Local Uterine Drug Delivery in a Mouse Model of Menstruation

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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and the antifibrinolytic medication tranexamic acid are the only non-hormonal medical treatments for heavy menstrual bleeding. They are effective, achieving up to 50% reduction in menstrual blood loss in women [1]. However, oral administration results in systemic side effects limiting their use in those with co-morbidities. Patient and Public Involvement (PPI) consultations have highlighted the patient's wishes to have at their disposal treatment options restricted to menses, as opposed to follow a continuous medication regime. We hypothesised that local delivery would be possible to maintain treatment efficacy and may limit off target effects.

MATERIAL AND METHODS

For the preparation of medicated cotton-pellets, ibuprofen (Ib) or tranexamic acid (TA) were first dissolved in ethanol or deionized water, respectively. Either 1.25 µl of Ib-stock (0.75 mg), 5 µl of TA-stock (0.75 mg) or 1.25 µl of Ib-stock + 5 µl of TA-stock were injected into a cotton-pellet and dried at ambient conditions. The drug release kinetics were monitored via UV/vis spectroscopy, mimicking physiological conditions with a phosphate buffered saline (PBS) solution (pH 4.0) at 37 ˚C.

Wild-type mice (C57BL/6JOlaHsd) underwent simulated menses after ovariectomy, sequential administration of exogenous oestradiol and progesterone and decidualisation via transcervical injection of oil. At the time of progesterone withdrawal, mice were fitted with cotton-pellets containing Ib, TA or both. Mice fitted with unmedicated cotton-pellets were used as controls. Uterine tissue was collected 8h ($t_{8,}$ endometrial breakdown) and 24h ($t_{24,}$ endometrial repair) after progesterone withdrawal. Endometrial breakdown/repair (histological grading) and menstrual blood loss (MBL, alkaline-haematin method) were quantified. Inflammatory mediators were examined by RT-qPCR.

RESULTS

To verify the benefits of local delivery of ibuprofen and tranexamic acid, medicated cotton-pellets were prepared by depositing the dissolved drugs onto the cotton fibers. After their drying, the resulting drug release kinetics in physiological conditions (PBS, pH 4.0 at 37 ˚C) revealed a different release behaviour for the two drugs: rapid full tranexamic acid release was monitored within 45 min, whereas a slow continuous ibuprofen release was observed. This can be attributed to the comparably low solubility of ibuprofen in aqueous solutions.

Local uterine delivery of ibuprofen and tranexamic acid revealed no significant differences in endometrial breakdown (t_8) or repair grade (t_{24}) compared to the unmedicated group. However, a trend towards enhanced repair was observed in the tranexamic only group at t_{24}, with 43.7% of mice reaching full repair compared to the 3.5% achieved in the unmedicated group. The amount of menstrual blood loss was not significantly different between the experimental groups, with trends of decreased MBL on Ib only (1.2±0.29µl) and TA only (1.08±0.57µl) compared to controls (2.7±1.38µl) at t_8. Inflammatory mediator mRNA showed no statistically significant differences between the

medicated tampons-treated mice compared to the unmedicated group. In conclusion, uterine drug delivery using medicated cotton-pellets is a feasible strategy for local drug administration in our mouse model of simulated menses.

[1] Maybin JA, Critchley HO. Medical management of heavy menstrual bleeding. Womens Health (Lond). 2016 Jan;12(1):27-34. doi: 10.2217/whe.15.100.