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Anesthetic efficacy of ketamine, ketamine-tramadol and ketamine-ketorolac in chicks

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Summary

Background: Ketamine produces ordinary general anesthesia characterized by weak hypnosis and analgesia leading to complications during surgical operations. **Aims:** The aim of this study was to evaluate the combination of ketorolac or tramadol to enhance ketamine anesthesia in 7 to 20-day-old chicks and its feasibility and practical application for induction of general anesthesia in veterinary medicine. **Methods:** Hypnotic and analgesic Median Effective Doses (ED_{50s}) of ketamine alone and combination with tramadol or ketorolac were determined by the up-and-down method, then the ED_{50} values of these combinations were used for measurement of hypnotic and analgesic criteria moreover, their effect on serum Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) was assayed. **Results:** Ketamine hypnosis and analgesia were increased when mixed with tramadol (26 and 39%) or ketorolac (27 and 40%), respectively. Ketamine-ketorolac mixture was better combination of inducing the faster onset of anesthesia and short recovery with the longest duration of action and enhancing analgesia when compared to ketamine alone or in combination with tramadol and is preferred for induction of anesthesia. The liver function enzymes, including AST and ALT, showed no significant difference among all above mentioned groups. **Conclusion:** The data of this experimental study reveal the superiority of using ketorolac (instead of tramadol) in combination with ketamine for induction of general anesthesia in the chicks.

Key words: Analgesia, Anesthesia, Ketamine, Ketorolac, Tramadol

Introduction

Ketamine is a drug which is used extensively for anesthetic induction of surgical operations in veterinary medicine and it produces its weak hypnotic and analgesic effects through antagonistic effect on N-methyl D-aspartate (NMDA) receptor in the central nervous system, causing a reduction in the amount of calcium entering the neurons that leads to induction of anesthesia (Finkel *et al*., 2009a; White and Trevor, 2009). Tramadol is an opioid drug widely used for producing its antinociceptive effect in the animals and humans through its mechanism of action on μ (Mu) receptors in the central nervous system by inhibiting the re-uptake of norepinephrine and serotonin and it is of benefit for relieving the symptoms of most types of pain and to treat chronic and postoperative pain (Natalini and Robinson, 2000; Valle *et al*., 2000; Finkel *et al*., 2002).

Ketorolac, in contrast, belongs to the non-steroidal anti-inflammatory drugs (NSAIDs) and as a pain-relieving agent, it works by non-selective inhibiting of the cyclooxygenase (COX1 and COX2) enzyme, which reduces the production of prostaglandins (Botting, 2006; Finkel *et al*., 2009b; Smyth and FitzGerald, 2009; Hilal-Dandan and Brunton, 2014). Ketorolac (like tramadol) is used as an analgesic to manage moderate to severe pain with fewer side effects than tramadol. Moreover, it is considered as an effective injectable NSAID and unlike central opioid analgesics such as tramadol and morphine cause many serious side effects like respiratory depression, drug abuse and also does not worsen the outcome of surgical operations (Jelinek, 2000; Ollé *et al*., 2000; Rainer *et al*., 2000; Shankariah *et al*., 2012; Hendarman *et al*., 2014). The main goal of this study was to evaluate the combination of ketorolac to enhance ketamine anesthesia in order to compare it with a mixture of ketamine and tramadol in the chicken and its feasibility and practical application for surgery in the veterinary medicine.

Materials and Methods

Experimental animals

Seven- to twenty-day-old broiler (Ross) chicks (average body weight between 74-185 g) were used in the current study. They were kept in cages at a temperature of 32-35°C with continuous lighting and the floor litter consisted of wood shavings. The chicks had access to drinking water and feed *ad libitum*. Ketamine (5% Hameln pharmaceuticals gmbh, Germany), tramadol (5% G.L. pharma GmbH, Austria) and ketorolac (3% as ketorolac trometamol, Normon, Spain) were dissolved in normal saline to prepare the doses at an injection volume of 5 ml/kg body weight, intraperitoneally (IP). The scientific committee at the College of Veterinary Medicine, University of Mosul has approved this study

and its related ethical considerations for the use of experimental animals.

Hypnotic Median Effective Dose (ED_{50}) of ketamine alone and its combination with tramadol or ketorolac in the chicks

First, the ED_{50} values of ketamine alone or in combination with tramadol or ketorolac were estimated by up-and-down method (Dixon, 1980) in order to determine the doses of them to be used in the later experiments. The initial dose of ketamine, applied to be injected at 15 mg/kg IP based on a previous study (Mousa, 2014) with an increase or decrease in the dose of 3 mg (marked as d).

The anesthetic (hypnotic) effect (characterized by loss of righting reflex) of ketamine alone was then determined after injection and the chick was marked as X when the loss of righting reflex occurs, if not, the chick was marked as O. Then the table value (K) was extracted from (Dixon, 1980) based on X-O consequences for 3 recorded chicks after changing the effect. Later, the ED_{50} value was estimated according to the following equation:

ED_{50} value= xf + Kd

Where,
xf: last dose used in the experiment

The same procedure was applied when the ED_{50} values of ketamine with tramadol or with ketorolac were estimated, except that the initial doses of tramadol and ketorolac were at 1 and 10 mg/kg, IP and the increase or decrease in doses were at 0.3 and 3 mg, IP. The changes in ketamine hypnotic efficacy were then determined as follows:

% Decrease in ED_{50} of ketamine hypnosis (increased efficacy)= [(ED_{50} of ketamine alone - ED_{50} of ketamine with tramadol or ketorolac) / ED_{50} of ketamine alone] × 100

Analgesic ED_{50} of ketamine alone and its combination with tramadol or ketorolac in the chicks

The ED_{50} value of ketamine alone that causes analgesia in 50% of the chicks was measured according to the up-and-down method described earlier. The analgesic effect of ketamine was measured via an electrostimulator apparatus (Scientific and Research Ltd., UK) for the induction of pain sensation in the chicks (Mousa and Mohammad, 2012; Mousa, 2014). In this experiment, the pain in the chicks was characterized by distress call then recorded as a voltage for each chick individually before and after 15 min of ketamine injection (Mousa and Mohammad, 2012; Mousa, 2014). Ketamine was observed to have an antinociceptive effect when the recorded voltage after injection was increased in relation to the voltage measured before ketamine injection (the chick will be marked as X), if there is no effect, the chick will be marked as O. Then the table value (K) will be extracted from Dixon's table and the ED_{50} value will be estimated as described in the above experiment. The same applied criteria were implemented in order to estimate the ED_{50} values of ketamine with tramadol or ketorolac. The increase in ketamine's analgesic effect will then be determined as follows:

% Decrease in ED_{50} of ketamine analgesia (increased efficacy)= [(ED_{50} of ketamine alone - ED_{50} of ketamine with tramadol or ketorolac) / ED_{50} of ketamine alone] × 100

Hypnosis induced by ketamine alone and its combination with tramadol or ketorolac in the chicks

In this experiment, 18 of 7 to 20-day-old chicks were used (6 chicks/group) and then divided as follows:

1. Ketamine alone, which represents a positive control group formed from injection of ketamine alone at 20 mg/kg IP, with the injection of 5 ml/kg IP of normal saline
2. Ketamine and tramadol group that was injected with ketamine and tramadol at 20 and 1 mg/kg IP, respectively
3. Ketamine and ketorolac group, formed from injection of ketamine and ketorolac at 20 and 25 mg/kg IP, respectively

The doses of ketamine, tramadol, and ketorolac were chosen according to the previous two experiments. The onset (min) of anesthesia (hypnosis-loss of righting reflex) was measured as the period from injection of ketamine (with or without tramadol or ketorolac) to the loss of righting reflex in each of the chicks. In the same manner, the duration (min) of hypnosis was calculated as the period from the loss of the righting reflex until the chicks came back and corrected their body to normal position, whereas the recovery (min) period was recorded as the period between the beginning of hypnosis and the return of chicks to movement and normal activity (Ruskoaho and Karppanen, 1984; Roder *et al*., 1993; Al-Zubaidy and Mohammad, 2005).

Analgesia elicited by ketamine alone and its combination with tramadol or ketorolac in the chicks

As in the previous experimental design, the other animals with the same numbers and distribution were used. Electrostimulation was applied to induce pain sensation in the chicks via electrostimulator apparatus. This apparatus could be used to examine the analgesic effect of drugs in the chicks (Dawood, 2002; Mousa, 2014).

The experimental groups of chicks were randomly divided as the previous experiment and the nociceptive effect was recorded as voltages. The voltages were measured before and after 15 min of IP injection of ketamine alone or with tramadol or ketorolac at 20, 1 and 25 mg/kg, respectively. The device was put on the water wetted skin in the area under the wing of the chicks for better conductivity and then the voltage was increased until the appearance of distress call in the chicks as an indicator of pain.

The recorded result shows an analgesic effect when there is an elevation in the voltages recorded after injection in comparison to the voltages measured before

the injection. In contrast, there is no analgesia when there was a reduction in the voltage after injection related to the voltage measured before the injection.

Measurement of aspartate transaminase (AST) and alanine transaminase (ALT)

After 2 h of ketamine (20 mg/kg, IP) injection alone or in combination with tramadol (1 mg/kg, IP) or ketorolac (25 mg/kg, IP), blood samples were obtained from the jugular vein of all groups of chicks (6 chicks/group). Serum AST (Plummer, 1987) and ALT activity (Reitman and Frankel, 1957) levels (expressed in U/L) were determined with the specified kit (Biolabo, France) by using the spectrophotometric analysis at 505 nm.

Statistical analysis

Parametric data of three groups were analyzed by one way analysis of variance, then subjected to the least significant difference while paired student t-test was used for statistical analysis to compare the means of two groups of parametric data (Katz, 1999; Petrie and Watson, 1999). Mann-Whitney U-test was applied to the non-parametric data (Runyon, 1977; Katz, 1999). The significance level was $P<0.05$.

Results

Anesthetic (hypnotic) ED_{50} of ketamine alone, ketamine-tramadol and ketamine-ketorolac combinations in the chicks

The anesthetic (hypnotic) ED_{50} values of ketamine, ketamine-tramadol and ketamine-ketorolac mixtures in the chicks were 11.63, 8.60, and 8.50 mg/kg, by IP injection, respectively. There was an increase in efficacy of ketamine's hypnotic effect (i.e. decrease in ketamine ED_{50} value required for 50% of the chicks to undergo hypnosis) when mixing tramadol or ketorolac by 26 and 27%, respectively (Table 1).

Analgesic ED_{50} of ketamine alone, ketamine-tramadol and ketamine-ketorolac combinations in the chicks

The analgesic ED_{50} value of ketamine alone required to cause analgesia in 50% of the chicks was 14.10 mg/kg IP, whereas this value was decreased when combining tramadol or ketorolac to be 8.60 and 8.50 mg/kg IP, respectively. The analgesic efficacy of ketamine was elevated by 39 and 40% after using tramadol or ketorolac, respectively (Table 2).

Table 1: Determination of the anesthetic (hypnotic) ED_{50} value of ketamine alone, ketamine-tramadol and ketamine-ketorolac in the chicks

Parameter	Result		
	Ketamine alone	Ketamine-tramadol	Ketamine-ketorolac
ED_{50} value = xf+Kd	11.63 mg/kg, IP	8.60/0.40 mg/kg, IP	8.50/13.50 mg/kg, IP
The range of the doses used	9-15	6-15/0.1-1	6-15/14-20
Initial dose	15 mg/kg	15/1 mg/kg	15/20 mg/kg
xf	9 mg/kg	6/0.1 mg/kg	9/14 mg/kg
K	0.878	0.861	-0.181
± d	3 mg	3/0.3 mg	3/3 mg
Onset of anesthesia	3-14 min	2-10 min	15-16
Number of chicks used	5 (XOXXO)	6 (XXOXXO)	7 (XXXOXOO)
% Decrease in ED_{50} of ketamine hypnosis (increase efficacy)	-	26%	27%

ED_{50}: Median Effective Dose, xf: Last dose, K: Table value, d: Increase or decrease in the dose (mg), IP: Intraperitoneally, X: Hypnosis (loss of righting reflex), and O: No hypnosis

Table 2: Determination of analgesic ED_{50} value of ketamine alone, ketamine-tramadol and ketamine-ketorolac in the chicks

Parameter	Result		
	Ketamine alone	Ketamine-tramadol	Ketamine-ketorolac
ED_{50} value = xf+Kd	14.10 mg/kg, IP	8.60/0.40 mg/kg, IP	8.50/13.50 mg/kg, IP
The range of the doses used	9-18	6-15/0.1-1	6-15/14-20
Initial dose	15 mg/kg	15/1 mg/kg	15/20 mg/kg
xf	15 mg/kg	6/0.1 mg/kg	9/14 mg/kg
K	-0.305	0.861	-0.181
± d	3 mg	3/0.3 mg	3/3 mg
Range of voltage before injection	5-9 volts	5-8 volts	6-9 volts
Range of voltage after injection	5-11 volts	5-12 volts	5-10 volts
Number of chicks used	5 (XOOXX)	6 (XXOXXO)	7 (XXXOXOO)
% Increase in ED_{50} of ketamine analgesia (increase efficacy)	-	39%	40%

ED_{50}: Median Effective Dose, xf: Last dose, K: Table value, d: Increase or decrease in the dose (mg), IP: Intraperitoneally, X: Analgesia, and O: No analgesia. Pain-induced by electrostimulator was measured before and after 15 min of ketamine, ketamine-tramadol and ketamine-ketorolac injection

Table 3: Hypnosis (anesthesia) induced by ketamine alone and its combination with tramadol or ketorolac in the chicks

Groups	Anesthesia (%)	Onset (min)	Duration (min)	Recovery (min)
Ketamine alone	100	4.83 ± 0.75	8.83 ± 0.98	60.83 ± 2.48
Ketamine-tramadol	100	2.67 ± 0.21[a]	13.67 ± 1.17[a]	72.67 ± 4.48[a]
Ketamine-ketorolac	100	2.33 ± 0.33[a]	14.33 ± 1.17[a]	56.83 ± 3.96[b]

The values represented mean±SE for 6 chicks/group. Ketamine was injected alone (20 mg/kg, IP) or with tramadol (1 mg/kg, IP) or ketorolac (25 mg/kg, IP). [a] Significantly different from the ketamine alone group at P<0.05, and [b] Significantly different from the ketamine-tramadol group at P<0.05

Table 4: Analgesia elicited by ketamine alone and its combination with tramadol or ketorolac in the chicks

Groups	Analgesia (%)	Voltage before injection	Voltage after 15 min of injection	Delta voltage
ketamine alone	100	6.33 ± 0.49	8.50 ± 0.43[a]	2.17 ± 0.60
Ketamine-tramadol	100	5.17 ± 0.17	8.83 ± 1.23[a]	3.67 ± 1.33
Ketamine-ketorolac	100	6.33 ± 0.61	11.67 ± 0.92[ab]	5.17 ± 1.30

The values represented mean±SE for 6 chicks/group. Pain-induced by electrostimulator was measured before and after 15 min of ketamine, ketamine-tramadol and ketamine-ketorolac injection. Ketamine was injected alone (20 mg/kg, IP) or with tramadol (1 mg/kg, IP) or ketorolac (25 mg/kg, IP). [a] Significantly different from voltage before injection in the same group at P<0.05 and [b] Significantly different from the ketamine group at P<0.05

Hypnosis induced by ketamine alone and its combination with tramadol or ketorolac in the chicks

Ketamine injection alone (control) or in combination with tramadol or ketorolac led to induction of anesthesia (hypnosis-loss of reflex) in 100% of the chicks. The onset of anesthesia was started in all groups of the chicks approximately at 2-5 min and the duration of anesthesia was 9-14 min, whereas the recovery from it happened 57 to 73 min after the beginning of anesthesia (Table 3). It appears from Table 3 that there were differences among groups that were injected with ketamine alone and those injected with ketamine with both tramadol or ketorolac regarding the onset, duration, and recovery from anesthesia. The resulted parameters recorded in Table 3 show that the mixture of ketamine and ketorolac was the best group for faster induction (onset) of anesthesia and the recovery from it with the longest duration of action that is mostly preferred for induction of anesthesia.

Analgesia elicited by ketamine alone and its combination with tramadol or ketorolac in the chicks

The administration of ketamine with tramadol or ketorolac was associated with analgesia in 100% of the chicks examined through an increase in delta voltages in all the groups. All experimental groups have significant elevation in voltages recorded after injection of drugs when compared to pre-injection voltages (Table 4). Table 4 also shows that the group that was treated with ketamine-ketorolac combination has an enhanced analgesia (higher post-injectable voltage and delta voltage recorded) when compared to the ketamine alone or in combination with tramadol.

Determination of AST and ALT levels in chicks injected with ketamine alone or in combination with tramadol or ketorolac

Table 5 shows that serum AST and ALT activities of the combined groups (ketamine-tramadol or ketamine-ketorolac) have no significant difference with the group that was injected with ketamine alone (positive control).

Table 5: Serum AST and ALT levels in the chicks treated with ketamine alone or in combination with tramadol or ketorolac

Groups	AST (U/L)	ALT (U/L)
Ketamine alone (+ve control)	116.50 ± 7.61	19.67 ± 2.28
Ketamine-tramadol	109.83 ± 1.35	15.83 ± 1.30
Ketamine-ketorolac	101.33 ± 7.18	19.17 ± 2.99

AST: Aspartate transaminase, and ALT: Alanine transaminase. The values represent mean±SE for 6 chicks/group. Blood samples were obtained after 2 h of ketamine injection alone (20 mg/kg, IP) or in combination with tramadol (1 mg/kg, IP) or ketorolac (25 mg/kg, IP)

Discussion

The aim of the current study was to evaluate and examine the combination of ketorolac or tramadol to enhance ketamine anesthesia and in order to compare it with the ketamine in the chicken and assessment its feasibility and practical application for induction of general anesthesia in the veterinary medicine. As noticed in the above experiments, the hypnotic and analgesic efficacy of ketamine was enhanced when tramadol and ketorolac were added as a mixture with ketamine. The better enhancement of ketamine's efficacy was when ketorolac was added, which elevated and improved the hypnotic and analgesic efficacy of ketamine by 27 and 40%, respectively (synergistic interaction) and was superior to tramadol addition. The hypnotic and analgesic ED_{50} values of ketamine-tramadol and ketamine-ketorolac were decreased in comparison to ketamine alone and as it was expected because both tramadol and ketorolac have an analgesic effect on different receptor sites and can potentiate the effect of ketamine (Finkel *et al*., 2009a; White and Trevor, 2009). On the other hand, the mixture of ketamine-ketorolac was estimated here as a better general anesthetic due to

its faster onset and recovery from anesthesia with longer duration as well as the good analgesic mixture in comparison to ketamine alone or with tramadol. This is thought to be described by the different mechanisms of action of centrally acting ketamine (White and Trevor, 2009) and peripheraly acting ketorolac (Smyth and FitzGerald, 2009) and may be related to their pharmacokinetic behaviors (Gupta *et al*., 2012; Zaidi and Ahmed, 2015), further studies are needed to evaluate the possible interaction on receptor sites. Other studies show that ketorolac was effective when used in combination with local and general anesthetics for induction of anesthesia (Gupta *et al*., 2012; Zaidi and Ahmed, 2015). Unlike tramadol, another benefit of using ketorolac with general anesthetics is its good analgesia, its lower cost, fewer side effects and absence of respiratory depression and drug abuse as well as not worsening the outcome of surgical operations unlike tramadol (Jelinek, 2000; Ollé *et al*., 2000; Rainer *et al*., 2000; Shankariah *et al*., 2012; Hendarman *et al*., 2014). The liver activity, metabolism and its function assayed through the estimation of the levels of serum AST and ALT in all groups of the chicks, treated with ketamine alone or in combination with tramadol or ketorolac, was considered in the normal ranges of chicken criteria (Mousa, 2014).

In conclusion, the data of this experimental study reveal the superiority of using ketorolac (instead of tramadol) in combination with ketamine for induction of general anesthesia in the chicks.

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Conflict of interest

The authors declare that they have no competing interest.

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