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Review Article

Cervical dilatation in bovines and potential drug therapy for incomplete cervical dilatation – A review

R. Yadav[1*], P. Yadav[2] and G. Singh[3]

[1]Department of Veterinary Gynaecology and Obstetrics, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar-125 004, Haryana, India; [2]Department of Veterinary Surgery and Radiology, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar-125 004, Haryana, India; [3]Department of Veterinary Clinical Complex, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar-125 004, Haryana, India

Abstract

Cervical dilatation is a prerequisite for the successful delivery of the fetus. Cervical dilation failure is a frequent problem in bovine obstetrics. The prolonged parturition process due to dilatation failure may contribute to an increased risk of infection, dehydration and unrecognized obstructed pain to the dam. The fetus, if alive, is exposed to the danger of infection, asphyxia, fetal mortality and morbidity. The bovine cervical dilation during parturition is a complex event involving many mechanical, hormonal and biochemical processes that are poorly understood. Some of the pharmaceutical agents experimented with for bovine cervical dilation includes antispasmodic, enzymes, beta 2 adrenergic, hormones and local agents. The results of their clinical use have, however, been suboptimal.

Key words: Antispasmodic agents, Bovine, Cervical dilatation, Uterine torsion

Highlights

- Incomplete cervical dilation after detorsion is a common complication in bovines.
- Most pharmaceutic agents suggested for cervical dilation have sub-optimal results.

INTRODUCTION

Cervix is composed of collagen fibrils that bind together to form collagen fibres. These collagen fibrils are highly aggregated, elongated helical protein molecules of molecular weight about 20000, which are formed from a pool of less aggregated collagen protein dispersed in the vacuoles of the ground substances (Gersh and Catchpole, 1960). Devkota and Singh (2017) observed the length of the cervix (5.9±0.9 cm) and diameter of the cervix (2.5±0.6 cm) in bovines, and these observations were like various previous studies (Ahmad *et al.*, 1987; Al-Fahad *et al.*, 2004; Kumar *et al.*, 2004; Carvalho *et al.*, 2010). The numbers of cervical rings in bovines vary from one to five, with an average of three rings (Bhalla *et al.*, 1964). Incomplete cervical dilatation is observed more frequently in buffalo than cattle, possibly due to fewer cervical rings in the former (Purohit *et al.*, 2011). The resistance caused by cervical visco-elastic properties, along with force induced by uterine contractions affects the cervical dilatation in bovines (Breeveld-Dwarkasing *et al.*, 2003a). In maternal causes, incomplete cervical dilatation is an important cause of dystocia. The improper dilatation of the cervix at parturition results in dystocia because of the relatively more cartilaginous nature of the cervix in bovines than other farm animal species (Sloss and Dufty, 1980).

In most cases, uterine torsion can be successfully detorted with modified Schaffer's method (Singh and Nanda, 1996). However,

Corresponding Author, E mail: drishiyadav.96666@gmail.com

after detorsion, it is difficult to achieve complete cervical dilation in most cases, which is a prerequisite for per-vaginal delivery. During induction, physiological changes occur in a sequence that causes biochemical and cellular changes in the cervix, necessary for dilatation (Breeveld-Dwarkasing *et al.*, 2003b). But, in torsion-affected animals, these sequential changes are prohibited due to ischemic cervix. A break in the sequence results in insufficient dilation of the cervix. Histopathological findings in torsion-affected animal cervix were haemorrhage, congestion, oedema, marked necrosis, fibrosis and tearing of the cervical wall (Honparkhe *et al.*, 2009). Barber (1995) reported that early correction of torsion might prevent cervical fibrosis.

Therefore, there is a need to actively manage the parturition process after detorsion rather than passive observation. Parturition is a complex process that involves myometrial contraction, dilatation of the cervix and expulsion of the fetus and placenta in an orderly manner. There is a need to research drugs that accelerate the parturition process, particularly the cervical dilatation stage. Thus, drugs or agents that can accelerate or initiate this process can be helpful. Very few pharmaceutical agents were tested for this purpose. In the present review, we describe cervical dilatation and potential agents that can be helpful for this purpose.

Cervical ripening and dilatation

During parturition, the cervix dilates many folds compared to minimal dilatation during estrus. At the time of parturition, there is the mechanical action of the cervical wall, and profound changes occur in the collagen layer under the influence of the maternal hormonal environment (Fitzpatrick, 1977). The mechanical changes in the cervical wall have been studied in induced ovines and caprines. It was concluded that the cervical wall revealed a marked increase in the liberation of hydroxyproline from collagen and a change in the pattern of extractable glycosaminoglycans in advanced induced cases (Fitzpatrick and Dobson, 1979). A sudden drop in progesterone and no estrogen increase will induce cervical ripening within a few hours (Ledger *et al.*, 1985). However, estrogen alone will also elicit softening in sheep (Fitzpatrick and Dobson, 1981). It seems likely that a local or paracrine release of PGE occurs in the cervix because no rises in levels of PGE in the maternal circulation occur at parturition, and PGE has inhibitory action of progesterone synthetase (Fitzpatrick and Dobson, 1981; Ledger *et al.*, 1983; Silver, 1990). Vesanen (1993) reported the presence of bovine cytosol estrogen (ERC) and progesterone receptors (PRC) in the bovine cervix. However, it was concluded that the concentrations of receptors were low compared to the uterus; interestingly, the expression of receptors varied depending upon stages of reproduction. Eissa *et al.* (1995) found that the concentration of oestradiol-17 beta increased markedly ($P<0.01$) at Day 10 prepartum (26.3 +/- 2.6 pg/mL); the concentrations were maximal (82.8 +/- 3.6 pg/mL) during labour and returned to their basal values (< 12 pg/mL) at Day 5 postpartum in buffalo cows while progesterone showed basal values (< 0.5 ng/mL) from Day 4 prepartum to Day 15 postpartum. Wang *et al.* (2001) supported the concept that estrogen might be involved in the final remodelling of the cervix via the modulating effects of the estrogen receptors. Hyaluronan (HA) is a glycosaminoglycan whose content in the cervix increases at estrus and intracervical application of low molecular weight HA, 52 h after progesterone sponge removal increases cervical penetration up to 3.4 cm in sheep (Perry *et al.*, 2010). Shi *et al.* (1999) suggested that cervical preparation for delivery started before the time of labor and cervical collagen content determines cervical resistance. Uppal *et al.* (2007) studied histoenzymic localization of different enzymes on buffalo foetii cervixes; their result revealed a moderate to strong localization of most of the enzymes in lamina epithelial and tunic muscularis, whereas the propria submucosa and serosa

showed weak activity. Acetyl-cholinesterase activity was localized in the neuronal elements. Torbehbar *et al*. (2007) studied the changes in the kinds and percentages of the epithelial and inflammatory cells of the external os region of the uterine cervices of the river buffaloes during different stages of pregnancy. They found that the percentages of the vacuolated and unvacuolated epithelial cells, the percentages of lymphocytes, eosinophils and basophils were statistically similar. However, significant changes were observed in the percentages and numbers of neutrophils. It was reported that as the pregnancy progressed, there was a significant increase in the percentages and numbers of neutrophils and monocytes. Collagen is approximately 35% and 70% of the stromal dry weight in the cervix for cycling and pregnant animals respectively (Vedernikov *et al.*, 2000; Breeveld-Dwarkasing *et al.*, 2003a). The cervical ripening process occurs in two stages which are gradual ripening and final ripening; gradual ripening starts during the last months of pregnancy and final ripening occurs at the time of onset of parturition (Winkler and Rath, 1999; Winkler *et al.*, 1999; Malmstrom *et al.*, 2007; Engelen, 2008). Nara *et al*. (1982) concluded that the gradual cervical ripening process is an important prerequisite for a successful final ripening and cervical dilatation at parturition. The cervical Matrix Metallo Proteinases activity is responsible for the denaturation of collagen during the gradual ripening stage which is characterized biochemically by water imbibitions (Maillot and Zimmermann, 1976; Breeveld-Dwarkasing *et al.*, 2003a; Engelen, 2008). MMPs are endopeptidases that are secreted into the ECM as zymogen. These MMPs are activated by proteolytic cleavage and inhibited by endogenous inhibitors: â2-macroglobulin and Tissue Inhibitors of Metallo Proteinases (TIMPs) (Engelen, 2008). As part of an "inflammatory" cascade MMPs denature and digest the collagen fibrils during final ripening (Watari *et al.*, 1999; Sennstrom *et al.*, 2000; Kelly, 2002; Keelan *et al.*, 2003; Winkler, 2003; Yellon *et al.*, 2003; Stjernholm *et al.*, 2004). The cervical tissue becomes well distensible, extremely soft and watery due to water imbibitions; these changes in the cervix are responsible for cervical dilatation when force is exerted by fetal parts or placenta during parturition (Dobson, 1988; Engelen, 2008). Engelen (2008) studied the electromyographic (EMG) activities in the cervical outer muscular layer and the cervical stromal layer and found that the cervical outer muscular layer showed distinct EMG activity, which began to increase twelve hours before starting dilatation of the cervix. The contracture and contraction, like EMG activity in unison with the myometrium, is shown by the outer muscular layer of the cervix. Independent from the myometrium, the outer muscular layer of the cervix showed more irregular EMG activity.

Drugs used for cervical dilatation

Roberts (1986) reported that the cervix may fail to dilate in bovines primarily due to fibrous induration or sclerosis and recommended the administration of 2 injections of relaxin (3000 IU) for the treatment of incomplete cervical dilatation. Duchens *et al*. (1993) reported that heifers treated with prostaglandin E2 (PGE2) showed cervical softening, congestion and mucus secretion, which were more pronounced in the pregnant heifers without affecting fetuses. Intracervical hyaluronidase treatment helps in shortening the time duration between detorsion to complete cervical dilatation in buffaloes (Singh, 2019). The duration of labor is reduced frequently by the administration of spasmolytic drugs. Out of these spasmolytic drugs hyoscine-butylbromide and valethamate bromide has been used to shorten the duration of labour (Phogat *et al.*, 1994; Samuels *et al.*, 2007).

Hyoscine butylbromide: Hyoscine butylbromide (HBB) is an anticholinergic and antimuscarinic medication that belongs to the parasympatholytic group of drugs. HBB is a semi-synthetic derivative of scopolamine that has shown spasmolytic function on the muscles of the female reproductive tract, especially the cervical-uterine plexus (Aggarwal *et al.*, 2008; Ibrahim *et al.*, 2014). It is an effective

Table 1. Currently available pharmaceutical agents which have been used for cervical dilatation

Sl.No.	Pharmaceutical agent	Trade name	Dosage	Route of administration
1.	Valethamate bromide	Epidosin	40-60 mg	I/M
2.	Hyoscine butyl bromide	Buscopan	120-140 mg	I/M
3.	Relaxin	Purified pig relaxin	3000 IU	I/M
4.	Sodium carboxymethyl cellulose (SCMC)	SCMC powder	1% SCMC	Intracervical massage for 4 to 5 times
5.	Estradiol benzoate	Pregheat	2mg	I/M
6.	Hyaluronidases	Hyalase	10,000 IU	Intracervical injection (Cervical muscles)
7.	Isoxsuprine	Soxurine	200-300 mg	I/M or I/V
8.	Clenbuterol	Clenbuterol HCL	0.3 mg	I/V
9.	Dinoprostone	Preg-out	2.5-5 mg	I/M

antispasmodic drug without the untoward side effects of atropine. HBB is a quaternary ammonium compound and has peripheral anticholinergic action but no central action, as it does not cross the blood-brain barrier. Scopolamine (l-hyoscine) is found chiefly in *Hyoscyamus niger* (Henbane). Scopolamine is l-hyoscine which is more active than d-hyoscine (Laurence *et al.*, 2006). It has effective anti-spasmolytic activity with a half-life of 4.5-5 hrs. Hyoscine butylbromide acts selectively on cervical-uterine plexus to overcome cervical spasms and cause dilatation of the cervix (Sirohiwal *et al.*, 2005). HBB does not affect uterine contractions (Aggarwal *et al.*, 2008). It gets distributed rapidly in body tissues except for the brain after administration and does not affect the central anticholinergic pathway. HBB act by inhibiting cholinergic transmission in the synapses of the abdominal and pelvic parasympathetic ganglia, thus relieving spasms in the smooth muscles of various abdominal and pelvic organs including cervical-uterine plexus (Corsen, 1983; Hotwani and Ainapure, 2000). HBB has been used to reduce the labor duration in several hospitals worldwide (Chan, 1963; Baracho *et al.*, 1984; Bhattacharya and Joshi 1985; Blasko and Demeter, 1998; Aggarwal *et al.*, 2008). Some researchers reported that the duration of labor, particularly the first stage of labor was reduced significantly by using HBB in relation to the placebo group (Samuels *et al.*, 2007; Kirim *et al.*, 2015; Kandil *et al.*, 2017). Rohwer *et al.* (2012) reported that various antispasmodic drugs, including valethamate bromide, rociverine, HBB, drotaverine hydrochloride and camylofin hydrochloride cause cervical dilation at a faster rate. Many studies evaluated the effects of the injectable or suppository form of HBB on cervical dilatation; most of these studies demonstrated the efficacy of HBB in augmenting labor (Sirohiwal *et al.*, 2005; Samuels *et al.*, 2007; Aggarwal *et al.*, 2008). However, there are contradictory studies that showed that HBB is not able to accelerate labor (Gupta *et al.*, 2008).

Valethamate bromide: Valethamate bromide is a quarternary ammonium agent that was introduced in the 1950s. It is anticholinergic and antimuscarinic and used to reduce labor duration with favourable results (Kuruvila *et al.*, 1992; Ambiye *et al.*, 1987; Madhu *et al.*, 2010). It acts directly on the cervix's smooth muscles in different species, including humans, and is safe for the mother and fetus (Sharma *et al.*, 1990; Sharma *et al.*, 2001; Madhu *et al.*, 2010). Sharma *et al.* (1990) used 20 mL of valethamate bromide (velocin vet) IM in bovines and found that it made the parturition process occur early than normal duration. The administration of

valethamate bromide in combination with dexamethasone resulted in successful cervical dilatation of 83.33% buffaloes and the average time taken was 23.0±2.37 hours from treatment time (Phogat *et al.*, 1994).

Collagenolytics: Collagenolytics may be helpful in breaking collagen fibres of the cervix and assisting its dilation. Sodium carboxymethyl cellulose (SCMC) is water soluble anionic linear cellulose ether prepared by treating cellulose with aqueous sodium hydroxide followed by reaction with sodium chloroacetate (Dumitriu, 1996). Earlier, SCMC was injected into the joint space of the knee and into the anterior chamber of the rabbit's eye, and no resultant inflammation was observed (Homsey *et al.*, 1973). Elkin *et al.* (1984) concluded that SCMC solutions could potentially prevent postoperative intraperitoneal adhesions in rats. SCMC (intraperitoneal administration) and vitamin E (orally) act synergistically to reduce intraperitoneal adhesions (Hemadeh *et al.*, 1993). Honparkhe *et al.* (2009) conducted a study to check the efficiency of SCMC massage on dilatation of the cervix of detorted buffaloes and found that cervical dilation was achieved in 78.9% of the cases after cervical massage. They concluded that it might be due to the collagenolytic activity of SCMC, which breaks collagen fibers of cervical tissue and assists in dilatation of cervix. Other collagenolytic agents such as thalidomide need experimentation for use as cervical dilating agent as current reports are lacking.

Hyaluronidases: Hyaluronidases are a group of enzymes responsible for causing the degradation of hyaluronic acid, which forms a fundamental component of the extracellular matrix and causes transient relaxation of connective tissue (Sawan and Hersant, 2021). In mice, it has been reported that cervical ripening and dilatation are related to the increase in the expression of hyaluronan synthase expression and the subsequent increase in Hyaluron (Kelly *et al.*, 2005). At estrus in the ewe, there are reports of an increase in the expression of two types of Hyaluron in cervical tissue (Perry *et al.*, 2010). Perry and co-workers found that when treated with low molecular weight hyaluronic acid, the cervical penetration increased significantly ($P \leq 0.001$) from 1.22 cm to 3.66 cm. Maradny *et al.* (1997) reported that hyaluronidases (20 mg) induced cervical ripening in pregnant and non-pregnant rabbits. It was also observed that the water content of cervical tissue was significantly increased, and collagen tissue was decreased markedly. Intracervical hyaluronidase treatment helps in shorten the duration between the detorsion of a buffalo to complete cervical dilatation (Singh, 2019). It can be a potential drug for dilating the cervix in bovines; more studies are required to prove its efficacy in bovines.

β-2 adrenergics: It was reported that the gravid myometrium of caprines and cattle has β-2 adrenoreceptors while non-gravid myometrium could not be classified based on type of beta-adrenoceptor (Larsen, 1997). The drugs such as isoxsuprine (200-300 mg intravenously) and clenbuterol (0.3 mg intravenously) may be used for cervical relaxation as they cause relaxation of the complete genital tract. Still results are not promising (Chouksey *et al.*, 2022). Generally, these drugs are used as tocolytic agents as most of the β-2 receptors are located in pregnant cattle endometrium. Studies reporting the occurrence of these receptors on the bovine cervix are lacking.

Prostaglandin E2 (PGE2): PGE 2 is used to maintain labour and ripen the cervix in human females (Ulmsten, 1979, Goeschen *et al.,* 1985). It was observed that uterine pressure increases in a dose dependent manner in bovines when there is an intravenous infusion of PGE2. Ledger *et al.* (1983) did infusion of PGE-2 into a cervical artery, and efficacy of this treatment was assessed by measurement of the extensibility *in vitro* of a strip of cervical tissue. After infusion of saline/ ethanol mixture extensibility was 2.84×10^{-3} +/- 0.3×10^{-3} min^{-1}; after infusion of PGE-2 it

increased significantly (P<0.02) to 8.6 X 10^{-3}+/- 1.8 X 10^{-3} min^{-1}. These reports suggest that *in vivo* cervical ripening is possible by PGE-2. This also showed that PGE-2 could soften the cervix even without uterine contractions or in uterine inertia. Hirsbrunner *et al.* (2007) reported significantly shorter duration (P<0.01) from the time of drug administration to the successful birth between treated and non-treated cattle with intravenous administration of 2.50 mg/mL of dinoprostone.

Conclusion

It is concluded that in spite of a large number of drugs suggested for the incomplete cervical dilatation treatment in bovines, their efficacy is sub-optimal.

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