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Evaluation Effect of Tramadol as Premedication on Ketamine in Mice

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الخلاصة

الأهداف: تقيم تأثير الجرع المختلفة من الترامادول عند اعطائه قبل التخدير بالكيتامين في الفئران. **المواد وطرائق العمل:** اعطي الترامادول بعدة جرع (٠,٢٠,٣٠) ملغم / كغم، بالخلب قبل ٢٠ دقيقة من اعطاء الكيتامين. **النتائج:** أدى اعطاء الترامادول بعدة جرع قبل التخديربالكيتامين إلى إحداث زيادة معنوية في زمن النوم والتسكين للكيتامين بدون ان يؤدي الى احداث اي تغير معنوي على فترة احداث التخدير في المجاميع المعاملة كافة. كما وأدى إعطاء الترامادول الى احداث تسديرا واضحا في الفئران حيث نلاحظ ان مراتب التسدير قد ازدادت في كافة المجاميع لكن هذا التسدير بقي لفترة زمنية اطول في المجاميع المعاملة بالترامادول والكيتامين مقارنة بالمجموعة المعاملة بالكيتامين لوحده وبالاعتماد على الجرعة. **الاستنتاجات:** من هذه الدراسة نستنتج بامكانية استخدام الترامادول قبل التخدير العام بالكيتامين لتحسين كفاءة التخدير.

ABSTRACT

Aims: The present study was designed to investigate the effect of different doses of tramadol as a premedication on ketamine anesthesia in mice. **Materials and Methods:** Tramadol used in different doses (0, 20, 30) mg/kg, I.P at 20 minute before treated with ketamine (50) mg/kg, I.P. **Results:** significantly increased in the duration of sleep and analgesia of ketamine without effect on the time of induction in all treated groups. The Numerical Sedation Score(NSS) was increased in all treated groups with tramadol pre treatment of ketamine but this NSS were stayed in long period in group treated with tramadol and ketamine in a dose depended manner in comparison with group treated with ketamine alone. **Conclusion:** Thus it can conclude that the possibility of using tramadol as a premedication with ketamine general anesthesia to improve anesthesia.

Keywords: Tramadol, Ketamine, General anesthesia, Sedation, Analgesia.

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INTRODUCTION

Ketamine hydrochloride is a dissociative anesthetic agent used in clinical medicine. Ketamine as the sole anesthetic produce amnesia, with catatonia, hypertonus, purposeful movement and vocalization may occur.[1] Ketamine is a general anesthetic drug[2] and its major metabolite norketamine, have a significant non-competitive blocking action on N-Methyl D-Aspartate (NMDA) receptors.[3] The role of NMDA receptor in modulating acute pain and the subsequent central sensitization has been demonstrated.[4_6] Ketamine produce profound visceral analgesia without somatic analgesia, and tonic clonic spasm of limb muscle may occur even in absence of surgical or other stimulations. [1] Ketamine therefore used in combination with muscle relaxants and analgesics, to produce a state of balance anesthesia.[7] It was therefore hypothesized that use analgesic drugs could substitute as premedication for ketamine anesthesia ,In our study ,used tramadol as premedication to produce good analgesia.

Tramadol, a synthetic analog of codeine, is centrally acting atypical [8] at μ-opioid, adrenergic and 5-hydroxytyptamine (5-HT) receptors. [9] Analgesic activity of tramadol is a result from it low affinity binding of parent compound to (μ) opioid receptor and higher binding of the M1 (o-desmethyllated) metabolite.[10] Tramadol is also a weak inhibitor of norepinephrine and serotonin reuptake,[11] In addition tramadol had been shown to relieve stress and anxiety , produce calmness , improve mood and sense well being.[12]

A combination of α_2 agonist and ketamine is commonly used for animal anes-

thesia[13] but use of tramadol as preanesthetic agent is uncommon , therefore the purpose of our study to was determine the onset , duration of analgesia, sleeping time (anesthesia) and recovery time of ketamine anesthesia after used tramadol as pre anesthetic.

MATERIALS AND METHODS

Male albino mice weighing 25-30 gm. were used for the study. The animals were approved from animal care housed in Dentistry Collage of Mosul University in Iraq. Animals were housed in rodent plastic cages at 22±2˚C on a 12hr Light/dark cycle, with free access to food and water. The mice were divided into 3 groups, each group consist of five animals. Group 1 served as a control and was given normal saline 0.9% intraperitoneally (I.P) and ketamine (50 mg /Kg I.P) , group 2, 3 were received tramadol hydrochloride ampoule 5% (Mepha Ltd Aesh-Basel swit-zerland) and ketamine hydrochloride solution 5% (Alhukamma company) at (20+50), (30+50) mg /Kg I.P respectively. The volume of injection in all treated animals is (5ml\kg). Ketamine injected after twenty minute from injection of tramadol. The mice were monitor to evaluate the following parameters:

A-Degree of sedation

The degree of sedation was assessed by a Numerical Sedation Score (NSS). [14]

The NSS consist of a scale ranging from 0 to 3:

0: No sedation

1: Mild sedation.(less sedation but still active)

2: Moderate sedation (drowsy, recumbent but can walk)

3: Intense sedation (very drowsy, unable to walk)

NSS was evaluated at 15 minute after tramadol injection, and stop after sixty minute from return righting reflex. NSS was not measure during sleeping time.

B- Duration of sleeping time:

The time interval between the loss and reappearance of righting Reflex.[15]

*C- Duration of analgesia***:**

The duration of analgesia was determined by tail pinching reflex.[15]

After ketamine administration the period in which the mice showed negative respond to tail pinching test was define as duration of analgesia (Surgical anesthesia). It was evaluated after 5,10, 15,20,30 from ketamine injected.

Statistical Analysis

The data were expressed as mean ± SD, difference between three experimental groups were statistically analyzed by one way analysis of variance (ANOVA) followed by the least significant difference test. The level of significance was at $p < 0.05$.[16]

RESULTS

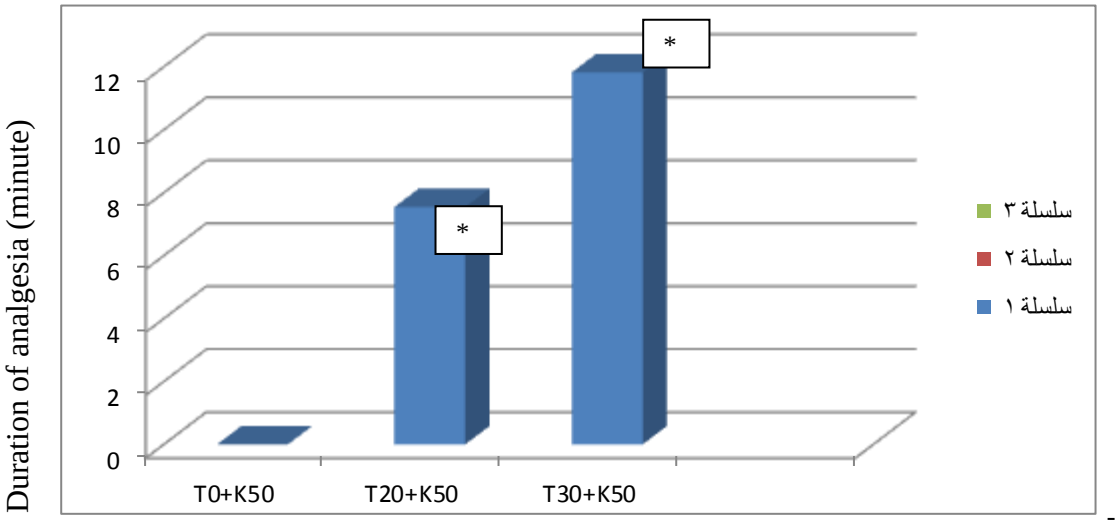
In the present study, sleeping time and analgesia were assessed in mice treated I.P with tramadol-ketamine (0+50), (20+50), (30+50) mg\kg, I.P respectively. The duration of sleep time and analgesia ranged from (8.4- 46.8) min and (7.2-11.82) min respectively, in a dose dependent manner, however this mixture produced a good analgesia in mice. The onset loss of righting reflex was not affected by increased the dose of tramadol, therefore the time of induction not significantly difference between all treated groups. Table (1), Figure (1).

Table (1): Effect of tramadol (0, 20, 30 mg /Kg, I.P) on ketamine (50 mg\kg I.P) general anesthesia (Induction, Sleeping, Recovery time) in mice

Tramadol mg\kg I.P	**Ketamine mg\kg I.P**	**Induction time (min)**	**Sleeping time (min)**	**Recovery time (min)**
0 (Normal saline)	50	2.07±0.7	8.4±3.4	12.2±3.1
20	50	1.90±0.8	38.07±4.6*	12.2±2.11
30	50	2.08±0.8	46.8±13.3*	24.3±3.8*a

Value are mean ±SE 5 mice /group. *Significantly different from the control group at $p < 0.05$.

A Significantly different from the group treated (tramadol 20+ketamine 50) mg\kg I.P at $p < 0.05$ **.**



Values are mean + SE 5 mice /group. * Significantly different from the control group at $p <$ 0.05.

Figure 1: Duration of analgesia was determined by tail pinching reflex in mice anesthetized with tramadol and ketamine.

Injection of tramadol at (0, 20, 30) mg\kg I.P pre administration of ketamine produce clearly sedation in mice after 15 min of tramadol injection. The Numerical Sedation Score (NSS) were (0) (1.2) (1.4) respectively according to the dose of tramadol. The NSS was increased immediately after return the righting reflex and reach the maximum score ranged in all treated groups, but the NSS quickly decline in group treated with ketamine alone after (10-20) min in comparison with others groups treated with tramadol and ketamine (20+50), (30+50) mg /Kg, I.P to (10-40), (10-60) min respectively, in a dose dependent manner. Figure (2).

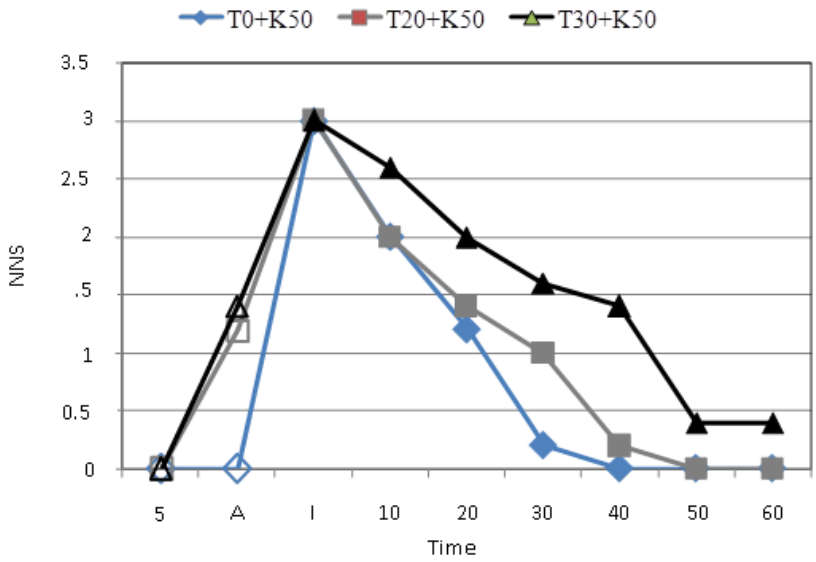


Figure (2): Changes in the degree of sedation in mice.

The mice were given saline, 20 or 30 mg\ kg of tramadol followed by ketamine(50 mg /Kg ,I.P).
T: Tramadol; K: Ketamine A: 15 minutes after Tramadol injection; I: Immediately after return of R.R

DISCUSSION

Ketamine, is commonly used as anesthetic agent in animals, is usually supplement with other sedative and is not recommended for major surgical procedure alone. [17] In our study, Premedication with tramadol were significantly increase the duration of sleep and recovery time without affecting on the induction time, while these doses of tramadol are successful to produce good analgesia represented by duration of surgical anesthesia, which had an analgesic potency of tramadol that cause enhanced of surgical general anesthesia. [18-19] The increase in surgical anesthetic time in a dose – dependent manner of tramadol.

The increase in the doses of tramadol would extended not only the period of analgesia but also the recovery time, this prolongation in the recovery time return to pretreatment with tramadol at 30mg I.P. This result agreement with other study suggested that administration tramadol at effective dose significantly increased the duration of surgical anesthesia.[20] The higher dose of tramadol result in higher and more sustained tramadol plasma concentration [21] and tramadol itself have analgesic effect. [22] The analgesic response of tramadol were increases by increasing the dose which lead to prolong duration and potency of tramadol, [23] and each of μ receptor agonist produce analgesia in dose related manner [24] but in our study the analgesic effect did not persist for long period.

Tramadol is a weak opioid agonist with antinociception effect through its action on μ receptor and the inhibition of neuronal reuptake of both noradrenalin and serotonin[25-26]. Noradrenergic descending pathway and serotonergic pathway innervated all level of the spinal cord and modulate afferent pain at this level, [27] therefore used tramadol inhibit the reuptake of norepinephrine at level of spinal cord to produce analgesic effect. [25, 28]

In the present study tramadol treatment at 20, 30 mg\kg I.P induce sedation effect at fifteen minute after injected and the degree of sedation effect depending on the doses of tramadol, this result agreement with previous study that described a dose-depended sedative effect of tramadol [29-31] but this result disagreement with other study reported no marked sedation effect of tramadol.[32]

Tramadol premedication were not significantly affected on induction of ketamine anesthesia even in increase the dose of tramadol while increase the dose of tramadol lead to increase the recovery time.

CONCLUSION

Over all, Tramadol premedication at different doses were significantly increased the duration of sleep and analgesia with ketamine anesthesia in dose-depended in mice without effect on onset of anesthesia and produced a good analgesia with less side effects of ketamine.

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