Therapeutic potential of extracellular vesicles in preclinical stroke models: a systematic review & meta-analysis

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BACKGROUND
Stroke is a global health problem, responsible for 6.7 million deaths annually, and resulting in disabilities in a third of survivors. Currently there is a paucity of clinically available regenerative therapies for stroke. Extracellular vesicles (EVs) are nanoscale membrane-bound vesicles which carry cargoes including DNA, RNA and proteins that are involved in intercellular signalling. Since 2013, EVs have been investigated for their potential as modulators of regeneration in the post-stroke brain, using preclinical stroke models. Our review aimed to provide a summary of the efficacy of therapeutic EVs in these studies, to inform future research in this emerging field.

METHODS
- Studies were identified by a comprehensive literature search of two online sources and subsequent screening (Figure 1). Studies using lesion volume or neurological score as outcome measures were included.
- Standardised mean difference (SMD) and 95% CIs were calculated using a restricted maximum likelihood random effects model.
- Publication bias was assessed with Egger’s regression and presented as funnel plots with trim and fill analysis.
- Subgroup analysis was performed to assess the effects of different study variables.
- Study quality and risk of bias were assessed using the CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) checklist.

RESULTS & DISCUSSION
20 publications were included in the systematic review, with a median score of 7 on the CAMARADES checklist (Figure 2). Of these, 19 studies with 43 comparisons were assessed in the meta-analysis, finding that EVs reduced stroke lesion volume, as shown by the forest plot in Figure 3 (SMD -1.95, CI -2.72, -1.18). Publication bias for lesion volume is presented in Figure 4a, with asymmetry confirmed by Egger’s regression test (p<0.0001). Trim and fill analysis predicted there are seven unpublished studies with neutral or negative impacts on lesion volume (Figure 4b) which when accounted for, reduced the effect size from -1.95 to -1.05.

CONCLUSIONS
EV-based interventions had positive impacts on brain damage in preclinical stroke models. These data are undermines by high risk of publication bias and limitations in study design including allocation concealment. However, given their efficacy across studies with notably different treatment regimens, the positive effects of EVs may be wide ranging in the contexts of neuroprotection, repair and regeneration. Thomas JM, Cunningham CJ, Lawrence CB, et al. Therapeutic potential of extracellular vesicles in preclinical stroke models: a systematic review and meta-analysis. Open Science 2020;e100047. doi: 10.1136/ijorf-2019-100047