Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol18Issue1abst222P.pdf

Comparison of general anaesthetic regimens on pulmonary and liver metastasis post-tumour resection surgery in a murine model of breast cancer

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Introduction: Breast cancer accounts for 7% of female cancer deaths[1]. While surgery is the mainstay of treatment, perioperative interventions, such as anaesthesia, may influence risk of metastasis during breast tumour resection[2]. However, no conclusive, prospective clinical or pre-clinical studies have been completed. Here, in the 4T1 model of breast cancer, we investigated the effects of sevoflurane, ketamine and xenon anaesthesia, as well as IV lidocaine, on metastatic burden and serum cytokines post-tumour resection surgery.

Method: Female BALB/c mice were injected with $2.5x10^4$ 4T1 tumour cells in the right inguinal mammary fat-pad. After 7 days, the resultant tumour was excised. Two concurrent studies were carried out investigating the effects of anaesthetics on breast cancer metastasis. The first compared sevoflurane (5% induction, 2-3% maintenance), intraperitoneal ketamine (100mg/kg)/xylazine (0.1mg/kg), sevoflurane (5% induction, 2-3% maintenance)/ketamine (50mg/kg)/xylazine (0.05mg/kg), or xenon (70% xenon, 30% O_2)/ketamine (50mg/kg)/xylazine (0.05mg/kg) anaesthesia. The second compared IV lidocaine (via tail vein cannulation, 1.5mg/kg bolus followed by a continuous infusion of 2mg/kg/hr) to sterile saline in mice anaesthetised with sevoflurane or ketamine/xylazine (administered as above). Sevoflurane was carried in a 30%O_2 70%N_2 gas mix and mice anaesthetised with ketamine/xylazine also received this gas mix. Ketamine/xylazine and lidocaine were solubilised in sterile saline. Fourteen days post-surgery, animals were culled, organs harvested and lung and liver specimens were examined for metastasis via the method described in Pulaski and Ostrand-Rosenberg[3]. Pro-inflammatory and pro-metastatic cytokines were profiled using a slide-based array (RayBiotech) in post-mortem serum.

Results: Inclusion of peri-operative lidocaine reduced lung metastatic colony count versus sevoflurane with saline (median (IQR)), 0(0-2) vs 22.5(0-481), p=0.02 (Mann-Whitney U test), n=21 and reduced the proportion of animals with pulmonary metastasis, (28.5% vs 52.5%, p=0.04 (Chi-squared analysis with Yeates correction; n=21). There was no significant change in metastasis between mice anaesthetised with sevoflurane, ketamine/xylazine, sevoflurane/ketamine/xylazine, or xenon/ketamine/xylazine general anaesthesia ($10 \geq n \leq 12$) (Mann-Whitney U test). Serum analysis demonstrated reduced pro-inflammatory and angiogenic cytokine expression in animals receiving lidocaine with sevoflurane and a slight reduction in G-CSF in ketamine-treated animals compared with sevoflurane (n=3) (ANOVA with post-hoc Bonferroni correction).

Conclusions: In this 4T1 murine model of breast cancer, lidocaine decreased pulmonary metastasis, when combined with sevoflurane anaesthesia. However, choice of general anaesthetic did not influence post-surgical metastasis to the liver or lungs.

References:

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