



## Therapeutic Evaluation of Metoclopramide in Gastrointestinal Tract Atony in Buffaloes

Jubin\*, Yudhbir Singh, Neelam and V. K. Jain

Department of Veterinary Medicine, Lala Lajpat Rai University of Veterinary and Animal Sciences,  
Hisar - 125004, Haryana, India

\*Corresponding Author E-mail: [jubinrukhaya1992@gmail.com](mailto:jubinrukhaya1992@gmail.com)

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### ABSTRACT

Gastrointestinal tract atony exists as one of the most common digestive tract ailments among buffaloes which results in great economic losses. Present study was conducted to evaluate the therapeutic effect of metoclopramide in gastrointestinal tract atony in buffaloes (n=12). Animals brought to the VCC with complaint of inappetance/anorexia, reduced or loss of defecation with or without mucus and melena, colic signs and loss of production were subjected to the therapeutic trial. Haemato-biochemical evaluation revealed neutrophilia, lymphopenia, hypocalcaemia, hypochloroemia, hypokalaemia, hyperglycemia with increased aspartate aminotransferase level in all affected animals. For therapeutic evaluation clinical cases were divided into two groups, each consisting of six animals. In animals of group I - Hypertonic saline and Calcium; and in group II - Metoclopramide, Hypertonic saline and Calcium were administered. More improvement in ruminal atony and desired haemato-biochemical alterations were observed in buffaloes of group II as compared to buffaloes of group I. Three animals were found to be recovered in group I and four in group II. Present study concluded that Combination of hypertonic saline, calcium and metoclopramide was more effective treatment in gastrointestinal tract atony in buffaloes.

**Key words:** Therapeutic, Gastrointestinal, Metoclopramide, Atony, Buffaloes.

### INTRODUCTION

Gastrointestinal hypomotility disorders are one of the most common digestive tract ailments among buffaloes which lead to great economic losses<sup>1</sup>. It is important to study the different prokinetic drugs efficacy from the point of restoration, normalization and facilitation of motility of gastrointestinal tract especially in buffalo. Prokinetic agents have the ability to

stimulate, coordinate and restore gastric, pyloric and small intestine motility<sup>2</sup>. An effective prokinetic drug must be able to induce gastrointestinal tract motility in a coordinated sequence of contractions and relaxation. A wide variety of drugs have been used for many years to induce gastrointestinal tract motility, but with little success.

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Rumenototics containing nux-vomica, ginger and tartar given orally have been found very less effective. Parasympathomimetics such as neostigmine or carbamyl choline should not be used to treat gastrointestinal tract atony as these drugs require effective vagal activity to produce the desired effects<sup>3</sup>. Metoclopramide as dopamine antagonist can block the effect of dopamine peripherally, which shows the increase in the amplitude and rate of reticulo-ruminal contractions in sheep<sup>4,5</sup>. Experimentally metoclopramide increases the rate of ruminal contraction and might be beneficial in ruminal atony<sup>3</sup>. Metoclopramide increases the amplitude and frequency of contraction, but only for 20 minutes and only at a dose rate of 0.3 mg/kg b. wt. intramuscularly<sup>6</sup>. Metoclopramide has been used for the treatment of vagal indigestion in cattle<sup>7</sup> but the knowledge about the treatment efficacy of this agent is very scarce. The effect of metoclopramide on reticular motility was previously described in adult cattle<sup>8</sup> and clinical cases of bovine rumen impaction were treated successfully with prokinetic drug metoclopramide<sup>9</sup>. Therefore, the present study was planned to evaluate the effects of metoclopramide as a prokinetic drug in gastrointestinal tract atony cases in buffaloes.

#### MATERIAL AND METHODS

The present study was conducted in gastrointestinal tract atony cases in buffaloes (age above 1 year) brought to Veterinary Clinical Complex (VCC), Lala Lajpat Rai University of Veterinary and Animal Sciences (LUVAS), Hisar. Based on history, clinical signs and radiographic examination; buffaloes found to be suspected to be the cases of non-traumatic gastrointestinal tract atony were included in the study. Six apparently healthy buffaloes were also included in this study as a control group to compare the findings of diseased animals with apparently healthy animals.

#### THERAPEUTIC TRIAL AND EVALUATION OF THERAPY

For therapeutic evaluation buffaloes affected with gastrointestinal tract atony were divided into two groups each consisting of six animals. In animals of group I - Hypertonic saline and

Calcium; and in group II - Metoclopramide, Hypertonic saline and Calcium were administered. Metoclopramide was given @ 0.3 mg/kg body weight (b. wt.) intramuscularly (OD). Calcium @ 5.75g/day was given by slow intravenous route. Potassium chloride (KCl) 1.5g and NaCl (Sodium chloride) 18 g were mixed in each liter of normal saline solution (NSS) and given intravenously. A total of three liters of hypertonic saline (KCl + NaCl) was given in one day. Antibiotic and supportive therapy in the form of antihistaminic, NSAIDs (Non-steroidal anti-inflammatory drugs), liver extract and vitamins were administered as per need of the case. Whole treatment was repeated for 3 days.

Therapeutic evaluation was done on the basis of remission of clinical signs and haemato-biochemical parameters on 1<sup>st</sup> day (day 1) and 3<sup>rd</sup> day (day 3) post-treatment.

#### SAMPLING AND HAEMATO-BIOCHEMICAL EXAMINATIONS

The blood samples were collected in ethylenediamine-tetraacetic acid (EDTA) vials. The whole blood samples were processed for estimation of Haemoglobin (Through spectrophotometrically using Drabkin's reagent); Packed cell volume (by microhaematocrit method) and Total leukocyte count (using a standard haemocytometer). Differential leucocyte count (DLC) was done through Giemsa staining of blood smear.

The blood was collected in vials without anticoagulant for harvesting serum and the serum samples were analyzed for estimation of biochemical profile using fully automated random access Clinical Chemistry Analyzer (EM 200TM, Erba Mannheim-Germany).

#### STATISTICAL ANALYSIS

The results obtained were analyzed statistically by two way ANOVA test with repeated measures using SPSS software. Significance level was set at  $p \leq 0.05$ .

#### RESULTS AND DISCUSSION

Changes in clinical vital parameters in buffaloes affected with gastrointestinal tract

atony before and after treatment are depicted in table 1. Significant variations of rectal temperature were not observed in animals affected with gastrointestinal tract atony and after the treatment in both groups. These findings are in agreement with Anderson *et al.*<sup>10</sup> they reported non significant variations in rectal temperature in animals affected with intestinal obstruction. Similarly, significant variations were not observed in heart rate and respiration rate before and after therapy and between the groups. These findings are in agreement with Kumar<sup>11</sup>, he did not observed any significant change in heart rate and respiration rate. However the mean value of respiration rate of group I animals were higher than the animals of group II. It might be due to the increase in blood pH and pCo2 values<sup>12</sup>.

Affected animals of all the treatment groups had lower mean values of ruminal motility on day 0. After administration of therapy ruminal motility increased in both groups and more increase in rumen motility was found in group II. The results were in agreement with the findings of Walker<sup>13</sup> and Braun *et al.*<sup>14</sup>, where atony of rumen was reported in cases of intestinal obstruction. Reduction in rumen motility can be explained as high concentration of amines in rumen might have resulted in their increased flow to abomasum and possibly may leads to an increased gastrin secretion in these buffaloes which subsequently decreases ruminal motility<sup>15</sup>.

All affected animals were examined per-rectally, and examination was found effective in diagnosis of gastrointestinal tract atony. Five cases were found to be affected with caecal dilatation and seven with caecal impaction. Sausage shaped distended intestine was observed in pelvic cavity and also in front of pelvic brim. Ballooning of intestine was found in severe cases of gastrointestinal tract atony (n=7). Hard and scanty faeces with or without mucus and digested blood was also observed. Cases with clotted blood (sometimes with scanty hard faeces and mucus) were common and such cases were suspected for proximal small intestinal atony (n=5). Animals

with evacuation of thick mucus only from rectum were suspected for small intestine atony. Some animals were presented with hard faeces with or without mucus were suspected for large intestine atony, while in other animal's rectum was found to be empty. Findings in present investigation are broadly in agreement with those reported by Mestry *et al.*<sup>16</sup>.

Haematological alterations in buffaloes affected with gastrointestinal tract atony before and after treatment are depicted in table 2. Significant variations were not found in Hb levels in before treatment and after treatment as well as within groups. But significant difference was observed in mean PCV within group II animals at day 0 and day 3. Normal levels of PCV and Hb in cases of intestinal obstruction were observed by Mohan *et al.*<sup>17</sup> However, Parsania *et al.*<sup>18</sup> reported higher Hb and PCV percentage in animals suffered with intestinal obstruction due to dehydration in animals which lead to haemoconcentration.

Statistically significant difference in TLC was found, between the groups and TLC decreased significantly in group II. Non significant variations in neutrophils count of group I animals was found while after treatment significant decrease in the neutrophils count was observed in group II animals. Significant decrease in lymphocyte count in group II after administration of therapy was observed. These findings are in agreement with Kumar<sup>11</sup>. He also observed high neutrophils and low lymphocyte percentage in his study in animals affected with gastrointestinal tract atony. Reversed neutrophils:lymphocytes ratio was also reported by Mohan *et al.*<sup>17</sup> in cases of intestinal obstruction. Observed lymphopenia in animals affected with gastrointestinal tract atony may be due to either catecholamine or glucocorticoid-response, neutrophilia indicates later stage of the disease<sup>19</sup>.

In animals affected with gastrointestinal tract atony significant increase in monocytes was observed. Monocytosis is observed in chronic stage of the disease<sup>3</sup>. After

treatment significant decrease in monocytes was observed. Rest of the parameters differed non significantly.

Biochemical alterations in buffaloes affected with gastrointestinal tract atony before and after treatment are depicted in table 3. Statistically significantly high level of alkaline phosphatase (ALP) in group II animals at day 0 than day 1 and day 3 was observed. ALT and AST levels in group I and II animals at day 0 were found to be significantly higher than the control values. After treatment significant decrease in ALT and AST was found in both groups but however their levels remained high as compare to the control values. Braun *et al.*<sup>20</sup> reported high levels of liver enzymes during his study. Smith<sup>21</sup> describes possible causes of increase in muscle and hepatic enzymes. Abomasal reflux results in hyper osmolality which leads to accumulation of water in the rumen, and thus haemoconcentration and tissue hypo perfusion. Poor tissue perfusion causes cellular destructions and it lead to increase in hepatic enzymes levels. After treatment decrease in levels of ALT and AST, reveals improvement in liver functions.

Urea and creatinine levels differed non significantly (within and between groups), but the mean urea levels were found higher at day 0 in both groups than control value. Similar findings were observed in buffaloes affected with rumen impaction<sup>22</sup>. The observed elevation in serum creatinine and urea levels could be attributed to a decrease in renal blood flow as a part of compensatory mechanisms to maintain circulation in hypovolemia associated with dehydration, leading to azotemia. Non significant alterations in urea and creatinine were observed after administration of therapy in both groups.

Significantly high glucose level was observed in group I animals at day 0. Youssef *et al.*<sup>22</sup> reported that buffaloes with acute rumen impaction were hyperglycaemia. The resulting hyperglycemia could be attributed to the stress or to the decrease peripheral utilization of glucose coupled with hepatic

glycogenolysis under the influence of corticosteroids released because of stress<sup>23</sup>.

Mean total protein and albumin value at day 0 in group I and group II animals were found to be lower than control value. Within group I significant high level was observed for total protein at day 3 and for albumin significant high level was observed in group II animals on day 3 in comparison to day 0 and day 1. Between groups non-significant difference was seen. Hypoalbuminaemia with normal serum total protein level was observed in buffaloes with impaction<sup>22</sup>, but serum total protein value showed no significant variation. The obtained hypoalbuminemia could be attributed either to the chronic starvation or failure of the liver to synthesize adequate amounts of proteins and increase in the levels of albumin and total proteins might be due to the improvement in liver functions leading to increase in protein synthesis<sup>24</sup>.

Mean sodium value at day 0 in affected animals was observed lower than control value. Significant improvement in level was observed in group II animals. Non significant difference between groups was observed. Hyponatraemia also observed by Radostits *et al.*<sup>3</sup> and Braun *et al.*<sup>20</sup> and could be due to compensatory mechanism for hypochloreaemia. Changes in the sodium and chloride concentration might reflect fluid balance changes in response to ruminal fluid hyperosmolality<sup>21</sup>.

Significant decrease in potassium level was observed in animals affected with GIT atony and after therapy significant increase in potassium levels were observed in both the groups. Hypokalaemia was also reported by Braun *et al.*<sup>20</sup> Mild to moderate hypocalcaemia and hypokalaemia are the commonly identified abnormalities of indigestion encountered during prolonged anorexia<sup>21</sup> and stress<sup>22</sup>.

Mean chloride value of group I and II animals at day 0 were found to be lower than control values. On day 1 and day 3 increase in mean chloride value was seen in both groups with significant increase in group II animals. Hypochloremia was observed in cases of

intestinal obstruction<sup>11,26</sup>. Abomasal reflux may lead to hypochloroemia<sup>27</sup>.

Calcium levels of group I and II animals at day 0 were found to be lower than normal reference value, but significant increase of calcium levels were observed in both groups after therapy in both groups. Non significant difference was found between groups. Hypocalcaemia was observed in reticulo- ruminal atony<sup>15</sup> and in intestinal obstruction<sup>11</sup>.

Statistically non significant difference of phosphorus levels and magnesium levels was found in both groups. Potassium was found within normal limit in cases of intestinal obstruction by Kumar<sup>11</sup>.

Three animals have been reported to be recovered in treatment group of hypertonic saline and calcium. Hypertonic saline and Ca treated animals recovered because they might be hypocalcaemic or suffering with electrolyte imbalance or both.

Fluid also diluted histamines and amines which effectively reduces reticulo-ruminal motility. Hans Raj<sup>15</sup> reported improvement in clinical cases after administration of systemic antihistaminic and fluid therapy. Fluid therapy might have diluted the histamine from circulation. He observed significant increased levels of plasma calcium, inorganic phosphorus, chloride, sodium and potassium in diseased treatment group. Improvement in the level of these minerals

may be attributed to supplementation of balanced mineral mixture.

Four animals have been reported to be recovered in treatment group of metoclopramide, hypertonic saline and Ca. Metoclopramide elicits its prokinetic effect as a dopamine D2 receptor antagonist and serotonin (5HT) receptor type-4 agonist, and direct stimulation of stomach and small intestine smooth muscles. Metoclopramide has been shown to increase the duration and frequency of antral and duodenal contractions, increase lower oesophageal sphincter pressure and relax pyloric sphincter. 5HT<sub>4</sub> receptor agonists increase GI motility through the stimulation of cholinergic neural transmission<sup>28</sup>. This combination of drugs probably improved electrolyte balance as well as stimulated smooth muscle contractions in effective manner as compare to other group. Present study revealed that combination of drugs metoclopramide, Hypertonic saline and Ca was more effective than HS and Ca combination.

In all cases animal starts defecation even after three doses. General demeanour and hydration status were found to be improved after fluid therapy. Antibiotic and supportive therapy like antihistaminic and multivitamins could be helpful in improvement of animal health by reducing histamine level, checking bacterial infection and providing life supportive vitamins.

**Table 1: Changes in clinical vital parameters in buffaloes affected with gastrointestinal tract atony before and after treatment**

Parameter	Group	Control values	Days		
			Day 0	Day 1	Day 3
Temperature (°F)	Group 1	101.6 °F	100.6	100.9	101.5
	Group 2	(100.4-102.8)	98.3	101.3	101.8
Heart rate (per min.)	Group 1	66 per min.	67.3	66.4	65.7
	Group 2	(48-84 )	58.2	64.2	65.7
Respiration rate (per min.)	Group 1	38 per min.	28.6	31.3	35.4
	Group 2	(26-50)	29.1	26	23
Ruminal motility (per two min.)	Group 1	3/2 min.	0	0.8	1.5
	Group 2		0	1.1	2.3

**Table 2: Haematological alterations in buffaloes affected with gastrointestinal tract atony before and after treatment**

Haematological parameters		Group 1 (n = 6)			Group 2 (n = 6)			Control Values
		0 day	1 day	3 day	0 day	1 day	3 day	
Hemoglobin (g/dl)		10.65±0.37	10.97±0.29	11.35±0.42	10.95±0.51	11.35±0.4	11.75±0.41	11.5(8-15)
TLC (10 <sup>3</sup> /µl)		12.86±2.62	12.62 <sup>B</sup> ±1.31	10.6 <sup>B</sup> ±0.58	6.66±0.91	6.35 <sup>A</sup> ±0.34	5.52 <sup>A</sup> ±0.36	8(4-12)
DLC (%)	N	59.63±9.0	57.72±8.02	53±3.53	57.07 <sup>b</sup> ±5.8	54.10 <sup>a</sup> ±5.49	49.05 <sup>a</sup> ±3.56	30(15-45)
	L	35.75±8.31	39.10±7.53	45.63±3.26	37.95 <sup>a</sup> ±4.93	41.73 <sup>b</sup> ±4.74	47.60 <sup>c</sup> ±2.98	60(45-75)
	E	0.60±0.44	0.45±0.33	0.13±0.04	0.45±0.23	0.40±0.19	0.3±0.09	10(0-20)
	B	0.52±0.12	0.3±0.04	0.13±0.02	0.5±0.14	0.3±0.04	0.22±0.05	1(0-2)
	M	3.50 <sup>c</sup> ±1.1	2.43 <sup>b</sup> ±0.8	1.1 <sup>aA</sup> ±0.34	4.03±1.13	3.47±1.05	2.83 <sup>B</sup> ±0.62	4.5(2-7)
PCV (%)		35.1±1.35	35.65±1.66	36.38±1.35	35.90 <sup>a</sup> ±1.11	36.85±0.94	37.60 <sup>b</sup> ±1.71	35(25-45)

**Note:** means bearing different superscripts in a row differ significantly ( $p < 0.05$ ) Small alphabetical letter indicates comparison within the group and capital alphabetical letters indicates the comparison between the groups. (TLC= Total Leucocyte Count; DLC= Differential Leucocyte Count; N= Neutrophils; L=Lymphocytes; E= Eosinophils; B= Basophils; M= Monocytes)

**Table 3: Biochemical alteration in buffaloes affected with gastrointestinal tract atony before and after treatment**

Biochemical parameters	Group 1 (n = 6)			Group 2 (n = 6)			Control Values
	0 day	1 day	3 day	0 day	1 day	3 day	
AST (IU/L)	121.67 <sup>c</sup> ±5.6	117.9b <sup>b</sup> ±20.3	106.9 <sup>a</sup> ±24.4	192.1 <sup>c</sup> ±40.68	158.3 <sup>b</sup> ±24.86	112.4 <sup>a</sup> ±5.25	105 (78-132)
ALT (IU/L)	44.62 <sup>b</sup> ±1.3	40.83 <sup>a</sup> ±1.32	39.5 <sup>a</sup> ±0.67	49.83 <sup>b</sup> ±3.93	48.83 <sup>a</sup> ±4.38	41.0 <sup>a</sup> ±1.81	25.5 (11- 40)
ALP (IU/L)	77.50±25.38	75.17±18.99	70.83±13.82	83.83 <sup>b</sup> ±9.95	78.5 <sup>a</sup> ±9.51	75.33 <sup>a</sup> ±9.68	244 (0-488)
BID (mg/dl)	0.0±0.0	0.0±0.0	0.0±0.0	0.17±0.17	0.0±0.0	0.0±0.0	0.2 (0.0-0.4)
BIT (mg/dl)	0.33±0.21	0.17 <sup>A</sup> ±0.16	0.15 <sup>A</sup> ±0.17	2.67 <sup>B</sup> ±0.8	2.0 <sup>B</sup> ±0.58	1.67 <sup>B</sup> ±0.49	1.5 (1-2)
Glucose (mg/dl)	99.83 <sup>b</sup> ±2106	96.83 <sup>b</sup> ±20.09	89.3 <sup>a</sup> ±19.85	69.67±9.04	68.67±11.64	65.67±12.78	60 (45-74)
Urea (mg/dl)	69.83±8.67	66±8.09	60.83±29.4	90.67±18.16	82.5±14.63	73.3±12.43	36.5 (18-55)
Creatinine (mg/dl)	1.67±0.33	1.67±0.21	1.5±0.22	1.33±0.21	1.17±0.17	1.15±0.23	1.5 (1-2)
Total protein(g/dl)	5.99 <sup>a</sup> ±0.43	5.94 <sup>a</sup> ±0.46	6.55 <sup>b</sup> ±0.43	6.08±0.66	6.47±0.59	6.87±0.58	7 (6.6-7.4)
Albumin (g/dl)	2.67±0.21	3.0±0.0	3.17±0.17	2.58 <sup>a</sup> ±0.13	2.83 <sup>a</sup> ±0.31	3.5 <sup>b</sup> ±0.22	3.25 (3.0-3.5)
Sodium (mmol/L)	131.35 ± 8.13	131.58±8.19	133.05±8.47	131.68 <sup>a</sup> ±2.18	132.13 <sup>b</sup> ±2.10	136.68 <sup>b</sup> ±1.65	142 (132-152)
Pottasium (mmol/L)	3.03 <sup>a</sup> ±0.24	3.29 <sup>a</sup> ±0.18	3.79 <sup>b</sup> ±0.14	3.1 <sup>a</sup> ±0.22	3.7 <sup>ab</sup> ±0.11	4.05 <sup>b</sup> ±0.23	4.85 (3.9-5.8)
Chloride (mmol/L)	90.87±6.5	95.97±3.16	101.8±5.53	93.52 <sup>a</sup> ±2.74	97.33 <sup>ab</sup> ±3.68	102.85 <sup>b</sup> ±2.04	104 (97-111)
Calcium (mg/dl)	6.17 <sup>a</sup> ±0.31	7.0 <sup>b</sup> ±0.0	8.57 <sup>c</sup> ±0.33	6.33 <sup>a</sup> ±0.84	7.3 <sup>a</sup> ±0.52	8.67 <sup>b</sup> ±0.21	9.6 (8.4-11)
Phosphorous (mg/dl)	4.4±0.61	4.58±0.72	4.7±0.7	4.6±0.23	4.72±0.15	4.7±0.21	5.65 (4.5-6.8)
Magnesium (mg/dl)	3.0±0.26	3.17±0.31	2.33±0.42	2.83±0.17	2.67±0.33	2.33±0.33	2.35 (1.7-3)

**Note:** means bearing different superscripts in a row differ significantly ( $p < 0.05$ ). Small alphabetical letter indicates comparison within the group and capital alphabetical letters indicates the comparison between the groups.

## CONCLUSION

Treatment with metoclopramide along with hypertonic saline and calcium lead to faster clinical recovery in buffaloes affected with gastrointestinal tract atony. Metoclopramide, hypertonic saline and calcium lead to increased ruminal atony, improved haematological alterations, liver function and electrolytes balance in animals. Therefore metoclopramide, hypertonic saline and calcium combination is recommended in treatment of gastrointestinal tract atony in buffaloes.

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