Comparative efficacy of mifepristone, cloprostenol and dinoprost along with vaginal application of misoprostol in whelping induction

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Abstract
Small litter size is considered high risk pregnancy in dogs from a probable dystocia due to prolonged gestation, uterine inertia and foetal oversize contributing to high neonatal mortality. Studies on medical induction of whelping are few and hence this study aims to investigate the efficiency and safety of medical induction of whelping in full term canine high risk pregnancies using progesterone antagonist, mifepristone; prostaglandin analogue, cloprostenol and natural prostaglandin, dinoprost tromethamine in combination with anterior vaginal application of PGE₃, misoprostol. A high number of puppies born alive at birth, a decreased medical and surgical assistance for completing the whelping process and the advantage of oral medication suggests induction of whelping using mifepristone with anterior vaginal administration of misoprostol a better choice than cloprostenol and dinoprost tromethamine.

Keywords: High risk pregnancies, canine, mifepristone, cloprostenol, dinoprost, misoprostol

Introduction
Low fecundity with three or fewer foetuses is usually a high-risk pregnancy in the dog. In pregnancies with small litter size, inadequate stimulus to initiate the parturition cascade result in extended duration of pregnancy and possible dystocia from relative foetal oversize and primary uterine inertia [8, 9]. Therefore, induction of whelping becomes inevitable for a successful outcome. Consequently it becomes mandatory to make sure that the foetus has accomplished but not exceeded its required gestational age before delivery [6]. Ideally, the treatment provided should induce parturition with a greater efficiency and within an expectant time frame and must be safe for the dam and the neonates. Mifepristone, being a synthetic steroid with high affinity towards progesterone receptors, could bind with those receptors and interfere endogenous progesterone from employing its biological effects and induces parturition [5]. A decrease in luteal progesterone secretion occurs after exogenous PGF₂α administrations, identical to the changes occurring prior to normal parturition [11]. Prostaglandin E₃ misoprostol accelerated the cervical dilatation soon after using antiprogestin, aglepristone in bitches treated for termination of pregnancy [11]. Vaginal misoprostol administration had a higher bioavailability and sustained serum level which is prerequisite for regular uterine contractions. This advantage of intravaginal misoprostol administration over oral administration of misoprostol was proved in human pregnancy termination [10]. The present study hence aimed to determine the efficacy of three treatment protocols in medical induction of whelping in canine high risk pregnancies with small litter size with respect to its success rate and safety for the dam and the neonates.

Materials and methods
The study was carried out in eighteen dogs of different breeds presented to the University Veterinary Hospital, Kokkalai and Mannuthy, Thrissur, KVASU with a history of not exhibiting any impending signs of parturition. The animals were subjected to detailed clinico-gynaecological examination and abdominal radiographic evaluation to record the pregnancy status with three or fewer foetuses. Trans-abdominal sonography was performed to assess the foetal viability and gestational age of the foetus based on the foetal head diameter and foetal organ development. Pregnant bitches with foetuses having foetal heart rate (FHR) of more than 200 beats per minute (bpm) and with a gestational age of at least 61±1 days determined by sonographic measurements of foetal head diameter were selected for medical induction of parturition.
Out of 18 bitches, 6 were distributed into three treatment groups of different therapeutic protocols for induction of whelping. Dogs in Group I was treated with mifepristone @ 5mg/kg body weight twice daily, orally for two consecutive days; Group II dogs were treated with a single subcutaneous administration of cloprostenol @ 2.5 μg/kg body weight and Group III dogs were treated with subcutaneous administration of dinoprost tromethamine @ 0.1mg/kg body weight. Twenty four hours following the institution of treatment, misoprostol @ 400μg was administered in anterior vagina (Fig 1) of all the dogs in the three treatment groups. Glycopyrrolate @ 0.01 mg/kg bodyweight was subcutaneously administered 15 minutes prior to prostaglandin administration. If the process of parturition was not initiated up to 72h after the commencement of treatment, medical induction of parturition was considered as a failure and was immediately subjected to caesarean section. Suitable medical management was carried out on failure of foetal expulsion within two hours of initiation of whelping or between expulsions of pups. Serum progesterone and cortisol concentrations were estimated by ELISA technique before treatment and on initiation of whelping. The data obtained during the study were subjected to statistical analysis using SPSS 24.0 version software.

Results and Discussion

Treatments with mifepristone, cloprostenol and dinoprost tromethamine in association with misoprostol successfully induced whelping with a great efficiency as substantiated by the overall induction response of 100 percent within 72 hours of treatment in group I, II and III. The mean (±SE) rectal temperature of the dogs in group I, II, and III before treatment were 101.78±0.22°F, 101.93±0.24°F and 101.88±0.20°F respectively and after the treatment temperature decreased to mean (±SE) of 99.55±0.20°F, 99.76±0.39°F and 99.68±0.24°F. This temporary drop of temperature before whelping was in accordance with observation of Weyden et al. (1989) [12] who suggested that in dogs, progesterone has a thermogenic effect within thermoregulatory centre.

The mean gestational age on the day of treatment calculated from the last day of breeding ranged between 60 to 63 days with a mean (±SE) of 61.67±0.42 days in group I, 60 to 63 days with a mean (±SE) of 61.17±0.54 days in group II and 60 to 64 days with a mean (±SE) of 61.83±0.60 days in group III. In sonographic foeto-biometry, assessment of foetal head diameter is the most accurate method to analyze the gestational age of the foetus in later stages of gestation by employing the formula (15 X head diameter) + 20 [6, 7]. The mean (±SE) gestation age determined by ultrasound measurements were 61.63±0.42 days with mean (±SE) BPD of 2.77±0.02 cm, 61.66±0.34 days with mean (±SE) BPD of 2.77±0.02 cm and 62.28±0.39 days with mean (±SE) BPD of 2.81±0.02 cm in group I, II and III respectively. This signifies that the treatment provided was without any impending signs of whelping even on sonographic GA determination of 61±1 days. The disparity between the gestational age assessment based on breeding dates and that by sonographic foetal measurements highlights the need for dependence on sonographic confirmation of foetal growth and viability, else would result in delivery of immature puppies.

The time taken for initiation of whelping in three treatment groups was comparable (35.58±3.54 h in group I, 36.00±2.79 h in group II and 36.58±1.22 h in group III). The earliest time for initiation of whelping (24.5 h) was noticed in mifepristone and misoprostol combination group while the maximum time for initiation of whelping (48 h) was noticed in the cloprostenol and misoprostol combination group. The time interval (mean ± SE) from initiation of whelping to the delivery of the entire litter in group I was 152.50±49.66 min, in group II it was 78.00±12.90 min and in group III, it was 102.00±21.06 min. The shortest duration of whelping (78±12.90 min) was observed in group II and the reason attributable to the lowest litter size. A beneficial effect of combination therapies in termination of pregnancies has been proved in human beings [2] and also in dogs [3]. Out of 18 bitches subjected to medical induction of whelping, 66.7 per cent bitches whelped normally, 27.7 per cent bitches required assistance in whelping and in 5.5 per cent bitches emergency caesarean section was performed. The assistance for delivery was provided in the form of manual traction and / or medical management with 25% dextrose, 10% calcium gluconate and oxytocin. The reduced incidence of dystocia encountered in the treatment groups could be attributed to the reduced foetal size as well as combined uterotonics effects provided by the combination of different drugs used for the induction. No maternal side effects for any drug used in the treatment protocols were noticed in any of the groups.

A decrease in serum progesterone concentration was noticed after treatment in all the dogs of treatment groups indicating the efficiency of the drugs in initiating the parturition. However, in mifepristone treated dogs the circulating progesterone at whelping was still higher (2.71±0.41 ng/ml) when compared to group II and group III (0.60±0.14 ng/ml and 0.90±0.18 ng/ml respectively). An increased circulating plasma progesterone concentration in the mifepristone treated group at the time of whelping has also been reported [4], who explained it on the basis of increasing binding of progesterone receptors by progesterone antagonists in place of natural hormone and also due to hypothalamic effect of the agent on GnRH neurons resulting in increased pituitary secretions of FSH and LH that stimulated corpora lutea cells to produce more progesterone. An increasing trend of serum cortisol levels were noticed in all the dogs after the treatment. Similar observations on the fluctuations of maternal cortisol concentration within the normal range during the last week of gestation (15-25 ng/ml) with elevated levels on the day before parturition (40-80 ng/ml) was recorded [5].

Number of puppies born alive in the three induced groups were 12 out of 13 (92.3%), 7 out of 10 (70%) and 9 out of 11 (81.8%) respectively. However the neonatal survival rate upto two weeks of birth did not differ significantly between the three groups.

Conclusion

The study revealed the merits of medical induction of whelping using combination of drugs in canine high risk pregnancy with small litter size as evident from a cent percent induction response within a relatively short and predictable period and also from the high puppy survival at birth. However, a high number of puppies born alive at birth and a decreased medical and surgical assistance for completing the whelping process makes induction of parturition using mifepristone with anterior vaginal administration of misoprostol a better choice than cloprostenol and dinoprost tromethamine (Table 1).
Table 1: Comparison of the efficacy of three treatment protocols in whelping induction

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group I (n=6)</th>
<th>Group II (n=6)</th>
<th>Group III (n=6)</th>
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<tbody>
<tr>
<td>Mean GA assessed by ultrasound on start of treatment (days)</td>
<td>61.63±0.42</td>
<td>61.66±0.34</td>
<td>62.28±0.39</td>
</tr>
<tr>
<td>Mean GA assessed by last breeding date to start of treatment (days)</td>
<td>61.67±0.42</td>
<td>61.17±0.54</td>
<td>61.83±0.60</td>
</tr>
<tr>
<td>Mean gestational length from ultrasound measurement to date of whelping</td>
<td>63.04±0.76 (61 to 64 days)</td>
<td>63.23±0.33 (61 to 63 days)</td>
<td>63.84±0.50 (62 to 64 days)</td>
</tr>
<tr>
<td>Mean gestational length from last date of breeding to date of whelping</td>
<td>63.14±0.76 (61 to 64 days)</td>
<td>62.66±0.52 (61 to 64 days)</td>
<td>63.35±0.63 (61 to 64 days)</td>
</tr>
<tr>
<td>Time of delivery of first pup from start of treatment</td>
<td>35.58±3.54 h</td>
<td>36.00±2.79 h</td>
<td>36.58±1.22 h</td>
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</table>

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<thead>
<tr>
<th>Nature of whelping</th>
<th>Vaginal delivery (n=6)</th>
<th>Vaginal delivery (n=5)</th>
<th>Caesarean section (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of puppies born alive</td>
<td>12 out of 13 (92%)</td>
<td>7 out of 10 (70%)</td>
<td>9 out of 11 (81.8%)</td>
</tr>
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Fig 1: Anterior vaginal administration of misoprostol

Acknowledgement
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References