The potential of biomaterial-based approaches as therapies for ischaemic stroke: a systematic review and meta-analysis

Faye Bolan, Irene Louca, Calvin Heal and Catriona J. Cunningham
Faculty of Biology, Medicine and Health, University of Manchester, AV Hill Building, Oxford Road, Manchester, M13 9PT
catriona.cunningham@manchester.ac.uk Twitter: @RegenMedCat

Background

Stroke is a global health problem with limited treatment options. There is currently great interest in the development of biomaterial-based therapies to promote brain repair and functional recovery. A broad range of strategies have been investigated including nanoparticles or liposomes as delivery vehicles and scaffolds as structural support for tissue regeneration. However, no systematic review and meta-analysis has been conducted assessing the efficacy of these approaches.

Methods

Studies were identified by searching electronic databases (PubMed, Web of Science) and reference lists of relevant reviews. Studies reporting infarct volume (brain damage) and/or neurological score as outcome measures were included. The CAMARADES (Collaborative Approach to Meta-analysis and Review of Animal Data in Experimental Studies) checklist was used to assess study quality. Standardised mean difference (SMD) and 95% confidence intervals were calculated using DerSimonian and Laird random effects. Publication bias was then visualised by funnel plots followed by trim and fill analysis of "missing" publications.

Results

Sixty six publications were assessed in the systematic review (Figure 1). The median CAMARADES checklist score was 5.5/10 (IQR 4.25-6). In particular, reporting of blinding (50%) and randomisation (35%) was low (Figure 2).

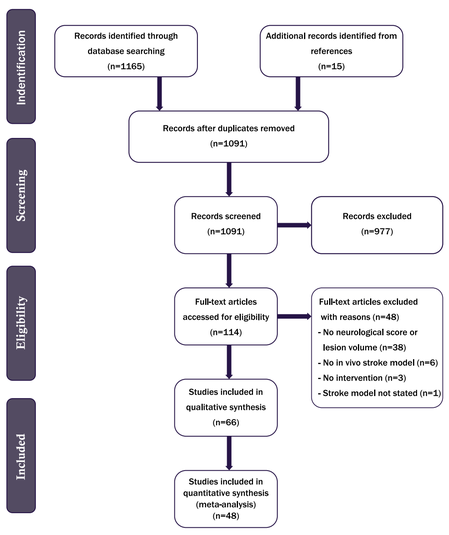

Figure 1: Flow chart summarising the search strategy and number of included studies.

CAMARADES Checklist Item	Overall	Scaffolds	Particles
(1) Peer-reviewed publication (%)	100	100	100
(2) Control of temperature (%)	50	42.1	53.2
(3) Random allocation to treatment or control (%)	56.1	52.6	57.4
(4) Blinded induction of ischaemia (%)	34.9	42.1	31.9
(5) Blinded assessment of outcome (%)	50	52.6	48.9
(6) Use of anaesthetic without significant intrinsic neuroprotective activity (%)	83.3	89.5	80.9
(7) Animal model (aged, diabetic or hypertensive) (%)	3	0	4.26
(8) Sample size calculation (%)	9.1	15.8	6.4
(9) Compliance with animal welfare regulations (%)	93.9	89.5	95.7
(10) Statement of potential conflict of interests (%)	62.1	73.7	57.4
Median quality (/10) (IQR)	5.5 (4.25-6)	6 (4-7)	5 (4-6)

Figure 2: CAMARADES checklist scores.

Forty eight publications (88 comparisons) were then assessed in the meta-analysis. As shown in Figure 3, biomaterial-based interventions reduced stroke infarct volume (SMD: -1.98, 95% CI: -2.63, -1.34).

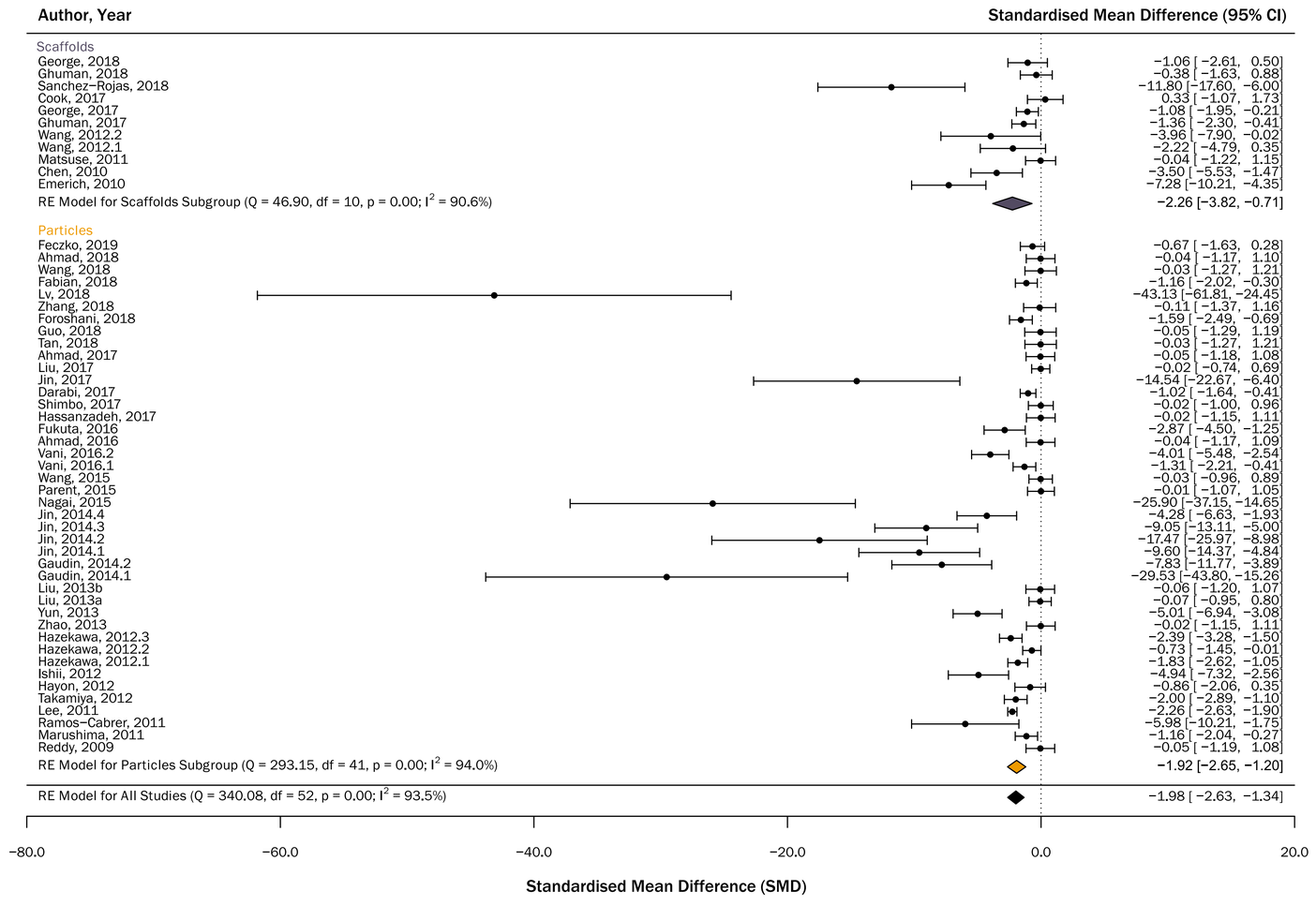

Figure 3: Effect sizes for biomaterial-based interventions on lesion volume. Forest plot of standardised mean difference (SMD) and 95% CI.

There was pronounced asymmetry in the funnel plot (Figure 4) indicating publication bias. Furthermore, trim and fill analysis estimated there were 25 unpublished studies reporting negative or neutral infarct volume data which, when adjusted for, reduced the effect size to -0.40 (95% CI: -1.57, 0.77; Figure 4B).

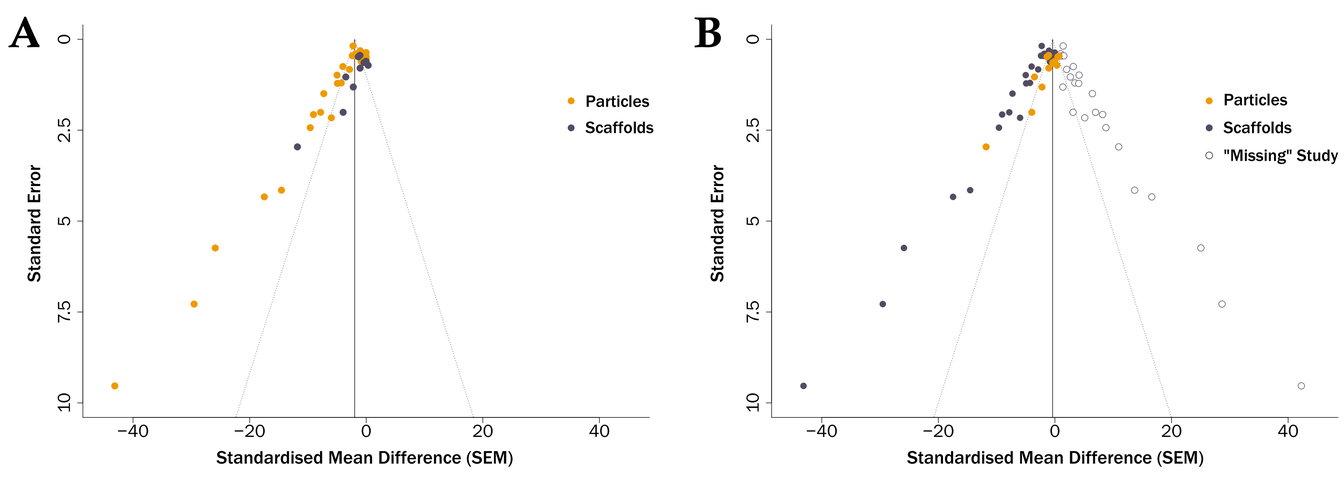

Figure 4: Funnel plot (A) of infarct volume outcome. Trim and fill analysis (B) showing estimated unpublished studies (unfilled circles). The solid vertical line indicates the adjusted effect size.

Conclusions

Biomaterial-based interventions decreased brain damage in preclinical stroke models. However, these data are undermined by the high risk of publication bias and limitations in study design including lack of blinding. Our study highlights the need to improve study design and reporting to aid the translation of biomaterial-based therapies to the clinic.

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