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Effect of dinoprost and cloprostenol on serum nitric oxide and corpus luteum blood flow during luteolysis in ewes

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ABSTRACT

In this study we compared the effect of dinoprost and cloprostenol on changes of corpus luteum blood flow during luteolysis. Ten nonlactating cyclic ewes were synchronized with double $PGF_{2\alpha}$ injections 11 days apart. At Day 10, the animals were classified into 2 groups and received the third dose of $PGF_{2\alpha}$ after confirmation of the presence of a mature CL. The first group received (12.5 mg/im) dinoprost and the second group received (250 μg/im) cloprostenol. A color Doppler ultrasound scan was performed by the same operator according to the following timeline: 0, 0.5, 1, 2, 4, 6, 12, and 24 hours, then every 24 hours until Day 4). The size, morphology, and blood flow of the CL was evaluated during the regression. The results showed that regression of the CL did not differ between the dinoprost and cloprostenol groups. There was no significant effect on diameter of the CL in both groups, though the size of the CL decreased gradually and slowly. Pretreatment progesterone concentration did not differ between groups. The results showed that the nitric oxide level was significantly increased within half an hour after the dinoprost treatment, and was significantly decreased in the cloprostenol group after half an hour. The blood velocity was increased significantly half an hour after the dinoprost treatment and it was decreased in the cloprostenol-treated group. In conclusion, both cloprostenol and dinoprost affect CL by controlling the nitric oxide level and blood supply of the CL via different mechanisms to induce luteolysis.

1. Introduction

The corpus luteum (CL) is a temporary endocrine gland that shows periodic growth, differentiation, and regression, and plays a major role in the reproduction cycle [1]. Without pregnancy, the CL undergoes morphological and functional regression. This process called luteolysis, which is characterized by ending of progesterone (P4) secretion, breakdown of the CL cells, decrease of vascular supply, proliferation of connective tissue, increase of cellular disorganization, and degeneration and phagocytosis of luteal cells [2].

For decades, prostaglandin F2α ($PGF_{2\alpha}$) was used to induce luteolysis. The effect of prostaglandins have been reported in domestic ruminants [2]. These include a dramatic decrease in luteal blood flow [3], inhibiting lipoprotein-stimulated steroidogenesis [4], a decrease in the number of small luteal cells [5], and release of luteal oxytocin [6]. CL growth is characterized by extensive angiogenesis. A network of capillaries lined with endothelial cells estimated to be half of all cells within the CL [2].

In the past decade, several studies showed a correlation between luteal blood flow and cyclic changes in P4 synthesis in cows [3,7–9]. A rapid decrease in the luteal blood flow has been proposed as one of the main luteolytic actions of $PGF_{2\alpha}$ [10]. In cattle, a luteolytic dose of $PGF_{2\alpha}$ analogue acutely increased the luteal blood flow surrounding the CL within

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30 minutes up to 2 hours [9]. After $PGF_{2\alpha}$ injection, the plasma P4 concentration decreased within 24 hours in cattle [11] and within 4 to 5 hours in ewe [12]. In cattle, different physiological responses to cloprostenol and dinoprost have been reported for luteolysis, receptor binding, intrauterine pressure, estrus expression, and conception rates [13]. It was reported that dinoprost was slightly more effective as a luteolytic product than cloprostenol but no differences in pregnancy outcome were detected [13,14].

Nitric oxide (NO) is a potent vasodilator that increases the ovarian blood flow [8]. In cattle, NO inhibited P4 secretion and induced apoptosis in luteal cells [15–17], whereas inhibition of NO synthesis stimulated P4 secretion, increased the lifespan of the CL, and counteracted $PGF_{2\alpha}$-induced luteolysis [18]. It was found that NO increased the luteal blood flow surrounding the CL [11]. Supporting this observation, NO synthase expression in bovine CL reached the highest level during the late luteal phase [17]. In ovine, endothelial NO synthase protein expression decreased in the regressed CL which was associated with a decrease in endothelial cells, pericytes, and vasculature [19].

The aim of this research was to study the effects of cloprostenol and dinoprost on changes in the luteal blood flow and serum NO during luteolysis in ewe CL.

2. Materials and methods

2.1. Animals and experimental design

The study was conducted during the breeding season at the farm of faculty of agriculture in Assiut University, Egypt. Ten nonlactating cyclic ewes ranging in age from 3 to 5 years and weighing 40 to 50 kg were assigned for the present study. Ewes were maintained indoors with outdoor access (latitude 31°2N and 27°2E). Ewes were synchronized using two im administrations of 2.5 mL (12.5 mg) dinoprost (Lutalyse, Pfizer Manufacturing, Purts, Belgium) 11 days apart. The animals were examined daily until ovulation occurred, and 10 days after ovulation the animals were examined to confirm the presence of a mature active CL. After that we gave the third dose of $PGF_{2\alpha}$ according to the group. Group 1: five ewes received 12.5 mg dinoprost (dinoprost tromethamine; Lutalyse, Pfizer Manufacturing). Group 2: five ewes received 1 mL I/M of cloprostenol 250 μg (as 263 μg cloprostenol sodium per mL of aqueous solution; Estrumate, Merck Animal Health, MSD). The bioequivalence among two doses of cloprostenol and dinoprost was calculated as the half dose given to cattle [20]. The time of dinoprost or cloprostenol administration considered as 0 hours.

2.2. Monitoring of blood vascular changes of CL

Ultrasound scanning was performed by the same operator according to the following schedule: 0, 0.5, 1, 2, 4, 6, 12, and 24 hours, then every 24 hours for 4 days, using a Doppler ultrasound scanner (Mylab30, Piemedical), equipped with a 6- to 8-MHz endorectal linear probe (Lv513). Examinations were conducted in the standing ewe. The urinary bladder was used as a guide to find the uterine horn. The probe was rotated laterally 90° clockwise and 180° anticlockwise to scan the ovaries and genitalia. The size and blood flow were detected using retrospective evaluation of ovarian sketches that provided topographical and diameter changes of the CL.

After morphological evaluation of CL, the power flow mode of the ultrasound scanner was activated for blood flow mapping. The blood flow color signals were evaluated around the entire perimeter of CL. The sectional area of the CL was estimated using the following equation: sectional area $= \pi/4 \times$ (sectional diameter)2 [7]. The colored area in the image that was obtained at the maximum diameter of CL was used as a quantitative index to express the blood flow within the CL. Areas of color represent regions with a flow velocity greater than 0.08 m/s. Recorded images and videos were stored on a USB Flash Drive (Adata, Adata Technology Co., Ltd.). The sectional area was calculated and the blood flow area (BFA) was quantified using Image J software (version 1.62) developed at the US National Institutes of Health (http://rsbweb.nih.gov/ij/). The blood flow velocity waveforms were recorded during three cardiac cycles to determine the time-averaged maximum velocity (TAMXV) for the CLs.

2.3. Blood collection and hormonal determination

The blood samples were collected using jugular venipuncture into heparinized tubes after each Doppler scan. Progesterone levels were determined using ELISAs provided by BioChek Inc. (Foster City, CA, USA). The range of the standards used was 0.5 to 50.0 ng/mL and the inter- and intrarun precision test showed coefficients of variation of 2.6% and 4.5%, respectively, and sensitivity of 0.0625 ng/mL. Nitric oxide level was analyzed using Colorimetric Determination of Nitrite (Biodiagnostic, catalog No. TA2532). The final products of NO *in vivo* were nitrite and nitrate. There is an exogenous source of nitrate from the diet, so the index of NO production is the nitrite. The Biodiagnostic nitrite assay kit provides an accurate and convenient method for measurement of endogenous nitrite concentration as an indicator of endogenous NO production in biological fluids. It depends on adding Griess reagents which convert nitrite into a deep purple azo compound in acid medium, and in the presence of nitrite the formed nitrous acid diazotise sulfanilamide and the product coupled with N-(1-naphthyl) ethylenediamine. The resulting azo dye has a bright reddish-purple color with an optical density that measured 540 nm. As for test sensitivity, when using the maximum amount of sample for the nitrite assay (100 μL), the detection limit was 2.5 μM.

2.4. Statistical analysis

The time of injection of $PGF_{2\alpha}$ was defined as 0 hours. The data of hormonal concentration, CL diameter, BFA, blood flow area percent, and blood velocity were expressed as mean ± SEM. All data were analyzed using repeated measures ANOVA to determine main effects of group and interaction of group by day. When main effect of group or group by day was observed, the difference of group means at specific time points were analyzed using the Student *t* test and JMP statistical software (version 5.1; SAS Institute, Cary, NC, USA). The different means were significant at $P < 0.05$.

3. Results

3.1. Changes in CL diameter and P4 concentration

The regression of the CL did not differ between the dinoprost and cloprostenol groups. The CL size decreased gradually and slowly in both groups (Fig. 1A).

Before treatment, P4 concentration was similar between the two groups (3.23 ± 0.3 ng/mL vs. 4.2 ± 0.9 ng/mL). At 4 hours after treatment, P4 concentrations in the dinoprost and cloprostenol groups significantly ($P \leq 0.05$) decreased (1.26 ± 0.8 ng/mL vs. 1.17 ± 0.8 ng/mL). At 6 hours after treatment, P4 concentration in the cloprostenol group decreased to less than 1 ng/mL (0.44 ± 0.02 ng/mL), and it was 48 hours before dinoprost was less than 1 ng/mL (0.35 ± 0.01 ng/mL) (Fig. 1B).

3.2. Changes in NO, TAMXV, and BFA

Nitric oxide was significantly increased within half an hour after the dinoprost injection, and it significantly decreased in the cloprostenol groups; after that NO did not significantly change in both groups until the end of the treatment (Fig. 2A).

The blood flow area increased under the effect of dinoprost in comparison with cloprostenol during the first 6 hours after treatment but not significantly (Fig. 2B). Before treatment, BFA represented approximately 10% of the total CL area. After half an hour from dinoprost injection, the detectable BFA acutely increased to be approximately 20% and in the cloprostenol group, BFA decreased to be 5% of the total CL area (Fig. 2C).

The blood velocity significantly increased half an hour after the dinoprost injection (Fig. 3) and it decreased after the cloprostenol injection (Fig. 4). After 1 hour, it was difficult to estimate the blood velocity (Fig. 2D).

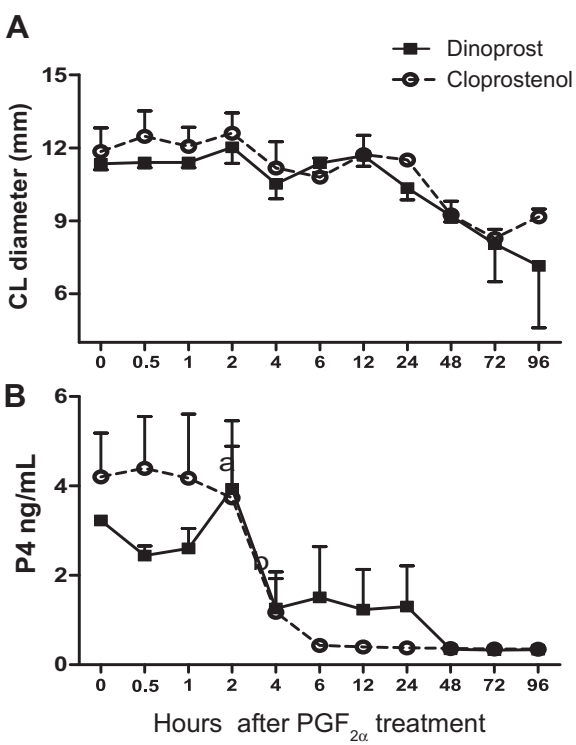

Fig. 1. (A) Diameter of the CL; (B) progesterone (P4) level after the injection of the two drugs. Data are mean ± SEM. Different letters (a and b) indicate significant differences at $P < 0.05$.

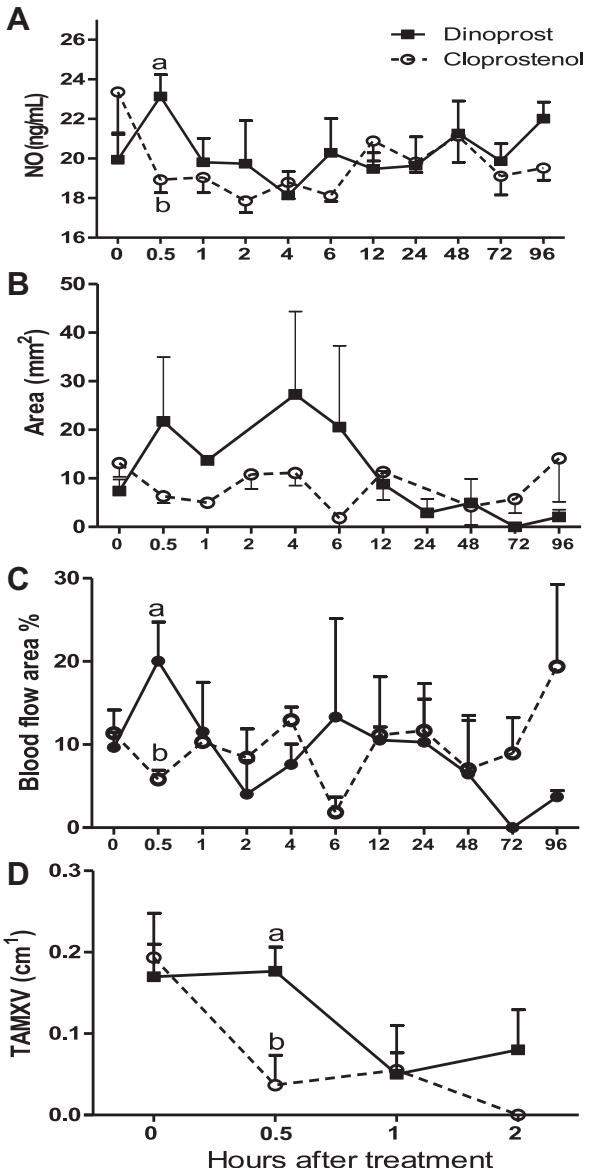

Fig. 2. (A) NO level; (B) blood flow area; (C) blood flow area percent; and (D) time-averaged maximum velocity after the injection of the two drugs. Values are mean ± SEM of each time period. Different letters (a and b) indicate significant differences at $P < 0.05$ between groups. NO, nitric oxide; TAMXV, time-averaged maximum velocity.

4. Discussion

In the present study, CL diameter in both groups was not affected up to 24 hours after $PGF_{2\alpha}$ injection and P4

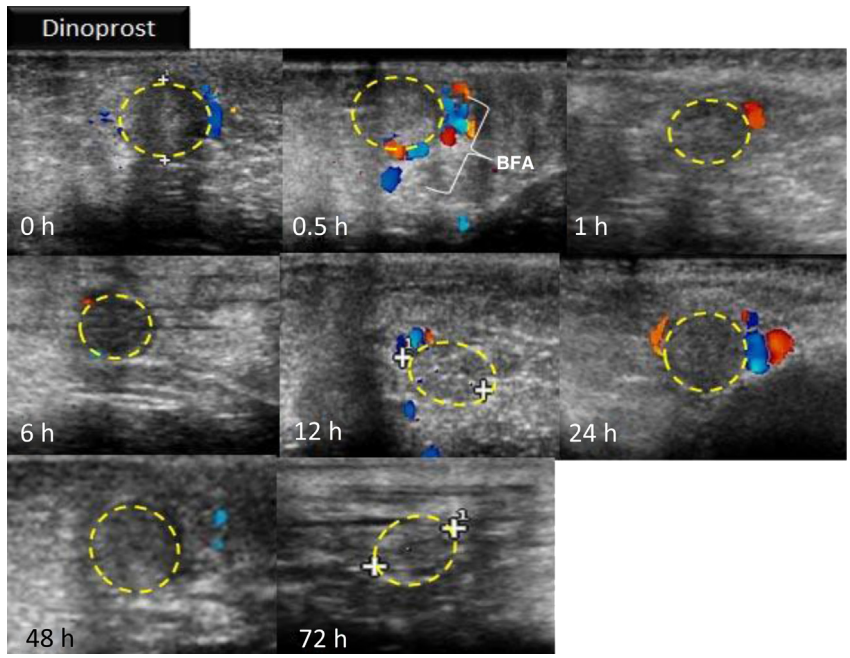

Fig. 3. Representative images of regressed CL of ewes showing acute increase in blood flow area and the intensity of color (velocity) half an hour after injection of dinoprost. Red represents the blood flow toward the transducer, and blue indicates blood flow away from the transducer. The color gain of the flow mode was set to detect movement of at least 0.08 m/s. BFA, blood flow area.

concentrations were quickly reduced within 4 hours. Similar to our results, P4 was decreased within 4 to 5 hours after $PGF_{2\alpha}$ treatment in nonsuperovulated ewes [12], and CL weight was decreased within 16 to 24 hours [21,22]. However, other studies observed that CL weight was not affected by $PGF_{2\alpha}$ injection [12,23]. It seems that $PGF_{2\alpha}$ did not decrease the total number of CL cells within the first few hours after injection but it affected cell function because P4

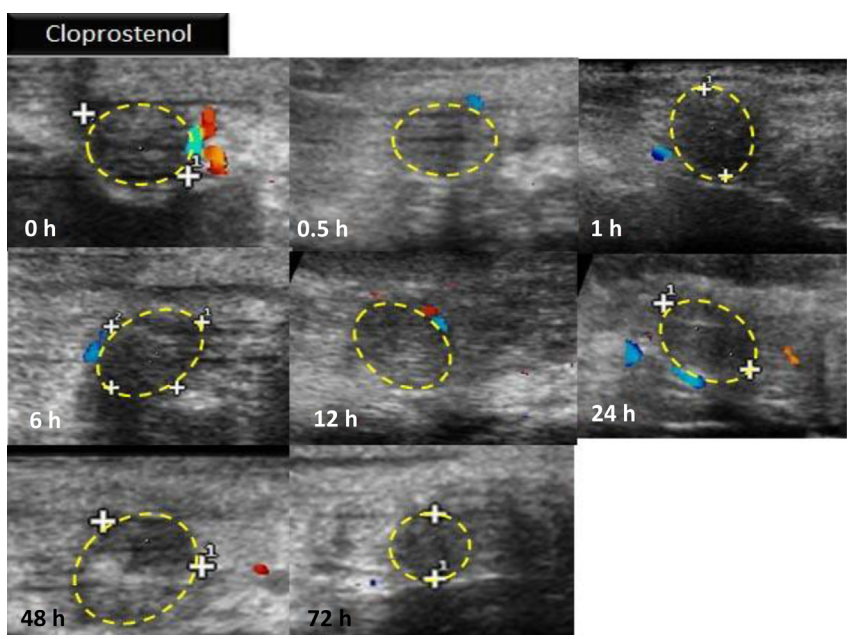

Fig. 4. Representative images of regressed CL of ewes showing acute decrease in blood flow area and the intensity of color (velocity) half an hour after injection of cloprostenol. Red represents the blood flow toward the transducer and blue indicates blood flow away from the transducer. The color gain of the flow mode was set to detect movement of at least 0.08 m/s.

declined within 4 hours after induction of luteolysis. Supporting this observation, a decrease in the total cell numbers was observed within 24 hours after $PGF_{2\alpha}$ treatment [12,21,24]. At 6 hours after treatment, P4 concentration in the cloprostenol group decreased to less than 1 ng/mL, and it takes 48 hours for dinoprost to be less than 1 ng/mL. It seems that ewes are sensitive to cloprostenol regarding the dose. Contreras-Solis et al. [25], who used several doses of cloprostenol (125 μg, 68.25 μg, and 38.5 μg) found no difference between the doses in luteolysis. The authors explain that low and high dose have the ability to induce luteolysis because they believe luteolysis is more a cascade of episodes than a single event. During the natural estrous cycle, the initial secretion of endogenous $PGF_{2\alpha}$ by the endometrium, in the absence of pregnancy, stimulates the secretion of oxytocin by the CL, which in turn amplifies secretion of the endometrial $PGF_{2\alpha}$ [26,27]. Finally, it seems that cloprostenol and dinoprost had nearly the same effect on CL size.

The results showed that at half an hour after treatment, dinoprost significantly increased NO and cloprostenol decreased it. Nitric oxide is one of several intraovarian mediators that influenced ovarian function, including follicular development and atresia, ovulation, steroidogenesis, oocyte quality, apoptosis, and luteal function [28–33]. In addition, NO is a vasodilator substance [8] and had a dualistic role on the CL depending on the dose [34]. The low NO concentration stimulated the enzymatic pathway of vascular cells, stimulated the genesis of the mitochondria, and increased cytochrome electron transport which stimulated the CL to produce P4 [35,36]. In contrast, the high intracellular NO was cytotoxic [22], and inhibited mitochondrial respiration [37] by stimulating mitochondrial fission [38], and induced apoptosis [39]. Besides, a high dose of NO reduced the cholesterol entering the cells [34]. Such changes would impair the action of the steroid acute regulatory protein, the rate-limiting step in steroidogenesis [40]. It was suggested that fast-acting NO inhibited mitochondrial movement in neurons [41]. In contrast, long-acting NO was proposed to be antiluteolytic in rats [42] and sheep [43]. Motta et al. [44] first suggested the dualistic role for NO in luteal function. Long-acting NO donors might stimulate luteal function, whereas fast-acting NO donors might more closely represent the rapid changes occurring within the CL. It seems that physiological changes in NO that occur within the luteolytic CL are closely similar to the mechanism of fast-acting NO donors [34].

In cattle, injection of $PGF_{2\alpha}$ or its analogue increased the blood vascular area and TAMXV of the CL [3,8]. Injection of cloprostenol causes the vascular endothelial growth factor mRNA to increase within 4 hours after the $PGF_{2\alpha}$ treatment [12] which results in acute hypoxia [45] in ewes.

The BFA increased under the effect of dinoprost in comparison with cloprostenol for the first 6 hours after treatment. The blood velocity was increased significantly half an hour after the dinoprost injection and it decreased after cloprostenol treatment. In cattle, CL blood flow acutely increased within 30 minutes to 2 hours after injection of the $PGF_{2\alpha}$ analogue [8,9]. We found that increase in the BFA was independent of changes in the blood velocity (TAMXV) which is similar to the result reported by Acosta et al. [8,9]. According to our results, it seems that dinoprost and cloprostenol induce luteolysis of the CL but with different mechanisms. Dinoprost increased the NO level and made the CL blood vessels hyperemic. In contrast, cloprostenol decreased the NO and caused vasoconstriction of the CL blood vessels. Those effects were transitory through the first hour.

According to our results, we speculated that dinoprost causes a rapid increase in NO levels within 1 hour after injection, and an increase of the intracellular NO causing its negative effect on the CL cells. In contrast, the cloprostenol significantly decreased the NO, causing a transient sever vasoconstriction which might cause acute hypoxia in the CL that leads to death of the cells.

4.1. Conclusions

Both cloprostenol and dinoprost affect the CL by controlling the NO level and blood supply of the CL but with different mechanisms to induce luteolysis.

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