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Neelkant
KVAFSU, Bidar, Karnataka, India

Dilipkumar D
Dean, Veterinary College, KVAFSU, Bidar, Karnataka, India

Manjunath Patil
Scientist (Animal Science), ICAR- Krishi Vigyan Kendra, Kalaburagi, UAS, Raichur, Karnataka, India

Bhagvantappa B
Associate Professor and Head, Veterinary Surgery and Radiology, Veterinary College, KVAFSU, Bidar, Karnataka, India

Venkatgiri
Assistant Professor, Veterinary Surgery and Radiology, Veterinary College, KVAFSU, Bidar, Karnataka, India

Pallavi
PG Scholar, Veterinary Surgery and Radiology, Veterinary College, KVAFSU, Bidar, Karnataka, India

Corresponding Author
Manjunath Patil
Scientist (Animal Science), ICAR- Krishi Vigyan Kendra, Kalaburagi, UAS, Raichur, Karnataka, India

Clinical and physiological changes in induction agents in drip form using guaifenesin and ketamine with or without dexmedetomidine under isoflurane anaesthesia for various surgeries in cattle

Neelkant, Dilipkumar D, Manjunath Patil, Bhagvantappa B, Venkatgiri and Pallavi

Abstract
The present study was conducted in 12 clinical cases presented to Veterinary Clinical Complex, Veterinary College, KVAFSU, Bidar for the treatment of various surgical affections in cattle. The cattle were randomly divided into two groups consisting of six animals in each group. The group- I animals were administered guaifenesin at the dose rate of 50 mg / kg body weight intravenously as 5% solution in normal saline along with ketamine at the dose rate of 3 mg/ kg body weight intravenously as drip form and maintained with isoflurane (1-2%). The animals of group- II were administered with preanaesthetic dexmedetomidine hydrochloride (2.5 µg/kg, IV) after 5 minutes followed by guaifenesin at the dose rate of 50 mg / kg body weight intravenously as 5% solution in normal saline along with ketamine at the dose rate of 3 mg/ kg body weight intravenously as drip form and maintained with isoflurane (1-2%). Though the induction and recovery were smooth and uneventful in both groups, Induction time was significantly earlier in group-II animals.
The recovery time, Recovery time to assume sternal recumbency, Recovery time to standing position was significantly quicker in group-I animals. The degree of analgesia and muscle relaxation was significantly greater in group-II animals. Physiological parameters like heart rate shows significant difference between the groups. Respiratory rate and rectal temperature were decreased significantly at maximum depth of anaesthesia in both the groups. Respiratory depression and bradycardia were more severe in group-II animals compare to group-I animals. In the present study both the anaesthetic protocols provided satisfactory surgical plane of anaesthesia in cattle. However, guaifenesin and ketamine drip with dexmedetomidine under isoflurane combination was ideal to perform major surgeries in cattle without any complications.

Keywords: clinical, physiological, guaifenesin, ketamine drip, dexmedetomidine

Introduction
Anatomical considerations in cattle carry the risk of complications like tympany regurgitation and aspiration pneumonia, which could be minimized by fasting the animal before anesthesia. In veterinary practice, intravenous anaesthetic drugs are commonly used for induction of anaesthesia in order to facilitate endotracheal intubation, oxygen administration and artificial ventilation. Maintenance of injectable anaesthesia can be obtained by infusion of intermittent boluses (IIB) or by continuous rate infusion (CRI). It has a cumulative effect and prolonged recovery from total anaesthesia, which is not desirable for patient (Malik, 2014) [22]. Hence inhalant anaesthetic agent, which provide predictable and rapid adjustment of anaesthetic depth. It helps in maintenance of general anaesthesia and minimizes the patient morbidity and mortality (Brosnan and Steffey, 2018) [5].
Dexmedetomidine has a quick onset and a relatively short duration of action, characteristics that renders it is suitable for a critical care unit, for post-operative cardiac and non cardiac patients. Dexmedetomidine produces important side effects such as hypotension and bradycardia with minimal respiratory depression (Afonso and Reis, 2012) [1]. It produces dose dependent sedation and analgesia, however, sedation does not increase in proportion to the increase in the dose however, cardio-pulmonary effects become more apparent (Kuusela, 2004) [14].
Guaifenesin, does not provide analgesia or produce unconsciousness. Therefore, it should not be used alone for any painful surgical procedure.

Guaifenesin available as powder which is reconstituted with normal saline or 5% solution in 5% dextrose. Guaifenesin administered intravenously in high concentrations (>10%) can cause hemolysis, hemoglobinuria and venous thrombosis (Lumb and Jones, 2015) [20].

Isoflurane is the most widely used inhalation anesthetic in veterinary medicine, having replaced halothane (Steffey and Mama, 2007) [28]. It provides safety of the patient and greater control over anesthetic depth. Most important is it has smooth and quick recovery from the anaesthesia.

Review of literature yielded paucity of information and reports on studies on guaifenssin and ketamine with or without dexmedetomidine as pre-anaesthetics with isoflurane anaesthesia in cattle, in India. Therefore, the present clinical study "Comparative evaluation of induction agents in drip form using guaifenesin and ketamine with or without dexmedetomidine under isoflurane anaesthesia for various surgeries in cattle" was undertaken.

Material and Methods

The study was conducted in 12 clinical cases presented to Veterinary Clinical Complex, Veterinary College, Bidar for the treatment of various surgical affections in cattle. Induction agent in drip form was evaluated by using guaifenesin and ketamine with or without dexmedetomidine under isoflurane anaesthesia for various surgeries in cattle. Twelve clinical cases of cattle presented to Veterinary Clinical Complex, Bidar were randomly divided into two groups *viz*., Group-I and Group-II consisting of 6 animals in each group. Body weight of the cattle anesthetized in the Group-I and Group-II were: 480.00 ± 14.05 and 357.66 ± 11.99 kg respectively. In the present study cattle were fasted for 24 hours and deprived of water for 12 hours prior to anaesthesia. Pre-operative fluid therapy was given to all the animals. The clinical status of the animals was assessed by recording heart rate, respiratory rate and rectal temperature and by conducting hematobiochemical examinations prior to anaesthesia.

In the Group-I, Guaifenesin was administered at the dose rate of 50mg / kg body weight intravenously as 5% solution in normal saline along with ketamine at the dose rate of 3mg/ kg body weight intravenously in the form of drip. Immediately after completion of solution the animals were restrained in lateral recumbency over the operating table.

In the Group-II, Pre-anaesthetic dexmedetomidine was administered at the dose rate of 2.5 µg/kg body weight intravenously. After 5 minutes of administration of dexmedetomidine, the animals were restrained in lateral recumbency over the operating table and general anaesthesia was induced by administering guaifenesin at the dose rate of 50mg / kg body weight intravenously as 5% solution in normal saline along with ketamine at the dose rate of 3mg/ kg body weight intravenously as drip form. Dosages of drugs used in both the groups were determined based on clinical trials and previous literature (Khattri *et al*., 2013 and Wall and Muir, 1990) [15, 32]. After induction, a Gunther's mouth gag was used to open the jaws. Oro-endotracheal intubation with cuffed Murphy type endotracheal tube of appropriate size was accomplished in all the animals by digital palpation of the epiglottis to direct endotracheal tube into the trachea. The endotracheal tube was connected to the Y piece of breathing tube of anaesthetic machine. Isoflurane was used for maintenance of anaesthesia by using the large animal anaesthetic machine Closed system was used for all animals. The 100% oxygen was given with flow rate set at 10 litres per minute for the first two minutes to increase the fraction of inspired oxygen concentration. The oxygen flow rate was then reduced to five to eight litres per minute based on the size of the animal. Initially isoflurane was given with higher concentration at 5% until downward rotation of eyeball. Later isoflurane concentration was reduced to 1-2%. The vapourizer setting was altered during anaesthesia as and when required to maintain uniform surgical plane of anaesthesia.

To evaluate the efficacy of anaesthetic protocol, the following parameters were recorded before, during and after anaesthesia.

Mean ± SE values of clinical observations *viz.*, onset of sedation (minutes), induction time (seconds), recovery time (minutes), recovery time to sternal recumbency (minutes), recovery time to standing position (minutes) were recorded. Other clinical parameters like degree of analgesia, degree of muscle relaxation and abolition of reflexes were evaluated before premedication at 0 minute and at 15, 30, 60 and 120 minutes interval after induction of general anaesthesia.

The time taken from administration of pre anaesthetic drug dexmedetomidine (group II) to the development of ataxia, drooping of eyelids and drowsiness in animals was considered as onset of sedation. Onset of sedation was recorded only in group- II animals, as in group- I animals dexmedetomidine preanaesthetic was not used. The time taken to induce general anesthesia after administration of anesthetic agent was considered as induction time. The time from discontinuation of the inhalant agent to the first spontaneous movement of any body part was considered as recovery time. The time taken by the animal from discontinuation of inhalant agent to the spontaneous regaining to sternal recumbency is considered as recovery time to sternal recumbency. The time taken by the animal from discontinuation of inhalant agent to the spontaneous regaining to standing position is considered as recovery time to standing position.

Degree of Analgesia was recorded by observing animals response to deep prick on the rib and at the coronary band with a 22G needle and was graded on 1-4 scale (Singh *et al.*, 2013) [30]. In addition, analgesia was determined by response of animal to surgical pain. Degree of muscle relaxation was assessed by observing abdominal muscles and reduced resistance to passive flexion of the limb and was graded on 1-4 scale (Singh *et al.*, 2013) [30]. Pedal and palpebral reflexes were evaluated for abolition of reflexes.

Physiological observations *viz.*, Heart rate (beats/min), Respiratory rate (breaths/min) and Rectal temperature (^{0}F) were recorded before pre-medication at 0 min and at 15, 30, 60 and 120 minutes interval after induction of general anaesthesia.

Results and Discussion

The details of all the clinical and physiological values recorded in the present study were given in table 1 & table 2 respectively.

Clinical observations

Onset of sedation (Minutes): Onset of sedation was recorded only in group- II animals, as in group- I animals dexmedetomidine preanaesthetic was not used. In group II animals onset of sedation ranged from 2.50 to 3.90 minutes. The Mean ± S.E values of onset of sedation were 2.90 ± 0.29 minutes. 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, Kuusela *et al.*, 2000 and Ahmad *et al.*, 2011) [2, 13, 3]. Mane *et al.* (2014) [23] observed a smooth and uneventful induction in horses premedicated with xylazine during ketamine-isoflurane anaesthesia.

Induction time (Seconds): In the Group-I (GK) animals, induction time ranged from 34 seconds to 42 seconds, with a mean induction time of 38.33 ± 1.20 seconds. Whereas, in the group-II (DGK) animals, induction time ranged from 25 seconds to 35 seconds, with a mean induction time of 30.17 ± 1.72 seconds. Induction time was significantly earlier (p<0.05) in Group-II (DGK) as compared to that in Group I (GK). The comparison between the groups revealed that there was statistically significant (p≤0.05) difference in the induction time which are in consistence with observations made by Kaur and Singh (2004) [10] who used midazolam-ketamine combination in buffalo.

Recovery time (Minutes): In the group-I animals, recovery time ranged from 8 minutes to 12 minutes, with mean recovery time of 9.47± 0.58 minutes. In the group-II animals, recovery time ranged from 12 minutes to 16 minutes, with a mean recovery time 12.67 ± 0.67 of minutes. The recovery time in cattle was significantly ($p\leq0.05$) quicker in group-I animals when compared to group- II animals. The comparison between the groups revealed, there was significant ($p\leq0.05$) difference in the recovery time. The recovery was smooth and uneventful in the animals of both groups, similar observations were reported in sheep during isoflurane anesthesia by Mohamadnia *et al*. (2008). Moolchand *et al.* (2014) [24] reported that xylazine caused hyperglycemia by reduction in insulin release and prolong recovery in sheep.

Recovery time to sternal recumbency (Minutes)

The recovery time to assume sternal position in cattle of group I ranged from 11 to 14 minutes and 14 to 18 minutes in cattle of group II. The recovery time to sternal position in cattle was significantly ($p\leq0.05$) quicker in group I animals when compared to group II animals. The comparison between the groups revealed, there was significant ($p\leq0.05$) difference in the recovery time to sternal recumbency. Kumar *et al.* (2014) [12] reported that the recovery time and time taken to regain sterna position were 7.25 ± 1.76 minutes and 21.37 ± 2.46 minutes in goats anaesthetized with dexmedetomidine andketamine. Dhawale *et al.* (2019) [9] after xylazine-guaifenesin- ketamine-isoflurane anesthesia in cattle. The longer duration required to attain sternal recumbency in the present study might be due to pre-anesthetics and ketamine used for induction.

Recovery time to standing position (Minutes)

The recovery time to standing position was significantly ($p\leq0.05$) quicker when guaifenesin and ketamine (group-I) under isoflurane general anaesthesia was used when compared to guaifenesin and ketamine with dexmedetomidine (group II) under isoflurane anaesthesia. The comparison between the groups revealed, there was significant ($p\leq0.05$) difference in the recovery time to standing position. Riazuddin *et al*. (2004a) [27] reported that the standing time was 45.50±3.01 after xylazine-guaifenesin-ketamine-isoflurane anesthesia in cattle. However, the standing time was only 6.70±1.02 minutes when only isoflurane is used to anesthetize cattle (Cantalapiedra *et al.*, 2000) [6].

Degree of analgesia: In cattle of group I, there was significant ($p\leq0.01$) increase in analgesia from 30 minute to 120 minute interval after anaesthetizing with guaifenesin-ketamine drip under isoflurane. In cattle of group II, there was significant ($p\leq0.01$) increase in analgesia from 15 minute to 120 minute interval after administering guaifenesin and ketamine drip with dexmedetomidine under isoflurane. Comparison between the groups revealed that the degree of analgesiawas significantly ($p\leq0.05$) greater at 15 minutes of induction in group-II animals when compared to group-I animals. Khattri *et al.* (2013) [15] observed good analgesia after administration of dexmedetomidine in buffalo calves. Kending *et al.* (1991) [16] and Ahmad *et al.* (2013) [3] explained that the analgesic action of dexmedetomidine is mediated spinally and by interruption of nociceptive pathways to the ventral root of the dorsal horn.

Degree of muscle relaxation: In cattle of group I, muscle relaxation was significantly ($p\leq0.01$) increased from 15 minutes to 60 minutes when guaifenesin and ketamine drip was used under isoflurane anaesthesia. Muscle relaxation was almost absent at 120 minutes. In cattle of group II, muscle relaxation was significantly ($p\leq0.01$) increased from 15 minutes to 60 minutes after administration of guaifenesin and ketamine with dexmedetomidine under isoflurane anaesthesia. Muscle relaxation was excellent up to 60 minutes after induction of general anaesthesia. At 120 minutes, the muscle relaxation was almost absent. Comparison between the groups revealed that the degree of muscle relaxation was significantly ($p\leq0.05$) greater at 15 minutes of induction in cattle of group-II when compared to group- I for guaifenesin-ketamine-isoflurane anaesthesia**.** Khattri *et al.* (2013) [15] observed good muscle relaxation in buffalo calves administered with dexmedetomidine.

Abolition of reflexes: Palpebral and pedal reflex was intact even after induction, mild (score =1) to moderate (score =2) abolition in cattle of both the groups. In group-I cattle, moderate to complete abolition of palpebral and pedal reflexes (score = 3) was recorded at 30 minutes of post induction. At 60 minutes of post induction all the cattle of group-I showed complete abolition of reflexes. At 120 minutes after induction all six animals showed mild palpebral and pedal refexes. In group-II cattle, complete abolition of palpebral and pedal reflexes (score = 3) was recorded at 30 minutes of post induction in all the animals, and it was continued up to 60 minutes of post induction. At 120 minutes after induction all cattle showed moderate to mild palpebral and pedal reflexes. Fuentes and Telez (1974) [8] and White *et al.* (1982) [33] reported that the swallowing, palpebral and corneal reflexes were unabolished under ketamine anaesthesia in cattle.

Physiological observations

Heart rate (beats/min): In cattle of group I, The heart rate was increased significantly *($p\leq0.01$)* from 15 minutes to 60 minutes when guaifenesin-ketamine drip under isoflurane anaesthesia was used. However, the heart rate returning towards normal at 120 minutes of post induction.In cattle of group II, The heart rate was decreased non-significantly at 15 minutes of post anaesthesia, which was then increased non-significantly from 30 to 60 minutes after administering guaifenesin and ketamine drip with dexmedetomidine under isoflurane anaesthesia. Comparison between the groups, the

heart rate showed significant (*p≤0.05*) difference from 15minutes to 60 minutes of post induction. Increase in heart rate was observed after administration of ketamine in dogs (Haskins *et al.*, 1985) [9], goats (Kumar *et al.*, 1986) [17] and horses (Muir *et al*., 1999) [25]. Lemke, 2007 [31] stated decreased heart rate might be due to reflex bradycardia as a result of α_2 agonist induced vasoconstriction. Bradycardia was observed after dexmedetomidine administration in goats (Kastner *et al.*, 2005) [18] and dogs (Ahmad *et al.*, 2011) [3].

Respiratory rate (breaths/min): In group-I animals, There was significant (*p≤0.05*) decrease in respiratory rate from 15minutes to 60 minutes when guaifenesin-ketamine drip under isoflurane anaesthesia was used. However the respiratory rate increased towards normal at 120 minutes of post induction. In group II animals, there was significant (*p≤0.01*) decrease in respiratory rate from 15minuets to 60 minutes of post induction. However, the respiratory rate increased towards normal at 120 minutes of post induction. Comparison between the groups showed significantly (*p≤0.05*) higher respiratory rate in group-I animals when compared to group-II animals from 15 minutes to 120 minutes intervals post anaesthesia. The Bradypnoea following induction of anaesthesia and remained low throughout the maintenance of anaesthesia in both the groups. Similar, findings were recorded by Kerr *et al*. (2007) [19], Yamashita *et al*. (1996) [34] in calves and cows respectively.

Rectal temperature (^{0}F): In group-I animals, there was significant (*p≤0.01*) decrease in rectal temperature was observed from15 minutes to 60 minute after guaifenesin-ketamine drip under isoflurane anaesthesia was used. However, the rectal temperature was increased towards normal at 120 minutes of post induction of general anaesthesia. In group II animals, There was significant decrease in (*p≤0.01*) in rectal temperature was observed from15 minutes to 30 minute when guaifenesin-ketamine drip with dexmedetomidine under isoflurane anaesthesia was used. However, the rectal temperature was increased towards normal 60 minutes to 120 minutes of post induction of general anaesthesia. Comparison between the groups, the rectal temperature showed significant (*p≤0.05*) difference at 30 minutes of post induction. Ahmad *et al.* (2011) [3] and Santosh (2011) [29] reported decreased rectal temperature after dexmedetomidine administration in dogs. Singh *et al.* (2013b) [30] observed a significant decrease in rectal temperature in buffaloes under dexmedetomidine-fentanyl-thiopentone-isoflurane anaesthesia.

Table 1: Mean ± SE., values of clinical in different groups under isoflurane anaesthesia for various surgeries in cattle

Parameters	Groups	Mean ± S.E
Induction time	Group I	38.33 ± 1.20^a
	Group II	30.17 ± 1.72^b
Recovery time	Group I	9.47 ± 0.58^a
	Group II	12.67 ± 0.67^b
Recovery time to sternal position	Group I	12.25 ± 0.44^a
	Group II	16.82 ± 0.61^b
Recovery time to standing position	Group I	15.15 ± 0.64^a
	Group II	21.50 ± 0.85^b

Means bearing superscript a, b differs significantly (*p≤0.05*) between the groups

Table 2: Mean ± SE., values of physiological in different groups under isoflurane anaesthesia for various surgeries in cattle

Parameter	Groups	Time interval in minutes				
		After guaifenesin-ketamine-isoflurane administration				
		0 Min	15 Min	30 Min	60 Min	120 Min
Degree of analgesia	I	0.00 ± 0.00	2.00 ± 00^a	2.67 ± 0.21**	2.83 ± 0.16**	2.50 ± 0.22**
	II	0.00 ± 0.00	2.83 ± 0.17^{**b}	2.83 ± 0.17**	3.17 ± 0.17**	2.83 ± 0.17**
Degree of muscle relaxation	I	0.00 ± 0.00	2.83 ± 0.16^{**a}	3.33 ± 0.21**	3.50 ± 0.22**	0.00 ± 0.00
	II	0.00 ± 0.00	3.50 ±0.22**^{b}	3.83 ± 0.17**	4.00 ± 0.00**	0.00 ± 0.00
Heart rate (beats/min)	I	69.33± 0.66	73.33±0.71^{**a}	74.16±0.60^{**a}	73.50±0.61^{**a}	69.33 ± 0.71
	II	69.16± 0.48	68.50 ± 0.34^b	69.16± 0.54^b	70.00 ± 0.58^b	69.83 ± 0.54
Respiratory rate (breaths/min)	I	27.33±0.42	24.66 ± 0.55^{*a}	23.83± 0.70^{*a}	25.33 ± 0.61*^{a}	28.33 ±0.42^a
	II	26.83±0.48	21.00 ± 0.52^{**b}	20.50± 0.62^{**b}	21.50 ± 0.56^{**b}	24.50± 0.34^b
Rectal temperature (^{0}F)	I	102.10±0.06	101.60±0.04**	100.90±0.10**^{a}	101.56±0.06**	101.91±0.07
	II	102.20±0.10	101.53±0.12**	100.25±0.17**^{b}	101.65±0.16	101.88±0.13

Means bearing superscript a, b differs significantly (*p≤0.05*) between the groups at corresponding intervals
Means bearing superscript* differ significantly (*p≤0.05*) from interval 'before' within the group at different intervals
Means bearing superscript** differ significantly (*p≤0.01*) from interval 'before' within the group at different intervals

Conclusion

Based on the clinical and physiological changes in induction agents in drip form it was concluded that, both the anaesthetic protocols provided satisfactory surgical plane of anaesthesia in cattle. However, guaifenesin and ketamine drip with dexmedetomidine under isoflurane combination was ideal to perform major surgeries in cattle without any complications.

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