Efficacy of tramadol as analgesic and mixed with ketamine, xylazine as anesthetic in rabbits

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Abstract:

This study were performed to evaluate the efficacy of Tramadol as analgesic and efficacy of using Tramadol in combination with other drugs like Ketamine and Xylazine in anesthetic protocols in rabbits.

15 adult New Zealand white rabbits divided to 3 equal groups were anesthetized intramuscularly in one syringe, group 1 with Tramadol 15 mg/kg B.W, group 2 with Tramadol 15mg/Kg B.W and Ketamine 30mg/Kg B.W, group 3 with Tramadol 15mg/Kg B.W and Ketamine 30mg/Kg B.W and Xylazine 5mg/Kg B.W, physiologic parameters were evaluated including : body temperature, heart rate, respiratory rate, muscle relaxation, analgesia and stages of anesthesia (Induction of anesthesia, surgical anesthesia and recovery time).The most significant changes were reported in G3 (T15K30X5) and this combination is useful regimen clinically for anesthetize rabbits due to the fast of induction anesthesia and the long surgical duration of anesthesia.

Key words: Tramadol, Ketamine, Xylazine, anesthesia, Rabbits.

كفاءة الترامادول كمسكن للألم وبعد خلطة مع الكيتاين والزايلازين كمخدر في الأرانب

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الخلاصة:

تمت هذه الدراسة لغرض تقييم كفاءة الترامدول كمسكن وكفاءة استخدام الترامدول مع ادوية اخرى مثل الكيتامين والزايلازين كبرامج تخدير في الأرانب. 15 ارنب ناضج سلالة محلية قسمت الى 3 مجاميع متساوية تم تخديرها بالحقن في العضلة في محقنة واحدة، المجموعة الأولى ترامدول 15ملغم/كغم من وزن الجسم، المجموعة الثانية ترامدول 15ملغم/كغم ، كيتامين 30ملغم/كغم من وزن الجسم ،المجموعة الثالثة ترامدول 15ملغم/كغم، كيتامين 30ملغم/كغم و زايلازين 5ملغم/كغم من وزن الجسم. تم تقييم المعايير الفسلجية المتضمنة : درجة حرارة الجسم، معدل ضربات القلب، معدل التنفس،

درجة الأرتخاء العضلي، درجة التسكين وايظاً تم تسجيل (وقت احداث التخدير، طول فترة التخدير الجراحي، وقت الأفاقة). معظم التغيرات المعنوية سجلت في المجموعة الثالثة (ترامدول15كيتامين30زايلازين5) ملغم/كغم وهذا المزيج يعتبر نظام مفيد سريرياً لتخدير الأرانب وذلك لسرعة احداث التخدير وطول فترة التخدير الجراحي.

Introduction:

In small laboratory animals there is no single best method for anesthesia (1). The selection of anesthetic drug or regimen depend on the available facilities and equipments, the type of surgical procedures, the physical status or temperament of the animals, the familiarity of the anesthetist with anesthetic drug, the personnel available for assistance and the cost of the anesthetic (2,3).

Tramadol (Zylol)® , (Searole)® , (Tramal)® is centrally acting analgesic drug which has been in clinical use in Germany for 17 years old and has launched in the united kingdom(4). Its used primarily as analgesic, but it has demonstrated usefulness in treating opioid withdrawal in human beings (5).

Tramadol crosses the blood brain barrier and placental barrier and has been found to produce humorous positive responses in vertebrates including analgesia for moderate and sever pain, antitussive, antidepressant, anti-inflammatory and immunostimulatory effects, an ability to lower glucose in diabetes and local anesthetic effect (6).

Ketamine is one of the dissociative agents that can be used as a sole agent for induction anesthesia or in combination with other agents for induction and maintenance (7). Its metabolized by the liver and excreted in urine (8).
It is an unsatisfactory sole agent for surgical procedures due to the poor muscle relaxation, therefore, it is used in combination with other agents such as Xylazine or Medetomedine to provide surgical anesthesia (9).

Xylazine is a typical α2 – adrenoceptors agonist, thiazine derivative drug, widely used as sedative and analgesic drug to treat various types of pain in all species of animals. It has sedative, analgesic, anesthetic and muscle relaxant properties in animals when used alone or in combination with other agents like Ketamine (10,11).

It gives a safe anesthetic effect in horses, cattle, sheep, goat, cat and dogs when co administrated with Ketamine to induce short period of surgical anesthesia (12,13).

Parenteral anesthetic combination such as Ketamine / Xylazine have become the agent of choice for anesthesia in the rabbits because Ketamine and Xylazine combination are effective , easily administered and inexpensive (14,15).

Material and methods:

The study performed on 15 healthy adult local breed rabbits of both sexes, divided into 3 equal

groups injected intramuscularly in one syringe as follows:
Group 1 injected with 15mg/Kg Body weight Tramadol (T15), Group 2 injected with Tramadol 15mg/kg B.W , Ketamine 30mg/Kg B.W (T15K30), Group 3 injected with Tramadol 15mg/Kg B.W, Ketamine 30mg/Kg B.W and Xylazine 5mg/Kg B.W (T15K30X5).

The following physiological parameters were evaluated including: body temperature, heart rate, respiratory rate, degree of muscle relaxation, degree of analgesia by recording before administration the drug at (time 0) then 5,10,20,25,30,45,60 minutes after drug administration also induction of anesthesia, surgical anesthesia and recovery time were recorded.

* Trabar – 100 (50mg/ml), Tramadol (100mg/ml), the ampoule contain 2 ml mepha.
* Ketamine – ELSaod 500 (50mg/ml) the vial contain 10ml, ELSaod pharma, Aleppo – Syria.
* Rompun 2% (Xylazine), (20mg/ml) the vial contain 50ml, Bayer – Germany.

Statistical Analysis:

All data of the experiment were analyzed statistically using the Completely Randomized Design (CRD) (Single – Factor), (16), and Duncan multiple range test was used to determined the differences among means of treatment (17).

Results:

There is no significant differences $P \leq 0.01$ & 0.05 between the groups in the body temperature in the time (0 , 5, 10 , 30 , 45 & 60) , while there was a high significant difference $P \leq 0.01$ & 0.05 between group 2 and group 1 in the time of 20 minute and no significant different $P \leq 0.01$ & 0.05 between group 2 and group 3 , also there was no significant different $P \leq 0.01$ & 0.05 between group 1 and group 3 in the time of 20 minutes (table 1).

Table (1) Show the changes in body temperature within (0, 5, 10, 20, 30, 45 and 60) minutes in group 1 that anesthetized with Tramadol, group 2 anesthetized with Tramadol & Ketamine and group 3 anesthetized with Tramadol, Ketamine & Xylazine.

Time (minutes)	Group 1 body temperature	Group 2 body temperature	Group 3 body temperature
0	a 38.46 ±0.42	a 37.50 ± 0.23	a 38.12 ± 0.40
5	a 37.76 ±0.42	a 37.06 ± 0.20	a 37.68 ± 0.48
10	a 37.54 ±0.28	a 36.76 ± 0.16	a 37.24 ± 0.52
20	a 37.38 ±0.32	b 36.50 ± 0.26	ab 37.22 ± 0.26
30	a 37.52 ±0.13	a 37.06 ± 0.24	a 37.44 ± 0.24
45	a 37.70 ±0.09	a 37.42 ± 0.18	a 37.64 ± 0.34
60	a 37.74 ±0.09	a 37.44 ± 0.17	a 37.64 ± 0.35

There was a significant differences P ≤0.01 & 0.05 in G2 comparing with G 1 and there was no significant differences P ≤0.01 & 0.05 between G2 and G 3, also there was a significant differences P ≤0.01 & 0.05 in G 3 comparing with G 1 in the heart rate (table 2).

Table (2) Show the hart rate within (0, 5, 10, 20, 30, 45 and 60) minutes in group 1 that anesthetized with Tramadol, group 2 anesthetized with Tramadol & Ketamine and group 3 anesthetized with Tramadol, Ketamine & Xylazine.

Time (minutes)	Group 1 heart rate	Group 2 heart rate	Group 3 heart rate
0	a 250.80 ± 7.96	b 222.20 ± 10.05	bc 199.80 ± 8.40
5	a 234.80 ± 6.67	ab 224.60 ± 6.10	b 200.20 ± 3.81
10	a 217.00 ± 6.16	a 215.40 ± 6.48	b 187.40 ± 2.16
20	a 206.80 ± 4.49	a 206.20 ± 5.93	b 177.00 ± 1.72
30	a 206.60 ± 17.82	a 215.00 ± 4.76	a 194.00 ± 0.17
45	a 204.20 ± 10.92	a 220.20 ± 5.15	a 204.00 ± 0.37
60	a 209.00 ± 10.78	a 223.80 ± 7.31	a 205.00 ± 8.51

There was no significant differences P ≤0.01 & 0.05 between group 1, 2 and 3 in the respiratory rate within (0, 5, 10, 20, 30, 45 and 60) minutes.

Table (3) Show the respiratory rate within (0, 5, 10, 20, 30, 45 and 60) minutes in group 1 that anesthetized with Tramadol, group 2 anesthetized with Tramadol & Ketamine and group 3 anesthetized with Tramadol, Ketamine & Xylazine.

Time minutes	Group 1 Respiration/minute	Group 2 Respiration/minute	Group 3 Respiration/minute
0	a 187.40 ± 9.62	a 180.00 ± 8.34	a 168.80 ± 7.62
5	a 177.20 ± 11.73	a 169.20 ± 7.63	a 158.20 ± 7.47
10	a 147.40 ± 17.76	a 154.40 ± 11.24	a 149.80 ± 8.47
20	a 153.60 ± 10.05	a 163.00 ± 6.24	a 152.00 ± 5.99
30	a 172.40 ± 10.83	a 175.60 ± 5.32	a 165.60± 6.79
45	a 188.40 ± 5.21	a 184.00 ± 5.24	a 177.40 ± 6.32
60	a 193.20 ± 3.51	a 187.60 ± 5.52	a 180.40 ± 6.98

There was no significant differences P ≤0.01 & 0.05 between group 1, 2 and 3 in the degree of muscle relaxant within (0 and 30) minutes, also there was a significant differences P ≤0.01 & 0.05 in G 2 and G3 comparing with G 1 in muscle relaxant within (5, 10 and 20) minutes and there was no significant differences P ≤0.01 & 0.05 between G2 and G 3 (table 4).

Table (4) Show the degree of muscle relaxant within (0, 5, 10, 20 and 30) minutes in group 1 that anesthetized with Tramadol, group 2 anesthetized with Tramadol & Ketamine and group 3 anesthetized with Tramadol, Ketamine & Xylazine.

Time minutes	Group 1 Degree of Muscle relaxant	Group 2 Degree of Muscle relaxant	Group 3 Degree of Muscle relaxant
0	a 0.00 ± 0.00	a 0.00 ± 0.00	a 0.00 ± 0.00
5	a 0.40 ± 0.24	b 2.20 ± 0.37	b 2.00 ± 0.00
10	a 2.20 ± 0.37	b 3.00 ± 0.00	b 3.00 ± 0.00
20	a 0.00 ± 0.00	b 1.60 ± 0.51	b 1.80 ± 0.37
30	a 0.00 ± 0.00	a 0.00 ± 0.00	a 0.00 ± 0.00

There was no significant differences P ≤0.01 & 0.05 between group 1, 2 and 3 in the degree of analgesia within (0, 10 and 30) minutes, also there was a significant differences P ≤0.01 & 0.05 in G 2 and G3 comparing with G 1 in degree of analgesia within (20) minutes and there was no significant differences P ≤0.01 & 0.05 between G2 and G 3, also there was a significant differences P ≤0.01 & 0.05 in G 2 comparing with G 1 and G3 within (5) minutes and there was no significant differences P ≤0.01 & 0.05 between G 1 and G 3 (table 5).

Table (5) Show the degree of analgesia within (0, 5, 10, 20 and 30) minutes in group 1 that anesthetized with Tramadol, group 2 anesthetized with Tramadol & Ketamine and group 3 anesthetized with Tramadol, Ketamine & Xylazine.

Time (minutes)	Group 1 Analgesia	Group 2 Analgesia	Group 3 Analgesia
0	a 0.00 ± 0.00	a 0.00 ± 0.00	a 0.00 ± 0.00
5	a 1.00 ± 0.00	b 2.40 ± 0.24	a 1.40 ± 0.24
10	a 2.40 ± 0.40	a 3.00 ± 0.00	a 2.80 ± 0.20
20	a 1.00 ± 0.63	b 2.20 ± 0.37	b 2.20 ± 0.20
30	a 0.00 ± 0.00	a 1.00 ± 0.00	a 0.60 ± 0.24

There is no significant differences P ≤0.1 % , 0.5 % between G 2 and G 3 in the induction of anesthesia and the surgical anesthesia, and there was a high significant difference P ≤0.01 & 0.05 in the recovery time (walk time) in G 3 in contrast with G 2 (table 6).

Table (6) Show the stages of anesthesia/ minutes in Group2 that anesthetized with Tramadol + Ketamine and Group 3 that anesthetized with Tramadol + Ketamine + Xylazine.

Stages of anesthesia in body temperature in minutes	G 2	G3
Induction of anesthesia	a 3.8 ± 0.31	a 2.8 ± 0.37
Surgical anesthesia	a 16.8 ± 1.78	a 18 ± 1.41
Recovery Time (Walk T.)	a 23.4 ± 1,81	b 27.6 ± 1.51

Discussion:

There was no effect of Tramadol on body temperature, while (TK), (TKX) decrease the body temperature at 20 minutes this result supported by (18,19)who found that Tramadol has limited effect on thermal threshold.

The addition of Xylazine cause decrease of rectal temperature (20) as in our study, the α 2 agonist depresses the thermoregulatory mechanisms in the body and either hypothermia or hyperthermia occurs depending on the temperature of environment (21), theses results occurred because of the loss of normal thermoregulatory mechanism due to the release of monoamines in the anterior hypothalamus since the nor adrenaline lowers and S – hydroxyl tryptamine (5HT) hypothalamus (22).

Tramadol group had no effect on heart rate while (TK) and (TKX) groups cause decrease in HR these results agree with (23,24), Tramadol has minimal cardiovascular effects in human and animals, while TK and TKX groups decrease the heart rate at the first 5 minutes followed by gradual increase until it reached to the normal or less than normal at 60 minutes, these results were consistent with previous studies (25,26).

In all groups there were no significant changes in respiratory rate, (27) found that there was no effect on respiratory rate when Tramadol is used in human, While TKX decrease RR but no significant changes in spite of Ketamine action on CNS depression (28).

Tramadol has no effect on degree of muscle relaxation while the combination between TK, TKX produce muscle relaxation in the time of 5, 10, 20 minutes and there were no muscle relaxation in the time of 30 minutes, that make these regimens unsuitable for surgical operations which take long time specially abdominal surgery, because of Ketamine produce profound analgesia with dose between 11 – 44mg/Kg without muscle relaxation (29), using Xylazine in combination with Tramadol and Ketamine cause CNS depression which lead to general anesthesia in 5, 10, 20 minutes and muscle relaxation (30), these results are supported by (31,32).

Tramadol not give analgesia in rabbits in 0, 30 minutes while in 5, 10, 20
minutes cause mild analgesia, this result agree with (33). The analgesia occurs due to the analgesic activity of Tramadol which interferes with noradrenaline and serotoniergic transmission and inhibits the neural reuptake of noradrenaline (34).

The combination between Ketamine and Tramadol increase the analgesic effects in 5, 20 minutes only, these results are in agree with (29,30), who found that the administration of Ketamine 22mg/Kg B.W prolong the duration

of analgesia between 20 – 40 minutes. Adding Xylazine to TK produce analgesia in 20 minutes only, this result agree with (35,36) also these results are in agreement with (37).

There was no changes in the induction of anesthesia, surgical anesthesia and recovery time in TK group while TKX cause significant increase in recovery time which is too long, this result agree with (34).

In conclusion : using Tramadol, TK dose not produce muscular relaxation, while adding of Xylazine to TK give a good surgical anesthesia making this protocol suitable clinically for anesthesia in rabbits for diagnostic procedure and for minor surgical operations.

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