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Comparative evaluation of valethamate bromide and hyoscine butyl bromide on cervical dilatation in water buffaloes after detorsion

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ABSTRACT

After detorsion, incomplete cervical dilatation is major cause of dystocia. The present study aimed to investigate the comparative efficacy of valethamate bromide and hyoscine butyl bromide on cervical dilation after detorsion and their effect on haematological and biochemical parameters of torsion detorted water buffaloes. A total of 18 buffaloes were selected for study which were divided into three groups of six animals each. After detorsion by Sharma's Modified Schaffer's method, animals with grade I and grade II cervix were selected for the study. Group I (control group) buffaloes were administered with dexamethasone (40 mg, I/M), cloprostenol (500 µg, I/M) and mifex (450 mL, slow I/V) after successful detorsion. Along with these drugs, in group II and group III, valethamate bromide (100 mg, I/M) and hyoscine butyl bromide (160 mg, I/M) were administered, respectively. The cervical dilation rate (CDR) of each group was calculated and compared. Blood samples were collected three times: before detorsion, after treatment and at parturition. Group III (2.17±0.07 cm/h) had significantly higher CDR followed by group II (1.39±0.21 cm/h), and control group (0.47±0.19 cm/h). Serum calcium levels were also elevated after treatment. Both drug combinations were found safe haematologically and biochemically.

Keywords: Buffaloes, Cervix, Hyoscine butyl bromide, Torsion, Valethamate bromide

Twisting of the uterus on its longitudinal axis is a more frequent maternal cause of dystocia in buffaloes with the incidence ranging from 53.57 to 83.33% out of total dystocia cases arrived in referral hospitals (Srinivas *et al.* 2007, Purohit *et al.* 2011, 2012). However, uterine torsion-affected buffaloes can be successfully detorted in most of the cases with modified Schaffer's method (Singh and Nanda 1996). Incomplete cervical dilation is a common complication in buffaloes after detorsion. Incomplete dilation after detorsion may force the cesarean section of the animal which hampers the future fertility and productivity of the buffaloes. Dilation of the cervix depends on the resistance caused by visco-elastic properties of the cervix and the force induced by uterine contractions (Breeveld-Dwarkasing *et al.* 2003). The cervix must be completely dilated at the time of parturition to provide enough space to pass the fetus.

The period time of parturition is very stressful to every animal and uterine torsion amplifies this stress. Incomplete cervical dilation leads to an increased first stage of parturition. This protracted parturition duration may contribute to increased risk of infection, dehydration, and unrecognized obstructed pain to the dam. Further, the fetus is exposed to the danger of infection, asphyxia, fetal mortality, and morbidity. Thus, there is a need of the active management of the parturition process after detorsion rather than passive observation.

Hafez (1973) found that the bovine cervix has a high muscular content. Immunohistochemical staining has demonstrated the distribution of smooth muscle cells over an outer muscular layer and within the deeper part of the stromal layer (Breeveld-Dwarkasing *et al.* 2000, Aalberts *et al.* 2007). Many antispasmodic agents like drotaverine, hyoscine butyl bromide, dicyclomine, valethamate bromide, etc. are found to hasten the first stage of labour in human females and are found to be safe for both mother and fetus (Sirohiwal and Dahiya 2005, Aggarwal *et al.* 2008, Pradnya and Tank 2016, Shettian and Shetty 2018). Hyoscine butyl bromide is a spasmolytic agent which acts as an anticholinesterase which is claimed to reduce the duration of labour by accelerating cervical dilation without compromising the maternal or fetal safety in human females (Sirohiwal and Dahiya 2005). It is also used for reducing abdominal pain in horses and other animals (Davies and Gerring 1983). Valethemate bromide is known to fasten the cervical dilation thus avoiding or minimizing cervical dystocia leading to prolonged labor. It is a potent and rapidly acting cholinolytic, spasmolytic and musculotropic agent (Dwivedi *et al.* 1999). No effective study on the effect of valethamate bromide and hyoscine butyl bromide on cervical dilation in buffaloes is available

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till now. Thus, the present study was planned to assess the efficacy of valethamate bromide and hyoscine butyl bromide on cervical dilation after detorsion in buffaloes with the hypothesis that these agents will fasten the first stage of parturition in torsion detorted buffaloes.

MATERIALS AND METHODS

Animals: Diagnosis of uterine torsion was done with careful per-rectal and per-vaginal examinations. Along with the determination of types of uterine torsion, the degree of uterine torsion was also determined based on vaginal folds constriction and broad ligament status. The buffaloes suffering from uterine torsion which were detorted successfully via Sharma's Modified Schaffer's method (Ghuman 2010) and having cervix soft (grade I) or soft and partially lobulated (grade II) were selected for the study. These buffaloes were subdivided into three groups having six animals in each group (n=6).

Experimental design: Detorsion of uterine torsion was followed by per-rectal and per-vaginal examinations of animals and grading of animals were done based on physical characteristics of the cervix. Buffaloes in which the external os of the cervix was soft and smooth, moderately soft and partially lobulated, and hard with lobulated were characterized into Grade I, Grade II, and Grade III respectively. Grade I and Grade II animals were included in the study and Grade III animals were subjected directly for cesarean section. Drugs were administered just after detorsion in all animals according to the experimental protocol (Table 1).

The cervical diameter was measured per-vaginally with the help of a handmade self-designed cervicometer which was made up of iron rods and scale at the time of detorsion and at parturition. Cervicometer was sterilized with 70% isopropyl alcohol before and after each measurement. Common induction protocols used in all groups included dexamethasone (Dexona® Vet Injection- Dexamethasone Sodium Phosphate Injection I.P. (Vet.) – Zydus AHL, Ahmedabad-382445), cloprostenol (Vetmate™- Cloprostenol Sodium IP (Vet)- Provimi Animal Nutrition India Pvt. Ltd. Bengaluru), and mifex (Mifex®- Calcium Magnesium Borogluconate Injection I.P. (Vet.) - Elanco, Bengaluru, India). Valethamate bromide (Epidosin- Valethamate Bromide injection, TTK Healthcare Limited, Chennai) and, hyoscine butyl bromide (Buscogast- Hyoscine Butylbromide Injection IP, Sanofi-Synthelabo (India) Pvt. Ltd., Mumbai) were used separately in group II, and group III.

Calculation of rate of cervical dilation: The rate of cervical dilation was calculated by the formulae

Linear Rate of cervical dilation = (Cervical dilation at parturition - Cervical dilation at drug administration) / (Duration between drug administration and parturition)

Haematological and biochemical study: Blood samples were collected from jugular venipuncture before detorsion, after treatment and, after per-vaginal delivery of foetus or at the time when it was confirmed that further dilation of the cervix was not possible and the animal will be subjected to cesarean section. Collected samples were used for haematological and serum biochemical studies. Haematological parameters included, haemoglobin (Hb), packed cell volume (PCV), total leukocyte count (TLC), differential leukocyte count (DLC), monocyte (M), lymphocyte (L), mean corpuscular hemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and mean corpuscular volume (MCV) were estimated in automatic analyzer MS4 (JLS380 MeletSchloesingLaboratoires - 9 Chaussee Jules Cesar- 95520 OSNY, France) after collecting blood samples in vials containing EDTA.

Blood samples for analysis of biochemical parameters were collected for estimation of alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), urea, creatinine, total proteins, albumin, globulin, albumin:globulin, phosphorus, and calcium. Serum was harvested by centrifugation at 3000 rpm for 20 min and then stored at -20°C. Biochemical parameters were analyzed with EM 200™ (Automated random access clinical chemistry analyzer, Erba Mannheim, Germany) analyzer using commercially available Transasia XL (M/S Transasia Biomedical Limited, Mumbai, India) system pack kits.

Statistical analysis: Data, expressed as mean±standard error of the mean (SEM), were analyzed using the General linear model (SPSS software (IBM Inc, USA). All haematological and biochemical results were considered statistically significant at the 95% confidence level ($P<0.05$) while cervical dilation rates were considered statistically significant at the 99% confidence level ($P<0.01$). The significant differences between groups for targeted parameters were determined by post-hoc Duncan's multiple comparison tests.

RESULTS AND DISCUSSION

Signalment and clinical observation: All the animals included in the study were female buffaloes of first to

Table 1. Experimental protocol designed for the study

Group (n=no. of animals)	Drug combination used	Investigated parameters
I (n=6) (control)	Dexamethasone (40 mg, I/M)-Cloprostenol (500 µg, I/M) – Mifex (450 ml, slow I/V)	Haemoglobin, total leukocyte count, differential leukocyte count, packed cell volume, urea, creatinine, alanine amino transferase, aspartate amino transferase, total proteins, albumin, globulin, calcium, phosphorous
II (n=6)	Dexamethasone-Cloprostenol – Mifex —Valethamate bromide (100mg, I/M)	
III (n=6)	Dexamethasone-Cloprostenol – Mifex – Hyoscine butyl bromide (160 mg, I/M)	

Table 2. Signalment and clinical observation recorded in buffaloes under study

Group	Gestation length (days) (Mean ±S.E.)	Parity	Site of uterine torsion	Direction of uterine torsion	Degree of uterine torsion	Rollings for detorsion	Grading of cervix
Group I (n=6)	305.2±4.99	1st (n=4) 2nd (n=1) 3rd (n=1)	Post-cervical (n=5) Pre-cervical (n=1)	Right (n=5) Left (n=1)	Mild (n=1) Moderate (n=4) High (n=1)	One (n=3) Two (n=2) Three (n=1)	Grade I (n=4) Grade II (n=2)
Group II (n=6)	297.5±2.69	2nd (n=2) 3rd (n=1) 4th (n=3)	Post-cervical (n=5) Pre-cervical (n=1)	Right (n=6)	Mild (n=1) Moderate (n=5)	One (n=4) Two (n=2)	Grade I (n=3) Grade II (n=3)
Group III (n=6)	299.8±2.45	1st (n=2) 2nd (n=3) 3rd (n=1)	Post-cervical (n=6)	Right (n=5) Left(n=1)	Mild (n=2) Moderate (n=4)	One (n=1) Two (n=2) Three (n=3)	Grade I (n=5) Grade II (n=1)

Group I, Dexamethasone (40 mg, I/M)-Cloprostenol (500 µg, I/M)–Mifex (450 ml, slow I/V); Group II- Dexamethasone-Cloprostenol–Mifex–Valethamate bromide (100 mg, I/M); Group III, Dexamethasone-Cloprostenol – Mifex – Hyoscine butyl bromide (160 mg, I/M).

fourth parity. Most buffaloes were belonging to first parity and second parity (n=12). All animals were in the advanced stage of gestation (Table 2). Sixteen animals were affected with uterine torsion of the right side. The most common site of occurrence of uterine torsion was post cervical (n=16). The degree of uterine torsion was moderate in most of the animals (n=13) followed by mild degree (n=4) and high degree (n=1). Most of the animals were detorted in one (n=8) and two rollings (n=6) followed by three rollings (n=4). After examination of the cervix per-vaginally, the cervix was classified into grade 1 (n=12) and grade II (n=6).

The maximum percentages of affected buffaloes belonged to first (33.3%) and second parity (33.3%) followed by third parity (16.5%), and fourth parity (16.5%). Analogous to the present study, Amin *et al*. (2011) and Jeengar *et al*. (2015) also reported the higher incidence of uterine torsion in pluriparous buffaloes. The suggested reasons behind are: larger abdominal cavity; stretching of pelvic ligaments; loose and long broad ligaments together with loosening of uterine tissue and decreased uterine tone in aged animals (Roberts 1986, Drost 2007, Aubry *et al.* 2008, Amin *et al*. 2011). However, some studies reported higher incidences in primiparous dairy animals (Mahmoud *et al.* 2020, Yadav *et al.* 2021). The average gestation length of affected animals was 300.17±1.64 days indicating that animals were at full term. Mahmoud *et al*. (2020) also reported that most torsions occurs at full term. The suggested reason behind this is the righting reflex which accounts for the active movements of the foetus in the uterus during late gestation and early stage of labor (Noakes *et al.* 2019). Wallowing in a pond has not seemed an etiological agent as only 12% of affected animals had a history of wallowing in a pond in the late gestation. The location of uterine torsion was on the right side in 92% of affected cases. Similar observations have been reported by various researchers (Srinivas *et al.* 2007, Hussein 2013, Jeengar *et al.* 2015, Mahmoud *et al.* 2020, Yadav *et al.* 2021).

The reason suggested for this is that the rumen prevents rotation of the uterus to the left side. The location of uterine torsion was post-cervical in 92% of the affected animals. Ali *et al*. (2011) reported similar results with 98.4% of cases occurring at the post-cervical locations. They suggested that foetal size and amount of foetal fluids might be determining factors for the location of uterine torsion in buffaloes. The calf survivability rate was 25% and this is highly dependent on the degree and duration of uterine torsion. A moderate degree of uterine torsion was present in 70.8% of cases. The main clinical symptoms observed were a history of colicky signs, kicking at the abdomen, reduced feed and water intake, restlessness but the most common sign was the failure of parturition.

Effect of drug combinations on cervical dilation rate: Incomplete cervical dilation after detorsion represents major challenge in vaginal delivery. The dilation of cervix is impaired by inhibitory impulses in the form of spasm (Brenda *et al.* 2010, Maria 2014). Protracted parturition due to delay in the first stage of parturition is very disturbing for a veterinary obstetrician. This protracted parturition leads to exhaustion to dam and stress to both foetus and dam. Complete cervical dilation is one of the effective results of straining forces of parturition. Breeveld-Dwarkasing *et al*. (2000) concluded that the smooth muscle cells within the stromal layer are grouped in small bundles with a random orientation, embedded in a connective tissue meshwork. The presence of high muscular content in the cervix is the physiological motivation for the fact that spasmolytic drugs and musculotropic drugs such as hyoscine butyl bromide and valethamate bromide can be used for augmenting cervical dilation. Hyoscine butyl bromide acts selectively on the cervical-uterine plexus and shows spasmolytic action without adverse effects on uterine contractions (Shettian and Shetty 2018).

The rates of cervical dilation were significantly ($P<0.01$) differing in valethamate bromide group (1.39±0.21 cm/h) and hyoscine butyl bromide group (2.17±0.07 cm/h) in comparison to the control group (0.47±0.19 cm/h) (Fig. 2). The time (Mean±S.E.) taken for parturition after treatment was 20.63±1.96 hours in Group I, 17.83±2.50 hours in Group II and 12.88±0.74 hr in Group III. There is no information found in the existing literature about the efficacy of hyoscine butyl bromide on cervical dilation in buffaloes and other ruminants. However, similar results

as in the present study have been observed in human females (Aggarwal *et al.* 2008, Pradnya and Tank 2016). Pradnya and Tank (2016) reported that the rate of cervical dilation under the influence of hyoscine butyl bromide (3.47 cm/h) is significantly higher as compared to the control group (2.73 cm/h) in which no drug was given. Aggarwal *et al*. (2008) in their study of 104 primigravidae women evaluated the role of hyoscine butyl bromide as a labor analgesic and found that the injection to the delivery interval was between 2-4 hours in the hyoscine butyl bromide group with a mean of 3 hr 46 min while maximum primigravidae in the control group delivered between 8-10 hours, mean of 8 hr 16 min and the labor was shortened by 4 hr 30 min in hyoscine butyl bromide group, which was significant. Tehalia *et al*. (2008) in a comparative study reported that hyoscine butyl bromide dilates the cervix at a significantly higher rate than drotaverine hydrochloride. Their reported cervical dilation rates for former and later were 4.5 cm/h and 2.6 cm/h respectively. Samuels *et al*. (2007) reported that hyoscine butyl bromide is effective in significantly dilating the cervix and reducing the first stage of labor and it is safe for mothers and neonates. Sirohiwal and Dahiya (2005) also found that the duration of the first stage of labor was (123.86±68.89 min) significantly lower in the hyoscine butyl bromide group when compared to the placebo group (368.05±133.0 min). The use of hyoscine butyl bromide intravaginally will subsequently increase its effect on cervix as vagina has rich blood supply (Hadadian *et al.* 2016). Further research could be planned with the use of hyoscine butyl bromide in the form of intravaginal suppositories.

Valethamate bromide is a quaternary ammonium compound that causes relaxation and dilation of the cervix by blocking muscarinic receptors present in the smooth muscles of the cervix. Inclusion of valethamate bromide in induction protocol results in an increased cervical dilation rate (1.39±0.21 cm/h) than the control group (0.47±0.19 cm/h). Patil (2014) reported that the combination therapy of dinoprostone gel @ 3 g and valethamate bromide @ 40 mg is found effective in buffaloes for cervical dilation within 6.5 h of treatment whereas inj. valethamate bromide took 21 h for the same. He concluded that the concurrent use of dinoprostone gel and valethamate bromide is better and faster as compared to valethamate bromide alone. The administration of valethamate bromide in combination with dexamethasone resulted in successful cervical dilation of 83.33% buffaloes and the average time taken was 23.0±2.37 h from the time of treatment (Phogat *et al.* 1994). Patil and Throat (2013) reported that valethamate bromide is an effective drug for cervical dilation and it dilates the cervix of cows and buffaloes within 6 h and 28 h respectively. There is no existing literature that compares the efficacy of these drugs on cervical dilation rate in buffaloes or any other animals. The results of our study may be used as a reference values.

Effect of drug combinations on haematological and biochemical parameters: There was no significant variation in any of the haematological parameters under study within the groups (Table 3). However, there was marked neutrophilia and leucocytosis in all the buffaloes under study. Marginal differences in clinical studies on haematology have been reported in torsion-affected buffaloes (Singla *et al.* 1992, Ali *et al.* 2011). There are various reports that uterine torsion-affected buffaloes suffer from normocytic normochromic anemia which may be due to relatively large loss of blood during abnormal parturition and accumulation of metabolic waste products (Amer and Hashem 2008).

The leukogram of torsion-affected buffaloes revealed

Table 3. Haematological profiles (Mean±Standard Error) of female buffaloes under study at different time intervals

Variable	Group	Time point		
		Before detorsion	After treatment	At parturition
Haemoglobin (g/dL)	I	10.40±0.89	10.52±0.63	9.53±0.62
	II	11.22±0.92	11.08±1.35	10.47±0.84
	III	11.88±0.43	11.75±0.45	11.48±0.30
Packed cell volume (%)	I	33.80±2.73	33.15±2.02	29.67±2.02
	II	40.50±4.69	37.32±4.62	35.68±3.22
	III	40.97±1.96	40.78±1.83	39.55±1.36
Total erythrocyte count ($\times10^6$/ mm^3)	I	4.95±0.50	4.81±0.31	4.55±0.47
	II	5.67±0.67	5.66±0.58	5.28±0.44
	III	6.15±0.43	5.46±0.27	5.36±0.19
Total leukocyte count ($\times10^3$/ mm^3)	I	8.33±1.22	7.99±1.26	8.75±1.38
	II	7.53±0.87	8.19±1.10	8.02±0.95
	III	10.49±0.39	9.44±0.47	9.72±0.44
Granulocyte (%)	I	68.28±5.07	73.77±3.74	75.05±1.81
	II	74.47±4.33	75.95±4.04	75.98±3.47
	III	77.75±1.91	79.28±1.68	78.80±1.63
Lymphocyte (%)	I	29.60±4.33	26.10±2.41	23.40±1.80
	II	24.30±4.31	22.87±4.09	21.17±2.05
	III	21.12±1.81	19.57±1.56	20.18±1.52
Monocyte (%)	I	2.12±0.79	1.80±0.65	1.50±0.32
	II	1.23±0.16	1.18±0.14	1.18±0.16
	III	1.23±0.15	1.15±0.15	1.18±0.14
Mean corpuscular haemoglobin (pg/cell)	I	19.82±1.25	20.23±1.11	20.33±1.12
	II	21.57±0.57	22.10±0.36	21.88±0.28
	III	21.17±0.85	21.12±0.69	21.47±0.69
Mean corpuscular haemoglobin concentration (g/dL)	I	31.35±0.80	31.83±0.71	32.40±0.54
	II	30.25±1.28	31.05±1.07	31.05±0.97
	III	28.05±0.49	28.40±0.51	28.65±0.48
Mean corpuscular volume (fL)	I	69.25±2.38	68.57±2.49	67.77±2.32
	II	71.30±1.53	70.97±1.74	70.83±1.83
	III	75.62±3.07	74.75±3.05	74.83±3.11

Group I, Dexamethasone (40 mg, I/M)-Cloprostenol (500 µg, I/M)–Mifex (450 ml, slow I/V); Group II- Dexamethasone-Cloprostenol–Mifex–Valethamate bromide (100 mg, I/M); Group III, Dexamethasone-Cloprostenol – Mifex – Hyoscine butyl bromide (160 mg, I/M).

Table 4. Serum biochemical profiles (Mean ± Standard Error) of female buffaloes under study at different time intervals

Variable	Group	Time point		
		Before detorsion	After treatment	At parturition
Aspartate amino transferase (U/L)	I	144.38±10.87	132.65±9.41	156.62±15.90
	II	155.98±6.50	149.70±4.03	166.92±7.93
	III	117.80±12.22	126.62±15.3	121.70±16.27
Phosphorous (mg/dL)	I	4.13±0.28	3.97±0.28	4.69±1.04
	II	4.38±0.41	3.67±0.21	4.09±0.51
	III	3.26±0.22	3.64±0.21	3.33±0.11
Urea (mg/dL)	I	24.30±3.88	23.80±4.20	24.87±4.72
	II	17.25±1.85	20.43±1.93	17.55±2.08
	III	16.02±1.86	16.98±2.38	17.35±2.03
Creatinine (mg/dL)	I	1.49±0.13	1.55±0.16	1.63±0.18
	II	1.44±0.08	1.42±0.08	1.45±0.11
	III	1.25±0.10	1.38±0.08	1.27±0.06
Calcium (mg/dL)	I	8.92±0.30^{A}	16.27±1.03^{B}	10.48±0.46^{A}
	II	8.80±0.18^{A}	16.00±1.33^{B}	9.65±0.63^{A}
	III	8.85±0.55^{A}	17.27±1.63^{B}	9.92±1.35^{A}
Total protein (g/dL)	I	6.51±0.26	5.82±0.29	6.50±0.23
	II	6.59±0.43	6.23±0.36	6.60±0.28
	III	5.64±0.46	5.90±0.31	5.48±0.22
Albumin (g/dL)	I	2.31±0.09	2.01±0.10	2.16±0.11
	II	2.20±0.08	1.98±0.11	2.23±0.11
	III	2.05±0.10	2.09±0.12	1.94±0.04
Globulin (g/dL)	I	4.20±0.26	3.82±0.24	4.35±0.15
	II	4.39±0.37	4.25±0.32	4.37±0.26
	III	3.59±0.39	3.81±0.23	3.54±0.21
Albumin: Globulin ratio	I	0.56±0.05	0.53±0.04	0.50±0.02
	II	0.52±0.04	0.48±0.05	0.52±0.04
	III	0.59±0.04	0.55±0.02	0.56±0.03
Alanine amino transferase (U/L)	I	66.18±2.79	60.68±2.70	66.73±3.98
	II	66.23±2.87	63.62±3.36	68.43±2.40
	III	60.23±3.10	61.97±4.96	61.28±5.39

Means with different superscripts (A/B) in a row show significant difference within groups *(*P<0.05*)*. Group I, Dexamethasone (40 mg, I/M)-Cloprostenol (500 µg, I/M)–Mifex (450 ml, slow I/V); Group II- Dexamethasone-Cloprostenol–Mifex–Valethamate bromide (100 mg, I/M); Group III, Dexamethasone-Cloprostenol – Mifex – Hyoscine butyl bromide (160 mg, I/M).

lymphocytopenia, neutrophilia, and monocytosis in association with eosinopenia (Ali *et al.* 2011, Amer and Hashem 2008). No significant difference (P<0.05) in any of the haematological parameters was observed within groups at different time intervals during the entire period of observation.

There was a significant increase in the mean serum calcium (P<0.05) levels after treatment in both groups compared with calcium levels before detorsion and at parturition (Table 4).

There was no significant variation observed in any of the other haematological parameters under study in the groups. There was a significant increase in the mean serum calcium (P<0.05) levels after treatment in all groups compared with calcium levels before detorsion and at parturition. The increased calcium level was due to the administration of calcium borogluconate.

No significant difference (P<0.05) in any other biochemical parameters was observed within groups at different time intervals during the entire period of observation. However, significant variations (P<0.05) observed among the groups at different time intervals were due to the individual serum profile status of affected animals. All the drug combinations were found safe haematologically and biochemically for treatment in affected buffaloes.

The present study recommends the use of hyoscine butyl bromide and valethamate bromide in the induction protocol of detorted buffaloes for cervical dilation. Hyoscine butyl bromide has the higher cervical dilation rate followed by valethamate bromide. All drug combinations were found to be safe in terms of haematology and biochemistry.

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