the area of analgesia. This approach offers increased efficacy due to additive or synergistic effects without increasing the dose. The ideal combination regimen would both enhance analgesic efficacy and reduce the side effects compared with either treatment alone.

Analgesia is an integral part of anesthesia; however, most of the sedatives and anesthetics have mild, if any, analgesic effects. Therefore, it is mandatory to use specific analgesic agents. However, the use of analgesic agents is not common in small ruminant practice (1). For instance, local anesthetics, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), as well as

other analgesics used in humans are all found to be effective for animal use. Differences in metabolism and distribution between various species, as well as financial considerations in larger animals can affect efficacy and thus limit their use (9). The choice of a specific drug combination depends on the degree of analgesia want to obtained, the duration of anesthesia required, the species of animal, along with the animal physical status.

In G1, the RR is increased sharply and significantly after 5 minutes of drugs injection, then decrease slowly. This result is in agreement with (37), who find the respiratory rate in sheep is increased within 5 minutes of drug administration in xylazine ketamine anesthesia. Also it is in accordance with (30), using xylazine ketamine in goats, and(38), using xylazine ketamine, diazepam anesthesia in sheep and goat. Also agreed with(39), using acepromazine ketamine anesthesia in sheep. Using of xylazine alone in sheep cause tachypnea. A range of xylazine doses alter respiratory mechanics and gas exchange, causing tachypnea (27). The position of animal may also has an effect on respiration. In the lateral, and more particularly dorsal recumbency the large mass of rumen and intestine may cause respiratory and cardiovascular distress due to pressure on diaphragm and great vessels. Pressure on diaphragm lead to decreased tidal volume and inadequate ventilation (40). The HR is also increased, although the xylazine, and the tramadol have cardiovascular depressant effect. This may due to the effect of ketamine. Ketamine appears to stimulate the cardiovascular system, producing increase in the heart rate, cardiac output and the blood pressure, due to the sympathomimetic effects of ketamine in blocking the reuptake of catecholamine (4,41). This result not in harmony with the previous studies(30,38,39). It seems these drugs have species specificity, and it need more investigations in future. The rectal temperature is increased. This result is in agreement with (42) in sheep. The rumen movement is decrease below the control reading. This result attributed to the effect of xylazine. The xylazine cause reduces in rumen motility (27). The muscle relaxation

and analgesia in G1 are moderate and extended 10 minutes only. This result attributed to the low doses of ketamine and xylazine used in this group. The analgesia is affected by the type of drug, species of animal, doses, and route of administration of drug (9). The α_2 agonists e.g medetomidine (43), and xylazine (44) give satisfactory analgesia in this species. Balanced analgesia using more than one class of drug such as α_2 -agonists, ketamine, and non-steroidal anti-inflammatory drugs provide the best analgesia for severe pain (43). The time of induction in G1 is short and taken 50 seconds only. The route of administration of sedatives, analgesics and anesthetic drugs are important for determining the induction, duration, and depth of each case. The IV route is the fastest for giving the effect, but is the shortest in duration (5). The IV administration of xylazine in sheep give the most rapid onset and give highest peak analgesia but it have short duration of action (28). The surgical anesthesia in G1 is 23 minutes, the combination of ketamine with α_2 -adrenoceptor agonists enhance the degree of analgesia, and prolongs anesthesia. The α_2 -agonists in combination with ketamine which are frequently used for induction and maintenance of anesthesia of sheep give satisfactory analgesia, and the degree of hypoxemia which occur after IV injection and during anesthesia are depend on individual or breed related factors (27).

Addition of tramadol, or paracetamol, make the induction and recovery are good. This result agreed with (45,46), who found the tramadol improve the quality of anesthetic induction and increase the duration of antinociception in IM xylazine ketamine anesthesia of pigs without increasing the duration of anesthesia nor causing additional depression of the measured physiological parameters. In human beings the combination between tramadol and ketamine give significant synergistic interactions with less CNS depression compared with single analgesic dose of ketamine (47). In our study we found the presence of tramadol with xylazine is beneficial. This result accorded with (48) found synergistic analgesic activities of tramadol and xylazine.

Paracetamol is an effective and well tolerated analgesic with an excellent safety profile within the therapeutic dose range up to 4 g/day in human beings. No adverse effects are seen on the cardiovascular and pulmonary system at the therapeutic doses in human beings, the only side effect seen is the liver damage or failure occur after over dosage (26).

The route of administration is important in injectable anesthesia in animals. Types of drug and species of animal are a factors affecting on choice of the route of administration. In cats giving of ketamine intravenously is superior to its administration intramuscularly (49). In sheep and goat administration of the anesthetic drugs by the IV route is preferable to make induction with intramuscular administration or inhalation anesthetics (1). Intravenous anesthetic drugs usually first administered as a large bolus (50). In relation to the role of the type of sedative and analgesic drugs, (28) proved that the intramuscular administration of xylazine 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 give 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 (28). The IM route is seen more reliable than the IV in sheep, it is easy to given, 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. In both groups of IM injection G2 and G3 in this study, most of the changes in the vital signs like the HR, RR, and RT are resemble the previous studies in sheep and goat. The induction time seen short 5.6, and 3.6 minutes respectively. The total recovery time also seen short, 5.6, and 7 minutes respectively. The combinations of these protocols seem give this beneficial effect. The duration of surgical anesthesia also increased with the increase of doses of both ketamine and xylazine in G2, and G3. Increasing ketamine dose enhances the

anesthetic properties of ketamine-xylazine-midazolam combinations in pigs. the lower dose ketamine combination is better for the induction of anesthesia, while the higher dose ketamine combination is preferable for surgery of short duration in pigs (51).

In conclusion; Ketamine, paracetamol, tramadol, and xylazine combination as anesthetic protocol is seen suitable for sheep anesthesia. The surgical anesthesia, and the depth of analgesia are increased with the increase of ketamine and xylazine doses, and the addition of tramadol, and paracetamol, enhance the quality of anesthesia and make the induction and recovery are good. The dose of $K_{10}T_2P_{10}X_1$ mg/kg by IM injection is seen the best between the three protocols

used in this experiment. It gives sufficient surgical anesthesia for minor operations, with fewer effects on the cardiovascular system, and short recovery time. The IM route of administration of anesthesia is seen more reliable than the IV route. It is easy to perform, with less excitement to the patient, further to increase the duration of anesthesia, and analgesia with less adverse effect on respiration, heart rate, and other vital signs of animal. The dose of $K_{20}T_4P_{10}X_{2.5}$ mg/kg by IM injection is superior in analgesia and duration of surgical anesthesia but with respiratory depression.

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