The effect HBOC-201 and sodium nitrite resuscitation after uncontrolled haemorrhagic shock in swine.

Background: Development of Haemoglobin-based oxygen carriers (HBOCs) as blood substitutes has reached an impasse due to clinically adverse outcomes attributed to vasoconstriction secondary to nitric oxide (NO) scavenging. Studies suggest haemoglobin exhibits nitrite reductase activity that generates NO and N(2)O(3); harnessing this property may offset NO scavenging. Therefore, the effects of concomitantly infusing sodium nitrite (NaNO(2)) with HBOC-201 were investigated.

Methods: Swine underwent uncontrolled liver haemorrhage before receiving up to three 10min 10ml/kg infusions of HBOC-201 (HBOC) with or without concurrent NaNO(2) (5.4μmol/kg [LD NaNO(2)] or 10.8μmol/kg [HD NaNO(2)]) or 6% Hetastarch (HEX) with or without HD NaNO(2) during "prehospital" resuscitation (15, 30 and 45min after injury). Definitive surgical care occurred at 75min; anaesthetic recovery at 120min. Animals were euthanised at 72h.

Results: NaNO(2) temporarily reduced systemic and pulmonary blood pressure increases from HBOC in a dose-dependent fashion. There was no significant effect between groups in indices of tissue oxygenation or survival. Adverse clinical signs requiring humane euthanasia occurred with highest frequency after HBOC+HD NaNO(2) (3 of 4 pigs) and HBOC+LD NaNO(2) (2 of 4 pigs). Gross evidence of pulmonary congestion was observed in 5 of 8 swine.
receiving a HBOC and NaNO(2) combination compared to 1 of 16 swine receiving HBOC alone, HEX alone, or HEX+NaNO(2). Gross lesions correlated with histological evidence of pulmonary oedema and congestion, and in 2 of 4 HBOC+HD NaNO(2) pigs, pulmonary fibrin thrombi also were found. No other pig had similar evidence of thrombi. Asymmetric pre-resuscitation cardiac index was a potential confounder.

**CONCLUSIONS:** A significant interaction between NaNO(2) and HBOC-201 ameliorated HBOC-201 vasoconstrictive effects, consistent with HBOC possessing a nitrite reductase activity that generates vasodilator NO equivalents. Results were relatively equivalent in survival and markers of tissue oxygenation. The highest dose of NaNO(2) was the most effective in reducing HBOC-associated pulmonary and systemic vasoactivity but also with the highest incidence of adverse events. In this model, the transient nature of NaNO(2) in off-setting HBOC-201 vasoconstriction makes it less clinically promising than anticipated and the combination of NaNO(2) and HBOC appear to increase the risk of pulmonary complications in a dose-dependent fashion independently of haemodilutional effects on haemostatic components.