Article preview

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Non-steroidal anti-inflammatory drugs at embryo transfer on pregnancy rates in cows: A meta-analysis

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Highlights

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  Present work highlights effect of NSAID at ET on pregnancy rates in cows.

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  NSAID treatment at ET was associated with a positive effect on pregnancy rates compared with no treatment.

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  NSAID at ET was relevant in cows with difficulty in passing the catheter from the cervix during ET.

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) at the time of embryo transfer (ET) are commonly used to improve pregnancy rates in cows. A meta-analysis was conducted on 16 trials from 9 publications involving control (n = 2335) and NSAID-treated (n = 2849) cows.

The meta-analysis explained the relative risk (RR) with its 95% confidence interval (CI) for pregnancy per embryo transfer (P/ET) after NSAID treatment under various circumstances. NSAID treatment with was associated on average with a 15% higher P/ET compared to no treatment (RR = 1.15, 95% CI = 1.07 to 1.2). The results also highlight that the use of NSAIDs at the time of ET was particularly effective in cows with difficulty in passing the catheter from the cervix during ET, with 71% more likely P/ET (RR = 1.71, 95% CI = 1.07 to 2.74) with the use of NSAIDs for these cows compared to other cows. The data were too limited to analyse the influence of NSAID molecules (flunixin meglumine [FM] and meloxicam), cyclooxygenase (COX) inhibitor type (non-selective COX inhibitor [both COX-1 and COX-2] and selective COX inhibitor [only COX-2]), embryo processing (embryo production, embryo conservation and embryo quality), stress, synchronization, breed and parity on the relationship between NSAIDs and P/ET.

Introduction

The most important bovine reproductive biotechnologies widely used to enhance genetic improvement in the cattle industry are artificial insemination (AI) and embryo transfer (ET). Artificial insemination allows genetically superior bulls to produce large numbers of progeny in a short interval. Embryo transfer enables genetically superior cows to likewise produce a large number of progeny in a short interval through transfer of their embryos into recipient females [1]. Embryonic mortality is recognized as a major issue in the dairy industry, as it decreases reproductive performance [2]. Embryonic loss, in part, is related to untimely secretion of prostaglandin (PG) F2α and premature luteolysis [3]. Several factors, such as transportation [4], heat stress [5,6], handling stress [7] and nutritional stress [8] promote PGF2α release and embryonic loss.

Embryo transfer requires stressful uterine manipulation for the recipient. Prostaglandins are increased during uterine manipulation and irritation, normally encountered with AI and ET techniques [9]. Excessive stimulation of the uterus by a high concentration of PGF2α during ET may contribute to early embryonic loss and upsets of implantation [10]. Bovine embryos are influenced by a high concentration of PGF2α in the uterine lumen which could negatively affect embryo viability and pregnancy rates [9,[11], [12], [13], [14], [15]]. Excessive manipulation during a difficult ET causes stress and can also cause inflammation in the recipient's genital tract. In addition to stress, prostanoid biosynthesis, including PGF2α, is significantly increased in inflamed tissue [16]. Prostaglandins are fatty acids derived from the metabolism of arachidonic acid by cyclooxygenase (COX), generating PGH2 and five other primary prostanoids: PGD2, PGE2, PGF2α, PGI2, and thromboxane A2 [17]. Cyclooxygenase, an evolutionarily conserved [18] bisfunctional enzyme, exists as two distinct isoforms, COX-1 or COX-2 [16]. COX-1 is a constitutively expressed enzyme responsible for maintaining protective and reparative mechanisms. Nevertheless, the adverse effects of NSAIDs that are not selective for COX type inhibition such as flunixin meglumine (FM) inhibit both COX-1 and COX-2, which likely accounts for most of the undesirable side-effects of NSAIDs such as gastrointestinal irritation, renal toxicity, and inhibition of blood clotting [19]. NSAIDs are designed to more specifically target the COX-2 isoform to avoid undesirable gastrointestinal side effects [20]. They inhibit uterine PGF2α release by COX inhibition. Nonsteroidal anti-inflammatory drugs act by competitively inhibition of the COX enzyme either non-selectively through both the COX-1 and COX-2 isoforms i.e., FM and ibuprofen or specifically through the COX-2 isoform i.e., meloxicam and carprofen [21]. Several investigations suggest that COX inhibitors such as ibuprofen [22], carprofen [23],

meloxicam [24,25] and FM [[26], [27], [28], [29], [30]] administered at the time of ET may enhance pregnancy per embryo transfer (P/ET).

The objective of this study was to analyse the association of NSAID treatments administered at ET with P/ET in recipient cows and to focus on factors that influence this relationship.

Section snippets

Literature search

Publications comparing NSAID-treated cows during ET to non-treated control cows were selected from the English-language literature through December 2020. The literature search was conducted in Google Scholar (http://scholar.google.com

), PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and Science Direct (http://www.sciencedirect.com

). The key words that were used separately or in various combinations for the search were cow, cattle, heifer, NSAID, embryo transfer, pregnancy, and rate. All of the

Results

The Begg and Mazumdar test ($P = 0.11$) indicated symmetry of the funnel plot. The radial and funnel plots did not suggest any publication bias (Fig. 2, Fig. 3). The treatment of recipients with NSAIDs at ET was associated with higher P/ET in 7 trials but no significant associations were observed in 9 trials. The estimated pooled effect size obtained with the random effect with no moderator (RR = 1.15, $P < 0.0001$) reported that the treatment was associated with 15% higher chances of P/ET compared

Discussion

The meta-analysis was conducted according to standard recommendations [31,33]. No publication bias was observed. Only the moderator cervix grade was significantly associated with the change in P/ET in cases of NSAIDs. For all other moderators, i.e., molecule, route of FM administration, COX inhibitor type, embryo conservation, quality and production, stress, recipient synchronization, breed and parity, no significant difference was observed in the association between using NSAIDs and P/ET for

Conclusion

Based on the information provided by the available studies, the treatment of recipients with NSAIDs at ET was an effective method to improve P/ET. The treatment was associated on average with 15% more likely P/ET compared with no treatment. The results also highlighted that the use of NSAIDs at ET is particularly relevant in recipients expected to have a grade II (difficult) cervix (cows with difficulty passing the catheter from the cervix during ET). To cope with limited data, larger-scale

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