New intriguing implications of epidural prostaglandin F 2 alpha (pgf 2α) administration in the dairy cow: a case report

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SUMMARY

Introduction - Prostaglandin F 2 alpha (PgF 2α) are widely used in bovine reproduction for induction of parturition, oestrus induction, luteolysis, whereas, in mice models, they have been supposed to modulate cervical ripening and uterine remodeling. Recent in vitro studies have shown that the I and II dorsal laminae of the rat spinal cord are endowed with prostaglandin F receptors which are mainly involved in the modulation of pain. The epidural route of administration of many substances has been successfully tested, in vivo, for the resolution of reproductive diseases in the dairy cow.

Aim - To describe the effects of the epidural PgF 2α administration in a dairy cow undergone caesarean section.

Materials and Methods: A pluriparous Brown-Swiss dairy cow underwent caesarean section on the 312th day after A.I., since, upon clinical examination, a vital calf in longitudinal anterior presentation was perceived, in absence of myometrial contraction and cervical opening. A female macrosomic calf, weighing 72 kgs was extracted; the calf died within half an hour after surgery, despite resuscitation procedures. At necropsy, teratologic traits were noted such as ram-like profile, lack of fusion of the frontal and parietal bones, microcephaly and pituitary agenesia, accounting for the inability of the alive foetus to perceive and transduce foetal stress to the mother and provoke calving. Oxytocin (10 I.U./100 kg B.W.) was administered intramuscular via to the mother, to stimulate cervical opening, lochia expulsion and milk ejection. Given the absence of oxytocin effect, 24 hour later dinoprost (25 mg) was given to the cow, with the same purposes and no results, therefore dinoprost (12.5 mg) was administered again, epidural via, 24 and 48 hrs later, in the sacro-coccygeal space.

Results - The epidural PgF 2α administration resulted in cervical dilatation, udder development and colostrum/milk production.

Discussion - The results obtained through the unusual epidural administration suggest the hypothesis that dinoprost may have travelled along the nervous fibers (neurocrine process), reaching the cervix and the udder provoking ripening and local prolactin synthesis, respectively. Another interpretation relies on possibility that the bovine spinal cord might bear prostaglandin F receptors such as it has been found in the rat and that, upon activation, dinoprost may have depolarized the fibers innervating the udder and cervix, triggering cervical dilatation and lactogenesis.

Conclusions - These preliminary and interesting results need testing on a wider number of cows and deepening with histological researches. In this way, the mechanism of action of epidural PgF 2α administration could be inferred. Anyway, this case report, in the present form, could widen the current knowledge about the therapeutic effects of prostaglandins, related to the unusual epidural route of administration.

KEY WORDS

Caesarean section, PgF 2α, epidural space, cervical ripening, lactogenesis.

INTRODUCTION

Prostaglandins can be considered analogs of the prostanoic acid, they belong to the family of the so-called eicosanoids and derive, together with thromboxanes and leukotrienes, from a common precursor, the arachidonic acid, via the constitutively expressed cyclooxygenase-1 (COX-1), inducible cyclooxygenase 2 (COX-2) and lipoxygenases1. Once released from the cell, prostaglandins (PG) act in an autocrine or paracrine fashion on their cognate heptahelical G coupled receptor, thus the five isoforms of prostanooids, i.e. PGE2, PGF2α, PGI2 and TXA2, bind to DP, EP, FP, IP and TP prostanooid receptors, respectively. Upon binding to prostanooid G coupled receptors, stimulation of phospholipase C occurs and, consequently, inositol-1,4,5-triphosphate (IP3) is formed which increases the intracellular calcium (Ca2+) concentration through its release from intracellular stores2. Particularly, TP, FP and EP1 receptors induce Ca2+ mobilization via the activation of the protein Gαq, making up a ‘contractile’ receptor group because they cause smooth muscle contraction. In human gynaecology, many reports evidence that prostaglandin E (PGE) and their synthetic analogs such as misoprostol (PGE1) and dinoprostone (PGE2) are commonly used for labour induction and cervical ripening, whereas, in buiatrics, PgF 2α and their synthetic analogs are usually employed to stimulate calving, for oestrus induction,
for luteolysis, to enhance myometrial motility, thus hastening uterine involution and helping solving uterine infections.

Furthermore, prostaglandins participate in the complex process of cervical ripening and tissue remodeling occurring at parturition; prostaglandin synthetizing enzymes were in fact shown to be up-regulated in mice models of dystocia, compared to healthy ones.

The uterus and cervix are mainly innervated by sympathetic fibers, consisting of the hypogastric, pudendal and caudal rectal nerve which, in turn, arise from L4-L5, S3-S4 and S4, respectively.

Brilliant in vitro studies from Suzuki-Yamamoto et al. (2003) showed the localization of prostaglandin F synthases in the rat spinal cord, whereas the same authors recently discovered the localization of FP receptors in I and II laminae of the dorsal horn of the spinal cord, i.e., in those portions implicated in pain transmission.

Sciorscì et al. (2003) and Rizzo et al. (2011) reported the successful results of the epidural route of administration of hormone analogues for the resolution of gynaecological disorders, in the dairy cow.

Given these premises, this paper describes and discusses the unexpected outcomes of the epidural PGE\textsubscript{2}α administration in the early postpartum of a dairy cow undergone caesarean section and giving birth to a microcephalic calf, after a prolonged gestation.

**CASE DESCRIPTION**

A pregnant Brown Swiss cow was referred to the Mobile Clinic of the Section of Veterinary Clinics and Animal Productions of the Department of Emergency and Organ Transplantation (D.E.T.O.) of the University of Bari, Italy, for caesarean section.

The multiparous cow (age 7 yrs, BCS 3.5, average milk yield per lactation 7500kg) was bred in a dairy herd in Noci (Bari, Italy) in a semi-intensive system (it was fed pasture and hay, concentrate and minerals; fresh water was available ad libitum). It had undergone A.I. with frozen semen from a Brown Swiss bull of proven fertility.

The cow didn’t return into heat 21 days after A.I. 40 days after A.I. pregnancy diagnosis was performed by transrectal exploration and ultrasonography (SonoSite, MicroMaxx-Bothell, WA, USA; multi-frequency linear probe set at 7.5 MHz). It was dried at the end of the 7th month after A.I. The cow didn’t show any sign of imminent calving, until the 310\textsuperscript{th} day after A.I., when a complete clinical examination was performed by the farm vet. The cow hadn’t shown signs of infectious diseases, nor any other complication (trauma, change of farm, transport, ecc.) had occurred during pregnancy. At transrectal palpation a vital, macrosomic calf in longitudinal, anterior presentation was perceived. At the investigation per vaginum, after the introduction of Gerosa speculum, the external cervical ostium was closed and the vagina appeared still. Despite oxytocin administration, the calf died within half an hour after the extraction. At necropsy; upon dissection, besides its big dimensions, teratologic traits were observed: ram-like profile, lack of fusion of the frontal and parietal bones, microcephaly and pituitary agenesis.

No NSAIDs were administered to the cows, at the end of surgery.

24 hrs after the caesarean section, soon after the daily antibiotic administration, 25 mg (5 mL) of dinoprost (Dinolytic®, Pfizer, Italy) were i.m. administered to the cow, since, upon clinical examination, the cervical ostium appeared still closed, despite oxytocin administration.

48 hrs after the caesarean section, no change was observed at the external cervical ostium and, due to the inefficacy of the intramuscular PgF\textsubscript{2}α administration (the elimination half life of dinoprost is 9 minutes in the cow)\textsuperscript{11}, 12.5 mg (2.5 mL) of dinoprost (Dinolytic®, Pfizer, Italy) were administered to the cow in the epidural space between the sacrum and the first coccygeal vertebra, after the daily antibiotic administration. The choice of this route of administration was based on the successful reports of Sciorscì et al. (2003)\textsuperscript{9} and Rizzo et al. (2011)\textsuperscript{10}. Ten minutes after the treatment, upon vaginal examination, a mild dilatation of the external cervical ostium was observed (2±1 cm), which didn’t increase at a further vaginal examination performed 15, 20 and 30 minutes after the treatment.

72 hrs (3\textsuperscript{rd} day) after the caesarean section, owing to the absence of changes in cervical ripening upon vaginal examination, 12.5 mg (2.5 mL) of dinoprost (Dinolytic®, Pfizer, Italy) were again administered to the cow, epidural via, after the daily antibiotic administration. 10 and 15 minutes after the treatment, a sharp dilatation of the cervical ostium was observed, which reached 20 cm, by 30 minutes after it.

Moreover, on the same day, the udder appeared to be slightly increased in volume even if it was still too little for milking; on the 4\textsuperscript{th} day after surgery, the udder reached the shape and dimensions typical of lactation and the breeder referred that about 5 kgs of colostrum were milked at morning and evening milking, respectively.

From the 5\textsuperscript{th} day after the caesarean section onwards, the cow was regularly milked twice a day and in two days’ time, the amount of milk produced went on increasing until reaching, on the 15\textsuperscript{th} day after surgery, 10 kgs milk for milking.

**DISCUSSION AND CONCLUSION**

This paper illustrates a rare case of prolonged pregnancy in a dairy cow, due to theratogenesis. Microcephalia and pituitary agenesis have already been reported to induce prolonged gestation, since these alterations lead to the absence of adrenocorticotropic hormone (ACTH) release from the hy-
pophisis and, consequently, to the lack of foetal cortisol, ne-
cessary for the onset of calving\textsuperscript{4}.

Despite the clinical rarity encountered, the exceptionality of
the case relies on the innovative therapeutic approach consi-
ing the epidural route of administration of PGF 2\alpha, in ve-
terinary medicine. The cervical dilatation, the development
of the udder and the onset of lactation in 48 hours' time af-
ter the epidural PGF 2\alpha administration are, in the author's
opinion, results that go beyond the best perspective.

As to the former effect, PGF 2\alpha are known to contribute to
cervical ripening, both directly and indirectly\textsuperscript{12}. Prostaglan-
dins are in fact released, among other substances such as me-
talloproteinases, cell adhesion molecules and nitric oxide,
by those leukocytes invading the cervix at parturition and di-
rectly participate to the breakdown and remodeling of the
cervical tissue; furthermore, prostaglandins released by the
endometrium enhance myometrial contractility which in,
turn, promotes cervical dilatation at parturition\textsuperscript{12}.

The cervical dilatation observed within 48 hrs after the epi-
dural PGF 2\alpha administration may have been directly stimu-
lated by the substance which, in turn, once injected in the
epidural space at the sacro-coccygeal level, may have reached
the eminences of the hypogastric, pudendal and caudal
rectal nerve arising from L4-L5, S3-S4 and S4, respectively\textsuperscript{6}.
From these sites, PGF 2\alpha may have travelled, via a neurocri-
ne process, to the cervical nerve endings and, upon release
into the cervix, it may have triggered smooth cervical mus-
cle contraction, thus contributing to cervical softening and
ripening\textsuperscript{11}.

For what concerns the udder development and the onset of
lactation observed in this clinical case, it is conceivable that
the double epidural administration of PGF 2\alpha may have so-
mehow triggered prolactin release which is the pivotal factor
determining the development of the mammary gland and
lactogenesis, in the mammary gland of the cow. In this re-
gard, a brilliant in vivo research conducted on mares has re-
cently shown that PGF 2\alpha triggers prolactin synthesis and
not vice versa\textsuperscript{13}. Moreover it is noteworthy that in many spe-
cies, including the cow, the mammary gland is capable of
synthesizing prolactin\textsuperscript{14}.

Given these premises and given the clinical changes observed
in the udder, it is inferable that PGF 2\alpha might have directly
or indirectly driven the stimulation of the local synthesis of
prolactin. In the direct view, PGF 2\alpha might have reached the
nervous eminences of the ileo-hypogastric, ileo-inguinal, ge-
nitor-femoral and pudendal nerve at the level of the first
four lumbar vertebrae\textsuperscript{6} and have travelled along the respecti-
ve fibers by neurocri, to reach the udder. Once in the
mammary gland, PGF 2\alpha might have bound to its specific
receptors, triggering local prolactin synthesis and secretion
and, consequently, the development of the gland as well as
lactogenesis\textsuperscript{12}.

The indirect mechanism of action of PGF 2\alpha on the udder is
strictly related to the potential presence of Prostaglandin F
receptors in the dorsal horns of the spinal cord, as it has al-
ready been shown in the rat\textsuperscript{5}. In this view, upon epidural
administration and binding to its receptors\textsuperscript{15}, PGF 2\alpha might
have evoked the activation of the fibers innervating the udd-
er, thus leading to the propagation of the depolarization in-
to the mammary gland. The depolarizing effect that is ex-
pected to reach the udder upon PGF 2\alpha epidural adminis-
tration may evoke, in "endometrial-like fashion", local
PGF 2\alpha release and consequent prolactin synthesis\textsuperscript{14}.

Concluding, this case study is, to the best of the author's
knowledge, the first to describe the clinical efficacy of epidi-
ral PGF 2\alpha administration in inducing a sudden cervical di-
latation and udder development in dairy cows. Moreover,
hereby, some potential interpretations of these unexpected
data are traced, that need to be deepened to better under-
stand the mechanisms of action underlying this therapeutic
success.

**CONFLICT OF INTEREST**

The authors declare they do not have any conflict of interest.

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