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Comparative evaluation of clinico-physiological, haemodynamic and haemato-biochemical effect of ketamine-guaifenesin and ketamine-midazolam as induction with isoflurane maintenance anaesthesia in buffaloes

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Abstract
The present study was undertaken to investigate the clinico-physiological, haemodynamic and haemato-biochemical effect of ketamine-guaifenesin and ketamine-midazolam as induction with isoflurane maintenance anaesthesia in 12 buffaloes divided into two equal groups. In group I, ketamine (2 mg/kg, IV) and guaifenesin (50 mg/kg, IV) while, in group II, ketamine (2 mg/kg, IV) and midazolam (0.05 mg/kg, IV) were used for induction of anaesthesia. The intubated buffaloes were connected to the large animal anaesthesia machine and isoflurane in 100% oxygen was given. Despite cardiopulmonary depression ketamine-guaifenesin and ketamine-midazolam as induction anaesthesia along with isoflurane maintenance anaesthesia provides clinico-physiological and haemodynamic stability in buffaloes.

Keywords: Anaesthesia, buffaloes, guaifenesin, ketamine, midazolam

Introduction
General anaesthesia in adult water buffaloes or cattle involves complications, such as regurgitation, bloat, aspiration pneumonia, nerve paralysis etc., which are not often encountered in small animals. To reduce the risk associated with these potential complications, adult cattle should be fasted from 18 hrs to 24 hrs under captive conditions. Additionally, pulmonary functional residual capacity may be better preserved in fasted anaesthetised animals (Tranquilli & Maze, 1993) [1].

Double Drip is the most commonly used method for inducing anaesthesia to be maintained with inhalants in ruminants. A constant-rate infusion of double drip can be used to provide a stable plane of injectable anaesthesia in ruminants. Double drip is created by adding ketamine (1 mg/ml) to 5% guaifenesin (Abrahamsen, 2008) [2].

Ketamine is a dissociative anaesthetic. Presently, ketamine is the most commonly used injectable anaesthetic in large animal practice. It produces dose dependent unconsciousness and analgesia (Cohen, 1973) [3]. Guaifenesin is a central muscle relaxant frequently used in large animal practice. It is not an anaesthetic, and does not produce anaesthesia or analgesia. Therefore, guaifenesin should always be used in combination with other anaesthetic(s), for example, ketamine, thiopental or propofol to provide good muscle relaxation during anaesthesia (Thurmon and Benson, 1993) [4]. Midazolam is a water-soluble benzodiazepine having sedative, hypnotic, anticonvulsant, muscle relaxant and cardiovascular protective properties (Mandrioli *et al.*, 2008) [5].

Isoflurane is highly volatile, having low blood solubility, provide rapid induction and recovery and easy control over the depth of anaesthesia. Renal blood flow is well maintained during isoflurane anesthesia and there is very little production of fluoride ions, coupled with less than 1 percent elimination via kidneys. It can generally be administered quite safely to animals with renal dysfunction (Hikasa *et al.*, 2002) [6].

Present study was conducted to see the clinico-physiological, haemodynamic and haemato-biochemical effect of ketamine-guaifenesin and ketamine-midazolam as induction with isoflurane maintenance anaesthesia in buffaloes subjected to diaphragmatic herniorrhaphy.

Materials and Methods

The present study was performed on 12 buffaloes presented for diaphragmatic herniorrhaphy. These buffaloes were randomly allotted in Group I and Group II, each consisting six buffaloes. All the buffaloes were withheld feed and water for 24 hours prior to administration of general anaesthesia. Buffaloes in group I were induced with intravenous administration of double drip solution of guaifenesin at the dose rate of 50 mg/kg body weight, as a 5% solution in lukewarm 5% dextrose normal saline and ketamine was added in solution at the dose rate of 2 mg/kg body weight. Buffaloes in group II were induced with intravenous administration of midazolam at the dose rate of 0.05 mg/kg and ketamine at the dose rate of 2 mg/kg body weight. Anaesthesia was maintained with isoflurane using a large animal anaesthetic machine (DRE Titan, USA).

Physiological parameters

The physiological parameters *viz*. rectal temperature (^{0}F), respiration rate (breaths/min) and heart rate (beats/min) were recorded before induction (0 min), after induction and at 15 minutes of interval up to 60 minutes after induction.

Haemodynamic parameter

The haemodynamic parameter like SpO_2 (per cent) was recorded before induction (0 min), after induction and at 15 minutes of interval up to 60 minutes after induction.

Haemato-biochemical parameters

Blood samples were collected in K3 EDTA blood collection vial for haematological study and clot activator vial for biochemical study at before induction, after induction (0 minute), 15 minutes, 45 minute and 90 minutes after induction. The haematological parameters *viz*. haemoglobin (g/dL), packed cell volume (per cent), total erythrocyte count (10^6 cells/cumm), total leukocyte count (10^3 cells/cumm) and differential leukocyte Count (DLC) *viz*. neutrophil (per cent), lymphocyte (per cent), eosinophil count (per cent) and monocyte (per cent) were measured by auto blood analyser. The biochemical parameters *viz*. creatinine (mg/dl), blood urea nitrogen (mg/dl), aspartate aminotransferase (IU/L) were estimated using fully automated biochemical analyser.

Results

Physiological parameters

In group I, the mean heart rate increased significantly (p<0.05) at after induction (0 minute) and decreased significantly (p<0.05) at 15 minutes, 30 minutes, 45 minutes and 60 minutes after induction while in group II, increased significantly (p<0.05) at after induction (0 minute) 15 minutes, 30 minutes, 45 minutes and 60 minutes after induction as compared to before induction. Significant change (p<0.05) in mean heart rate was observed at before induction, after induction (0 minute), 15 minutes, 45 minutes after induction on comparison of between group I and II at different time intervals. In present study, at after induction (0 minute) increased heart rate in both the groups at after induction (0 minute) might be due to cardiac stimulation effect of ketamine. Thereafter, gradual bradycardia up to 60 minutes after induction in both the groups which was positively correlated with Muchalambe *et al.* (2018) [7] who observed gradual bradycardia during maintenance with isoflurane up to 60 minutes after induction cattle anaesthetized with midazolam-propofol followed by maintenance on 0.5 per cent to 1 per cent of isoflurane but negatively correlated with Kerr *et al.* (2007) [8] who observed decreased heart rate throughout the anaesthetic period in the xylazine-guaifenesin-ketamine group compared with the isoflurane group in calves.

In both the groups, the mean respiration rate increased significantly (p<0.05) at after induction (0 minute) but decreased significantly (p<0.05) at 15 minutes, 30 minutes, 45 minutes and 60 minutes after induction as compared to before induction. The mean respiration rate showed significant change at before induction on comparison of between group I and II at different time intervals. In present study, increased respiration rate in both the groups at after induction (0 minute), might be due to effect of ketamine. Thereafter, the gradual decreased in respiration rate up to 60 minutes after induction in both the groups which was not correlated with Dzikiti *et al.* (2009) [9] who observed decreased respiration rate after induction with butorphanol-midazolam in goats but Muchalambe *et al.* (2018) [7] who also observed bradypnea during maintenance of anesthesia on isoflurane in cattle. Tank (2017) [10] who also observed decrease respiration rate during maintenance period and decrease heart at after induction which was not positively correlated with finding in present study at after induction (0 minute).

The mean rectal temperature did not show any significant change (p>0.05) in within group and between groups at different time intervals. The gradual decreased in rectal temperature was observed in present study. It might be due to decreased skeletal muscle activity and decreased metabolic rate. Similarly, Hikasa *et al.* (1994) [11] who observed slight decreased rectal temperature during sevoflurane anaesthesia. following administration of atropine-guaifenesin thiopental anaesthesia. Tank (2017) [10] also observed non-significant decrease in rectal temperature throughout the anaesthetic study (butorphanol tartrate-ketamine-guaifenesin). Malik *et al.* (2011) [12] who observed increase rectal temperature up to 15 minutes after premedication with medetomidine-butorphanol and maintained on thiopental sodium in buffaloes which was differed from findings in present study.

Haemodynamic parameter

In both the groups, the mean SpO_2 decreased significantly (p<0.05) at after induction (0 minute), 15 minutes, 30 minutes, 45 minutes and 60 minutes after induction as compared to before induction. Significant change in the mean SpO_2 was observed at after induction (0 minute) and 60 minutes after induction on comparison of between group I and II at different time intervals. Similarly, Tank (2017) [10] also observed decrease SpO_2 level throughout the anaesthetic study (butorphanol tartrate-ketamine-guaifenesin). Sutaria (2020) [13] also observed decrease level of SpO_2 after ketamine-midazolam-isoflurane and ketamine-diazepam-isoflurane anaesthesia in buffalo.

Haemato-biochemical parameters

The mean haemoglobin did not show any significant difference (p>0.05) at different time interval as compared to before induction but significant change was observed at 90 minutes on comparison of between groups at different time intervals. Similarly, Tank (2017) [10] observed non-

significantly decreased haemoglobin level after ketamine-guaifenesin isoflurane anaesthesia in bovine. Kiliç (2008) also observed decreased haemoglobin level after detomidine-midazolam-ketamine anaesthesia. The findings partially in agreement with Hikasa *et al.* (1994) [11] who observed non-significant decrease in haemoglobin level during sevoflurane anesthesia following administration of atropine-guaifenesin-thiopental.

The packed cell volume fluctuated non-significantly ($p>0.05$) in both the groups at different time intervals. Similarly, Hikasa *et al.* (1994) [11] who observed non-significant difference in packed cell volume throughout the anaesthetic study in Holstein cows maintained on sevoflurane following administration of atropine-guaifenesin-thiopental anaesthesia. Agrawal *et al.* (1983) also observed non-significant changes in value of packed cell volume following glyceryl guaiacolate-thiopentone sodium anaesthesia. Similar findings were observed by Kiliç (2008) who observed non-significant change after detomidinemidazolam-ketamine anaesthesia.

The mean total erythrocyte count fluctuated non-significantly ($p>0.05$) in both the groups at different time intervals. Similar to present study, Tank (2017) [10] who observed non-significant reduction in total erythrocyte count at 45 minutes after induction as compared to baseline value after induction. However, in contrast to present study, Thangaurai *et al.* (2015) [16] who also observed significant difference in total erythrocyte count in cattle pre medicated with midazolam, induced with ketamine and guaifenesin and maintained on isoflurane. The finding in present study differed from Muchalambe *et al.* (2018) [7] who observed significantly decreased total erythrocyte count between 30 minutes and 60 minutes after induction with midazolam-propofol when compared to pre-anaesthetic level.

The value of total leucocyte count non-significantly fluctuated in both the groups at different time intervals. Similar to present study, Tank (2017) [10] who observed non-significant change in total leucocyte count after ketamine-guaifenesin-isoflurane anaesthesia in bovine. Thangaurai *et al.* (2015) [16] who also observed significant difference in total erythrocyte count in cattle pre medicated with midazolam, induced with ketamine and guaifenesin and maintained on isoflurane. In contrast to present study, Muchalambe *et al.* (2018) [7] who observed significantly decreased total leucocyte count between 30 to 60 minutes after induction with midazolam-propofol when compared to pre anaesthetic level.

The mean value of lymphocyte count showed non-significant change in group I but increased significantly at 15 and 45 minutes after induction in group II as compared to before induction. The findings in group I were corroborated with Gnanasekar and Vijayalakshmi (2016) who observed non-significant change in lymphocyte count after xylazine-ketamineguaifenesin anaesthesia in cattle. The findings in group II did not correlate with Muchalambe *et al.* (2018) [7] who observed decrease lymphocyte count between 30 minutes and 60 minutes after midazolam-propofol-isoflurane anaesthesia in cattle when compared to pre anaesthetic level.

The mean value of monocyte count showed non-significant fluctuation at different time intervals in both the groups. Similarly, who observed non-significant change after xylazine-ketamine-guaifenesin anaesthesia in cattle. Muchalambe *et al.* (2018) [7] also observed non-significant change after midazolam propofol-isoflurane anaesthesia in cattle. The mean neutrophil count increased significantly at 45 minutes after induction in both the groups. However, Hikasa *et al.* (1994) [11] who observed non-significant change in value of neutrophil count at any time after anaesthesia maintained on sevoflurane following administration of atropine-guaifenesin-thiopental in Holstein cows. The findings in present study were differed from Muchalambe *et al.* (2018) [7] who observed significant increase between 30 minutes and 60 minutes after midazolam-propofol isoflurane anaesthesia in cattle. Neutrophilia in present study might be due to stress caused by anaesthetic drugs.

The mean serum creatinine showed non-significant change in group I but significantly increased at 90 minutes after induction in group II. Similar to findings in group I, Hikasa *et al.* (1994) [11] who observed non-significant change in value of serum creatinine at any time after anaesthesia maintained on sevoflurane following administration of atropine-guaifenesin thiopental in Holstein cows. In contrast to findings in group II, Muchalambe *et al.* (2018) [7] who observed non-significant change in serum creatinine in cattle induced with midazolam-propofol and maintained on isoflurane anaesthesia.

In present study, blood urea nitrogen showed non-significant fluctuation in both the groups. Similarly, Hikasa *et al.* (1994) [11] observed non-significant change in value of blood urea nitrogen after anaesthesia maintained on sevoflurane following administration of atropine-guaifenesin thiopental in Holstein cows. However, Muchalambe *et al.* (2018) [7] who observed significant increase in blood urea nitrogen in cattle induced with midazolam-propofol and maintained on isoflurane anaesthesia.

In present study, serum aspartate transaminase fluctuated non-significantly in both the groups. In contrast to findings in group I, Hikasa *et al.* (1994) [11] who observed slight increase in aspartate transaminase 1 day after discontinuation of anaesthesia maintained on sevoflurane following administration of atropine-guaifenesin thiopental in Holstein cows. The findings in group II did not correlate with Muchalambe *et al.* (2018) [7] who observed increased serum aspartate transaminase at 24 and 48 hours after midazolam-propofol-isoflurane anaesthesia.

Table 1: Mean ± standard error values of Physiological and haemodynamic parameters in group-I and group-II at different time intervals

Parameters	Group	Time interval					
		Before induction	After induction (0 min)	15 min	30 min	45 min	60 min
Heart rate (beats/min)	I	65.50 ± 1.50^{bA}	81.63 ± 1.64^{cA}	57.00 ± 1.96^{aA}	55.75 ± 2.53^{a}	50.75 ± 1.79^{aA}	50.38 ± 1.46^{a}
	II	54.67 ± 3.70^{bB}	74.17 ± 2.26^{cB}	63.33 ± 2.16^{aB}	62.17 ± 1.56^{a}	59.67 ± 1.67^{aB}	56.00 ± 1.53^{a}
Respiration rate (breaths/min)	I	18.63 ± 1.75^{bA}	22.88 ± 1.38^{c}	9.50 ± 0.78^{a}	8.38 ± 0.91^{a}	7.00 ± 0.42^{a}	6.88 ± 1.90^{a}
	II	13.83 ± 0.79^{bB}	19.83 ± 1.08^{c}	9.00 ± 2.31^{a}	7.33 ± 1.74^{a}	6.33 ± 0.99^{a}	5.50 ± 0.72^{a}
Rectal temp. (^{0}F)	I	98.84±0.44	99.19±0.36	99.19±0.36	98.86±0.33	98.55±0.30	98.41±0.32
	II	99.03±0.74	99.57±0.61	99.27±0.53	98.57±0.49	98.35±0.33	97.97±0.37
SpO_2 (per cent)	I	96.63 ± 0.71^{c}	85.38 ± 1.02^{bA}	73.63 ± 0.65^{a}	72.5 ± 0.63^{a}	73.38 ± 0.82^{a}	86.63 ± 0.53^{bA}
	II	97.83 ± 0.48^{c}	81.17 ± 0.65^{bB}	73.00 ± 0.58^{a}	73.33 ± 0.56^{a}	72.17 ± 0.48^{a}	82.33 ± 0.67^{bB}

Mean bearing different superscript (a, b, c, d) differ significantly within group ($p<0.05$)

Mean bearing different subscript (A, B) differ significantly between groups ($p<0.05$)

Table 2: Mean ± standard error values of haemato-biochemical parameters in group I and group II at different time intervals

Parameters	Group	Time interval				
		Before induction	After induction (0 min)	15 min	45 min	90 min
Haemoglobin (g/dl)	I	13.91±0.55	13.64±0.66	13.55±0.65	13.56±0.53	13.46±0.46^{A}
	II	13.02±0.85	12.63±0.81	12.10±0.85	12.27±0.70	11.83±0.68^{B}
Packed cell volume (per cent)	I	39.69±1.23	40.16±0.68	39.80±0.59	40.63±0.68	40.18±0.26
	II	35.67±1.79	34.42±1.81	34.03±1.47	35.37±1.42	30.48±2.48
Total erythrocyte count (10^6 cells/cumm)	I	6.89±0.31	6.77±0.34	7.19±0.31	7.31±0.24	7.19±0.20
	II	6.83±0.51	6.76±0.52	6.99±0.54	7.01±0.48	6.96±0.48
Total leucocyte count (10^3 cells/cumm)	I	7.49±0.65	7.40±0.74	7.68±0.44	7.53±0.51	7.89±0.39
	II	7.40±0.89	7.02±0.89	7.28±0.60	7.57±0.41	8.07±0.32
Lymphocyte count (per cent)	I	54.68±1.65	55.65±1.58	53.00±3.00	51.05±2.15	51.85±1.44
	II	55.37±1.77^{b}	54.93±1.45^{b}	49.25±3.75^{a}	45.10±2.24^{a}	49.87±3.86^{ab}
Monocyte count (per cent)	I	1.25±0.10	0.99±0.12	0.99±0.12	1.00±0.14	1.18±0.11
	II	1.30±0.08	1.02±0.12	0.83±0.15	1.08 ± 0.19	0.73±0.24
Neutrophil count (per cent)	I	37.49±0.58^{a}	38.00±0.53^{ab}	41.65±1.03^{ab}	43.76±0.71^{b}	41.58±0.50^{ab}
	II	37.75±1.78^{a}	39.53±1.75^{ab}	42.05±1.69^{abc}	48.03±2.26^{c}	45.46±3.65^{bc}
Serum creatinine (mg/dl)	I	2.22±0.12	2.40±0.15	2.52±0.14	2.64±0.15	2.48±0.15
	II	2.25±0.14^{a}	2.29±0.14^{ab}	2.48±0.11^{ab}	2.57±0.14^{b}	2.53±0.12^{ab}
Blood urea nitrogen (mg/dl)	I	99.33±6.21	98.49±5.90	95.41±4.88	99.64±3.09	96.61±3.07
	II	97.39±9.11	101.6±8.46	100.82±7.52	102.83±5.87	101.80±3.78
Serum aspartate transaminase (IU/L)	I	152.93±16.93	157.11±17.86	163.64±18.18	151.89±18.12	168.83±17.66
	II	172.20±28.09	174.83±31.45	176.77±29.11	174.13±22.89	175.62±29.95

Mean bearing different superscript (a, b, c, d) differ significantly within group (p<0.05)
Mean bearing different subscript (A, B) differ significantly between groups (p<0.05)

Conclusion

On the basis of the findings of the study described above, it is concluded that Ketamine-guaifenesin as induction with isoflurane maintenance anaesthesia provided better clinico-physiological and haemodynamic stability in buffaloes compared to ketamine-midazolam-isoflurane anaesthesia.

Conflict of Interest

Not available

Financial Support

Not available

Reference

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