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Clinical and biochemical evaluation of romifidine-ketamine and xylazine-ketamine induction combination for isoflurane anaesthesia in cattle

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Abstract
The study was conducted in 12 clinical cases presented to TVCC, Bidar. Twelve animals were randomly divided in to two groups viz., Group-I and Group-II consisting of six animals in each group. Group –I animals received romifidine (10µg/kg) intravenously, 10minutes later ketamine was given @3mg/kg body weight intravenously for induction of anaesthesia. In Group-II animals xylazine (0.1mg/kg) was administered intravenously, 10 minutes later ketamine was given @3mg/kg body weight intravenously for induction of anaesthesia followed by immediate intubation, maintenance of anaesthesia was done under isoflurane in both the groups. Anaesthetic combinations were compared by clinical and biochemical observations. The induction and recovery were smooth and uneventful in both the groups. Induction was quicker in group-I animals. Clinical and biochemical parameters like induction time, onset of sedation, analgesic score, degree of muscle relaxation, palpebral reflex and recovery time were fluctuated within normal limit. Induction time was quicker and faster followed by onset of sedation was earlier in group-I. Creatinine, alanine transaminase, aspartate transaminase and serum urea nitrogen were fluctuated within normal range in both the groups. In conclusion romifidine as pre-anaesthetic for ketamine and isoflurane anaesthetic maintenance was a better combination than xylazine –ketamine and isoflurane anaesthetic maintenance in cattle.

Keywords: cattle, romifidine, xylazine, isoflurane, first time in India

1. Introduction
Anaesthesia is an indispensable pre-requisite to most of the surgical interventions, so that the surgeon can perform surgical intervention with maximum precision and efficiency. An ideal anaesthetic produces sleep, amnesia, analgesia and muscle relaxation. However, all these characteristics cannot be provided by a sole agent and therefore a combination of drugs is used. In last two decade, there has been a tremendous advancement particularly in the field of large animal anaesthesia.

In recent year, intravenous anaesthetics with rapid onset, redistribution and clearance have become available, which create the possibility of maintaining anaesthesia even in large ruminants using these intravenous agents (Malik *et al.*, 2012).

General anaesthesia in large ruminants is induced by either injectable or inhalation techniques, available drugs include thiobarbiturates, ketamine, guaifenesin, tiletamine-zolazepam, propofol, isoflurane and sevoflurane (Carroll and Hartsfield, 1996).

The duration and intensity of cardiovascular depression depends on the type of α-2-Adrenoceptor agonist, its dose and route of administration (England and Clarke, 1996) [8]. The muscle relaxant, sedative and analgesic effects of xylazine are utilized in the xylazine-ketamine combination.

Inhalation anaesthetics are unique among all anaesthetic agents because they are administered and in large part removed from the body via lungs. Isoflurane is the most widely used inhalation anaesthetic in veterinary medicine, having replaced halothane (Steffey and Mama, 2007) [21]. It offers safety to the patient and provides greater control of anaesthetic depth to anaesthetist (Paddleford, 1999) as compared to intravenous anaesthesia or even total intravenous anaesthesia that has also been practiced in veterinary anaesthesia. However, it is common practice in cattle to induce anaesthesia with intravenous or parenterally administered anaesthetics and then to maintain anaesthesia with an inhalant agent. A2-adrenergic agonist drug used to induce tranquilization and or sedation, provides good muscle relaxation and analgesia during surgery, however, it carries the risk of suppressing the cardiovascular system.

Currently ketamine is used as induction agent in cattle, along with several pre-anaesthetic agent, xylazine (Arai *et al.*, 2006), diazepam (Riazuddin *et al.*, 2004a), acepromazine (Kumar *et al*., 2012) [13] and guaifenesin (Riazuddin *et al.*, 2004b) under isoflurane anaesthesia in cattle in India.

2. Materials and Methods
The study was conducted in 12 clinical cases presented to TVCC, Veterinary College, Bidar, presented with various surgical conditions. Twelve clinical cases were randomly

divided in two groups *viz.*, group-I and group-II with six animals in each group, the group-I animals were given romifidine[1] HCl @10µg/kg body weight intravenously, 10 minutes later ketamine[2] HCl was given @ 3mg/kg body weight intravenously for the induction of anaesthesia followed by immediate intubation, the animals were maintained on 5 per cent to 1 per cent of isoflurane. Group-II animals were given xylazine[3] HCl @ 0.1mg/kg body weight intravenously. 10 minutes later ketamine HCl was given @ 3mg/kg body weight intravenously for the induction of anaesthesia followed by immediate intubation, the animal were maintained on 5 per cent to 1.5 per cent.

The clinical parameters *viz.*, induction time, onset of sedation, analgesic score, degree of muscle relaxation, palpebral reflex score and recovery time. Biochemical parameters *viz.*, creatinine, alanine transaminase (ALT), aspartate transaminase (AST) and serum urea nitrogen were estimated at 0, 10, 30, 60 and 120 minutes after ketamine administration.

3. Results

3.1 Clinical Observation

3.1.1 Induction time (seconds)

In group-I animals, induction time ranged from 29 seconds to 34 seconds, with a mean induction time of 32.00±0.85 seconds. In group-II animals, induction time ranged from 38 seconds to 42 seconds, with a mean induction time of 38±0.60 seconds. The induction of anaesthesia was significantly earlier ($p \leq 0.01$) in group-I as compared to that of in group-II.

3.1.2 Onset of sedation (minutes)

In the group-I animals, onset of sedation ranged from 6 minutes to 9 minutes, with a mean onset of sedation of 7.00±0.52 minutes. In group-II animals, onset of sedation ranged from 8 minutes to 11minutes, with a mean onset of sedation of 9, 17±0.48 minutes. The onset of sedation was significantly faster ($p \leq 0.01$) in group-I animals as compared to group-II animals.

3.1.3 Analgesic score

The Mean ±SE values of analgesic score in cattle of group I animals, before induction, immediate after 10 minutes, 30minutes, 60minutes and120minutes after induction were; 0.00±0.00, 2.33±0.33, 3.00±0.00, 2.50±0.43 and 2.17±0.31 respectively.

The Mean ±SE values of analgesic score in cattle of group II animals, before induction, immediate after 10 minutes, 30 minutes, 60 minutes and 120 minutes after induction were; 0.00±0.00, 1.17±0.17, 2.00±0.00, 2.33±0.33 and 2.83±0.60 respectively.

The analgesia was absent before anaesthesia in both the groups of animals. Pain was significantly abolished from 0 minutes to 60 minutes in both the groups. The level of significance was at $p \leq 0.01$ at all the intervals in both the groups except that it was significant at $p \leq 0.05$ in group-II animals at 0 minutes. There was non-significant difference in the analgesia level produced between the groups at all the intervals of study.

3.1.4 Degree of muscle relaxation

In group-I, moderate muscle relaxation (Score =2) was recorded at 10 minutes after administration of romifidine in most of the animals, except for two animals, which recorded mild (Score = 1) muscle relaxation. Excellent muscle relaxation (Score= 3) was recorded after 30 minutes of romifidine and ketamine admiration in all the animals of group-I. At 60 minutes excellent muscle relaxation was recorded (score= 3) in most of the animals except one animal which recorded moderate muscle relaxation (score = 2). After 60 minutes of anaesthesia all the animals showed decreased muscle relaxation came to moderate (score = 2) muscle relaxation.

In group-II, mild muscle relaxation (Score =1) was recorded at 10 minutes after administration of xylazine in most of the animals, except for two animals, which recorded moderate (Score = 2) muscle relaxation. Excellent muscle relaxation (Score= 3) was recorded after 30 minutes of xylazine and ketamine administration in all the animals of group-II, except two animals which recorded moderate (score = 2) muscle relaxation. At 60 minutes excellent muscle relaxation was recorded (score= 3) in most of the animals of group-II. After 120 minutes of anaesthesia all the animals showed decreased muscle relaxation came to moderate (score = 2) muscle relaxation.

3.1.5 Palpebral reflex score

Palpebral reflex was intact even after induction (0 minutes), mild (score =1) to moderate (score =2) abolition in the animals of the both groups.

In the group-I animals, complete abolition of palpebral reflex (score = 3) was recorded at 30 minutes of post induction, except one animal showed moderate (score = 2) abolition of palpebral reflex. At 60 minutes of post induction all the animals of group-I showed complete abolition of reflex. At 120 minutes after induction all six animals showed moderate palpebral reflex.

In the group-II animals, complete abolition of palpebral reflex (score = 3) was recorded at 30 minutes of post induction in three animals, another three animal showed moderate (score = 2) abolition of palpebral reflex. At 60 minutes of post induction all the animals of group-II showed complete abolition of reflex. At 120 minutes after induction three animals showed moderate palpebral reflex and another three animals showed mild palpebral reflex.

3.1.6 Recovery time (Minutes)

In the group-I animals, recovery time ranged from 8 minutes to 13 minutes, with mean recovery time of 10.50±0.88 minutes. In the group-II animals, recovery time ranged from 9 minutes to 14 minutes, with a mean recovery time of 10.83±0.79 minutes.

The comparison between the groups revealed that there was no statistical significant ($P \geq 0.05$) difference in the recovery time.

3.2 Biochemical Observation

3.2.1 Creatinine (mg/dL)

The Mean ±SE values of Creatinine in cattle of group I and group II are given in table 1.

The mean ± S.E, values of group-I animals before anaesthesia, 10 minutes after pre-anaesthetic administration, and then at 30

minutes, 60 minutes and at 120 minutes after induction were;1.30±0.13, 1.18±0.12, 1.23±0.12, 1.21±0.16, 1.20±0.11 respectively. The corresponding interval values in group-II animals were; 1.28±0.12, 1.21±0.11, 1.17±0.07, 1.20±0.07, 1.21±0.11 respectively. The creatinine value fluctuate within normal physiological limits in both the groups. There was no significant difference (P≥0.05) within the groups or between the groups at all intervals of the study.

3.2.2 Alanine transaminase (ALT) (IU/L)

The Mean ±SE values of Alanine transaminase (ALT) in cattle of group I and group II are given in table 1.

The Mean ±SE values before pre-anaesthetic administration,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in group-I animals were; 31.00±2.28, 29.67±2.08, 30.00±3.72, 28.17±3.60 and 29.67±1.78 respectively. The corresponding interval values in group-II animals were; 33.33±2.75, 31.67±2.59, 30.50±3.19, 31.17±2.96 and 31.67±2.59 respectively.

The serum alanine transaminase value fluctuated within normal physiological limits in both the groups. There was no significant difference (P≥0.05) within the groups or between the groups at all the intervals of the study.

3.2.3 Aspartate transaminase (AST) (IU/L)

The Mean ±SE values of Aspartate transaminase (AST) in cattle of group I and group II are given in table 1.

The Mean ±SE values before pre-anaesthetic administration,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in group-I animals were; 25.50±2.71, 24.67±1.45, 24.67±2.19, 27.17±2.68 and 25.50±2.71 respectively.

The corresponding interval values in group-II animals were; 28.17±17, 28.33±2.35, 26.67±2.56. 33.67±4.61 and 28.33±2.55 respectively.

The serum aspartate transaminase value fluctuated within normal physiological limits in both the groups. There was no significant difference (P≥0.05) within the groups or between the groups at all the intervals of the study.

3.2.4 Serum Urea Nitrogen (mg/dL)

The Mean ±SE values of Serum urea nitrogen in cattle of group I and group II are given in table1.

The Mean ±SE values before pre-anaesthetic administration,10 minutes after pre-anaesthetic administration, 30 minutes, 60 minutes and 120 minutes after induction in group-I animals were; 17.58±2.77, 17.32±2.66, 15.65±2.27, 17.32±3.08 and 17.62±2.11 respectively.

The corresponding interval values in group-II animals were; 19.18±1.91, 18.32±1.92, 18.13±1.87, 18.35±2.34 and 19.18±1.91 respectively.

4. Discussion

4.1.1 Induction time

The induction time was significantly quick in the animals pre-medicated with romifidine –ketamine –isoflurane combination as compared to that in the animals pre-medicated with xylazine -ketamine-isoflurane. However, in the present study quick induction in group-I animals might be due to administration of ketamine after induction was smooth in both groups, which are in agreement with observation made by Kour and Singh (2004) [12] who used midazolam-ketamine combination in buffalo.

Riazuddin *et al*. (2004a) reported 2.21±0.11 minutes as induction time under xylazine–guaifenesin-ketamine anaesthesia as a triple drip in cattle.

4.1.2 Onset of sedation (minutes)

In group-I animals, onset of sedation was earlier as compared to that of group-II animals. It could be due to high lipophilic properties and rapid biotransformation of alpha-2 adrenergic groups. Rapid onset of sedation recorded in the present study was confirmed to the observation made in earlier studies following the administration of medetomidine /dexmedetomidine in dogs (Amarpal *et al.,* 1996, Kuushal *et al.,* 2000 and Ahmad *et al.,* 2011) [20].

4.1.3 Analgesia

An excellent analgesia was recorded at maximum depth of anaesthesia in both groups of animals. The pain was significantly abolished from 0 to 60 minutes in both the groups. There was non-significant difference in the analgesic level produced between the groups at all the intervals of study. The analgesic action might be due to stimulating central pre-synaptic alpha-2 adrenoceptors which inhibits nor-epinephrine release from adrenergic nerve terminals (Hsu, 1981) and interruption of nociceptive pathway to the ventral root of the dorsal horn (Kending *et al.,* 1991 and Ahmad *et al.,* 2012). Similar finding were recorded (Pawde *et al.,* 2000) [20] and (Al-Redah, 2011) [4].

4.1.4 Degree of muscle relaxation

An excellent muscle relaxation was recorded at maximum depth of anaesthesia in both groups of animals. The degree of muscle relaxation was significantly increased from 0 to 60 minutes in both the groups. There was non-significant difference in the degree of muscle relaxation level produced between the groups at all the intervals of study. All alpha-2 agonist are known to produce good muscle relaxation (Lemke, 2004) which could be due to inhibition of interneuronal transmission of impulses at the level of CNS. The findings of present study was confirmed to the observation of earlier researcher, who reported greater muscle relaxation when dexmedetomidine or medetomidine was combined with opioid and /or ketamine in cats or dogs (Ko *et al.,* 2000 and Selmi *et al.,* 2003) [11, 19].

4.1.5 Palpebral reflex score

The present study showed that, in both the groups of animals, the palpebral reflex was brisk and present before induction of anaesthesia. A sluggish palpebral reflex was present even after induction in all animals, similar findings were recorded, after xylazine-ketamine anaesthesia in buffalo calves (Chandrashekhar *et al.,* 2003) and after midazolam-ketamine induction in buffalo (Amandeep and Singh, 2004) [5]. However, two to five minutes after starting administration of isoflurane at 4 to 5 per cent, the palpebral reflex started testing negative in most of the animals. Similar observation during maintenance of anaesthesia with isoflurane, was recorded by

Singh *et al.*, (2013) [20] after thiopental induction in buffalo.

4.1.6 Recovery time (minutes)

Statistically there was no significant difference between the groups in the time taken for the animals to recover after discontinuing the isoflurane. The Mean±SE values of recovery time were: 10.50±0.88 and 10.83±0.79 minutes in Group-I and Group-II animals respectively. The recovery was smooth and uneventful in the animals of both groups, similar finding were reported in sheep during isoflurane anaesthesia by Mohamadnia *et al.* (2008).

4.2. Biochemical observation

Creatinine value remained within normal limits and no significant changes in the value were observed throughout anaesthesia in all animals. Similar findings were recorded after midazolam –ketamine anaesthesia in goats (Abu-Ahmad, 2013) [1] and isoflurane anaesthesia in sheep (Hikasa *et al.*, 2000). However, increase in the creatinine value were reported after acepromazine-ketamine and diazepam-ketamine anaesthesia in goats (Akhare *et al.*, 2003) [3], xylazine-butorphanol-midazolam-ketamine anaesthesia in horse (Malik and Singh, 2007) [15], detomidine-midazolam-ketamine anaesthesia in calves (Nuh, 2008) [16] and dexmedetomidine-butorphanol-ketamine combinations in dogs (Sharma *et al.*, 2014) [22].

Alanine transaminase (ALT) and aspartate transaminase (AST) fluctuated within normal limits in all the animals. Abu-ahamad (2013) [1] observed no significant change in the alanine transaminase and aspartate transaminase during midazolam and ketamine anaesthesia in goats. All general anaesthetics lover the circulation to liver (Malik and Singh, 2007) [15] and changes in alanine transaminase and aspartate transaminase during present study might be due to this fact.

Serum urea nitrogen was fluctuated within normal limits. A similar finding was observed by Abu-Ahmed (2013) [1] during midazolam –ketamine anaesthesia in goats. However Nuh (2008) [16], observed increase in serum urea nitrogen value after detomidine-midazolam-ketamine anaesthesia in calves.

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