Original Research

Clinical Efficacy of Mifepristone and Misoprostol in Induction of Parturition in Female Dogs with Single Pup Syndrome

Vijay Peetala*, Virupakshaiah Chandrashekara Murthy, Narasimha Murthy, Upendra Hanagal Achuthrao, Bisalere Mallappa Ravindranath and Gurubasayya Panchaxarayya Kalmath

Department of Veterinary Gynaecology and Obstetrics, Veterinary College, Hebbal, Bengaluru, INDIA

***Corresponding author:** vijay.vety09@gmail.com

Rec. Date:	Jan 14, 2019 09:43
Accept Date:	Jun 23, 2019 19:48
DOI	10.5455/ijlr.20190114094349

Abstract

Successful management of high-risk pregnancy like single pup syndrome is a challenging task. The objective of the present study is to assess the efficacy of antiprogestagen mifepristone and prostaglandin misoprostol in induction of parturition in bitches bearing single puppy. The study was conducted on 12 pregnant dogs bearing single puppy with gestational age of 63.00 ± 0.42 days as confirmed by ultrasound scanning. The dams with singleton litter showing signs of parturition without any medical intervention were considered under control group (n=6). Though, initiation of parturition has occurred in control group, the animals had dystocia and assisted whelping was performed. The animals that hadn't shown any signs of parturition even after 62 days of gestation were included in treatment group (n=6) and induced parturition by administering mifepristone @ 5 mg/kg BW per orally twice a day at 12 hours interval followed by intra vaginal administration of misoprostol @ 200 µg for bitches with ≤ 20 kg BW and 400 µg for bitches with > 20 kg BW, 12 hours after second dose of mifepristone. All the animals in the treatment group whelped live singleton puppies normally and the mean time taken for the expulsion of the single pup from the time of initiation of treatment was recorded as 28 ± 2.74 hrs. Hence it is concluded that the combined use of mifepristone and misoprostol is safe and effective for the induction of parturition in female dogs with single puppy syndrome.

Key words: Antiprogestagen, Dystocia, Singleton Litter, Parturition

How to cite: Peetala, V., Virupakshaiah, C., Murthy, N., Upendra, H., Ravindranath, B., & Kalmath, G. (2019). Clinical Efficacy of Mifepristone and Misoprostol in Induction of Parturition in Female Dogs with Single Pup Syndrome. International Journal of Livestock Research, 9(8), 257-262. doi: 10.5455/ijlr.20190114094349

Introduction

Dogs are polytocous animals with overall mean litter size of 5.4 (range 1 - 18) (Borge *et al.*, 2011). But in some instances, single fetus pregnancy is observed in bitches termed as "single pup syndrome" (Jackson,

2004) and is considered as high-risk pregnancy. Single fetus pregnancy, singleton pregnancy, singleton litter are the terms commonly used for this condition. Successful management of high-risk pregnancy like single pup syndrome is a challenging task. Though Jackson (2004) suggested caesarean section as safest option in singleton pregnancies, it is expensive, invariably involves surgical risk; leading to unsatisfactory pup survival rate. These complications can be avoided by medical induction of whelping. The criteria for use of drugs to induce parturition are that, they should induce whelping with a high efficiency and within a predictable short time frame after treatment. In addition, treatment should be safe for both the bitch and puppies, inducing a normal parturition without side effects. Several drugs such as prostaglandins (Meier and Wright, 2000), antiprogestins (Baan *et al*., 2005), either alone or in combination (Reddy *et al*., 2012) were used in induction of parturition in bitches. Mifepristone when used alone to induce parturition in bitches with singleton pregnancies lead to incomplete abortion (Jayakumar *et al.*, 2017). Hence, the present study was planned to assess the efficacy of the combined use of mifepristone and misoprostol in induction of parturition in bitches bearing single puppy.

Materials and Methods

In the present study, real time B - mode ultrasound scanner (Aloka, Prosound α6, Japan) was used to diagnose the single puppy syndrome, gestational age and viability of the fetus. Bi Parietal Diameter (BPD) was determined by measuring the distance between the parietal bones of the fetus (Fig. 1) by inbuilt callipers when visualised on a longitudinal scan of the fetus. Then gestational age (GA) in days was calculated using the formula GA = (15 x BPD) + 20 that was prerecorded in the software. The viability of the fetus was recorded based on the fetal heart rate measured as number of beats per minute (Fig. 2) and fetal movements.

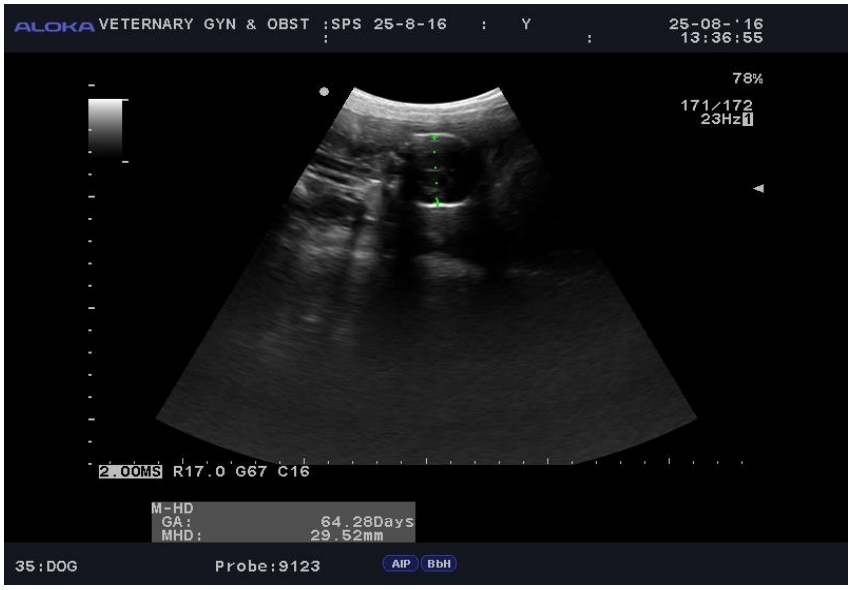

Fig. 1: Assessment of gestational age by measuring bi-parietal diameter using by ultrasound scan

DOI 10.5455/ijlr.20190114094349

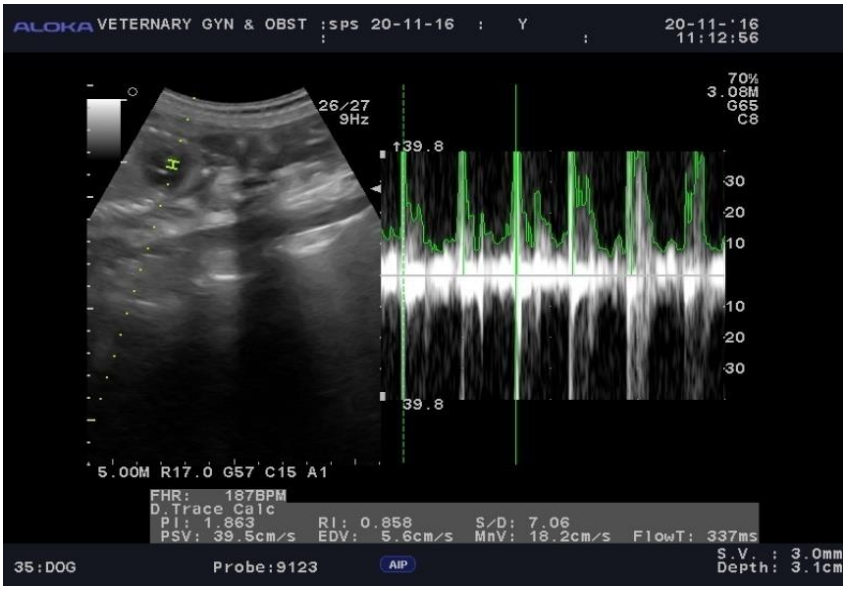

Fig. 2: Determination of fetal heart rate by ultrasound scan

Experimental Design

The animals that were confirmed to be pregnant having singleton pup by ultrasound scanning were considered for the study. Among these animals, dams that showed the signs of parturition without medical intervention were taken as control group. The animals that hadn't shown any signs of parturition even after 62 days of gestational age as confirmed by ultrasonography were included in treatment group. The parturition in treatment group was induced by administering mifepristone @ 5 mg/kg body weight per orally twice a day at 12 hours interval followed by misoprostol @ 200 µg for bitches with ≤ 20 kg body weight and 400 µg for bitches with > 20 kg body weight intra vaginally 12 hours after second dose of mifepristone. The time taken for the delivery of fetus from administration of mifepristone was recorded.

The female dogs with single pup syndrome in which parturition was initiated naturally but failed to deliver the fetus were treated for uterine inertia after evaluating the fetal viability using ultrasonography. The medical treatment for uterine inertia consisted of intravenous infusion of 10 % Dextrose (1g/kg BW), followed by 10 % Calcium gluconate (CALCIUM-SANDOZ®, Novartis India Limited) @ 0.2 ml / kg BW I/V, but not exceeding a total dose of 10 ml and Oxytocin @ 2 IU, I/M fifteen minutes after calcium administration. If the bitch hasn't whelped the pup within 30 minutes after the treatment, caesarean section was performed.

Results and Discussion

In control group, all the animals were presented with the complaint of dystocia. The physical and genital tract examinations indicated that parturition process was initiated. Dark greenish vaginal discharges and vaginal relaxation were observed in all animals with palpable fetal parts (pervaginum) in 50 per cent (3/6)

 DOI 10.5455/ijlr.20190114094349

of the animals. This spontaneous whelping might have started due to increased serum relaxin concentrations that cause cervical dilatation and relaxation of vulva along with vaginovestibular junction. The parturition starts within 1 to 2 hours after the greenish black discharges passes from vulva following the separation of placenta (Johnston *et al*., 2001). Though greenish discharges were noticed from the vulva in control group, they failed to deliver fetus resulting in dystocia which was in accordance with observations of Smith (2007), who stated that, the stimulus from the single fetus may not be sufficient to initiate the cascade of events in parturition resulting in extended parturition process and ending up in dystocia or uterine inertia. The probable reason for the control group of animals ending up in dystocia might be the failure of fetus to rotate by 180^0 from the ventral position before entering into pelvis (Jackson, 2004). The singleton might not make spontaneous movements before entering into pelvis due to its oversize and the fetal maldisposition will be exacerbated by the intrauterine fetal death (Hajurka *et al.*, 2005)

In this study, in the control group, three animals were presented with dead singleton and other three with live singleton as confirmed by ultrasound. Eventually all the animals suffered dystocia required medical or surgical assistance during whelping. In the treatment group the physical and genital tract examinations in the treatment group indicate that parturition process was not initiated even after 63 days of pregnancy as confirmed by ultrasound scanning (Fig. 1). The fetal heart rate estimated by ultrasound in the treatment group of the present study was 204.00 ± 13.85 bpm indicating that the fetuses were not under stress. Davidson (2008) suggested that the heart rates of 150–160 bpm indicate fetal stress. The heart rates <130 bpm is suggestive of poor pup survival and the pups are to be delivered within 1-2 hours. Hence, parturition was induced instead of planning for elective caesarean to minimise the risk to both fetus and dam. The mean time taken for the expulsion of single pup from the time of initiation of treatment (first dose of mifepristone) was recorded as 28 ± 2.74 hrs and in individual animals it ranged between 16 to 36 hours. However, in 16.67 per cent of animals (1/6) delivered the puppy within 16 hours from initial dose of mifepristone not necessitating the administration of misoprostol. The present study reported the delivery of live pups in 100 per cent (6/6) cases of single puppy syndrome in treatment group.

Jayakumar *et al.* (2017) administered mifepristone alone @ 5mg/kg twice daily orally for two days to six pregnant bitches having singleton litter after 64 days of gestation. The authors reported that only 33.34 per cent (2/6) bitches delivered live foetuses within 49 hours after initial dose of mifepristone while 66.66 per cent (4/6) bitches underwent assisted whelping. However, in the present study, mifepristone was used in combination with misoprostol, a synthetic prostaglandin E_1 analogue. It was observed that 100 per cent (6/6) bitches delivered live pups without the need of assisted whelping or surgical intervention. In presence of progesterone, mifepristone acts as a competitive progesterone receptor antagonist. The relative binding affinity of mifepristone at the progesterone receptor is more than twice that of progesterone. Mifepristone interferes with the endogenous progesterone causing detachment of the embryo/fetus and also sensitizes

 DOI 10.5455/ijlr.20190114094349

the uterus to the contractile action of prostaglandins (Sandhu, 2016). Misoprostol is a synthetic prostaglandin E_1 analogue being used for induction of abortion, cervical priming and management of post-partum hemorrhage in humans (Tang *et al*., 2007). It causes relaxation of cervix and stimulates uterine contractions after selective binding to EP_2/EP_3 receptors (Weeks and Faundes, 2007).

In addition to the actions of mifepristone, the fetal oversize in singleton litters demand/require cervical ripening and relaxation, which was accomplished by usage of misoprostol that proved to be 100 per cent effective as observed in the present study. Hence, mifepristone can be used in combination with misoprostol to improve its efficacy. Mifepristone is also an antiglucocorticoid with relative binding affinity of more than 10 times that of hydrocortisone at the glucocorticoid receptor level (Sandhu, 2016). The partial block of the glucocorticoid receptors by anti progestins trigger the production of ACTH from the pituitary gland and increasing the production of cortisol that helps in the fetal lung maturity and improving the survivability of the pup (Baan *et al*., 2005).

Conclusion

It is concluded that the combined use of mifepristone and misoprostol is safe and effective for the induction of parturition in female dogs with single puppy syndrome not necessitating surgical intervention and thereby minimizing adverse effect on maternal, fetal and/or perinatal health.

References

1. Borge, K. S., Tonnessen, R., Nodtvedt, A. and Indrebo, A. (2011). Litter size at birth in purebred dogs – A retrospective study of 224 dogs. *Theriogenology*,75: 911–919.
2. Baan, M., Taverne, M. A. M., Kooistra, H. S., De Gier, J., Dieleman, S. J. and Okkens, A. C., (2005). Induction of parturition in the bitch with the progesterone - receptor blocker aglepristone. *Theriogenology,* 63: 1958- 1972.
3. Davidson, A. P. (2008). Dystocia management. *In: Current Veterinary Therapy.* Bonagura JD, Twedt DC, editors. Kirks', Saunders Elsevier. 14: 992 – 998.
4. Hajurka, J., Macak, V., Hura, V., Stavova, L. and Hajurka, R. (2005). Spontaneous rupture of uterus in the bitch at parturition with evisceration of puppy intestine – a case report. *Veterinary Medicine.* 50 (2): 85 – 88.
5. Johnston, S. D., Root Kustritz, M. V. andOlson, P. N. S. (2001). Canine parturition – Eutocia and dystocia. *In*: *Canine and Feline Theriogenology* (Johnston SD, Root Kustritz MV, Olson PNS, eds. Toronto) WB Saunders., *pp* 105 – 128.
6. Jayakumar, C., Chinnu, P. V., Amritha, A. andUnnikrishnan, M. P. (2017). Challenges in management of canine high-risk pregnancies with single pup syndrome. *Indian Journal of Canine Practice*, 9(1):22 – 25.
7. Jackson, P. G. (2004). Dystocia in the dog and cat. *In*: Handbook of Veterinary Obstetrics by Jackson P.G.G. Edn. 2nd., W.B. Saunders Company, Philadelphia., *pp* 141 –166.
8. Meier, S. and Wright, P. J. (2000). The induction of parturition in the bitch using sodium cloprostenol. *Theriogenology*,54: 457 – 465.
9. Reddy, K. R. C., Sada siva rao, K.and Raju, K. G. S. (2012). Induction of whelping in bitches using dinoprostone, cloprostenol and mifepristone. Proceedings of the 7th International Symposium on Canine and Feline Reproduction - ISCFR, Whistler, Canada.

 DOI 10.5455/ijlr.20190114094349

10. Sandhu, H. S. (2016). Gonadal hormones. *In*: Essentials of veterinary pharmacology and therapeutics. *Edn*. 2nd., Kalyani Publishers, New Delhi., *pp* 770 – 800.
11. Smith, F. O. (2007). Challenges in small animal parturition - Timing elective and emergency caesarian sections. *Theriogenology*, 68: 348 – 353.
12. Snedecor, G. W. and Cochran, S. W., 1994. Statistical Method, *Edn*. 8th., The lowa state university press, Ames., IOWA, USA
13. Tang, O.S., Gemzell-Danielsson, K. and Ho, P. C. (2007). Misoprostol: Pharmacokinetic profiles, effects on the uterus and side-effects. *International Journal of Gynaecology and Obstetrics*,99: 160 – 167.
14. Weeks, A. and Faundes, A. (2007) Misoprostol in obstetrics and gynaecology. *International Journal of Gynaecology and Obstetrics*, 99: 156 – 159.

DOI 10.5455/ijlr.20190114094349