The UK resuscitative endovascular balloon occlusion of the aorta in trauma patients with life-threatening torso haemorrhage: the (UK-REBOA) multicentre RCT

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Scientific summary

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Scientific summary

Background

Trauma is a major cause of death and disability. Trauma (physical injury) disproportionately affects the young, killing those who might otherwise have lived long and productive lives. The most common cause of *preventable* death after injury is haemorrhage. The addition of resuscitative endovascular balloon occlusion of the aorta (REBOA) to current standard care is intended to provide earlier, temporary haemorrhage control, to facilitate transfer to an operating theatre or interventional radiology suite, for definitive haemostasis.

Objectives

The UK-REBOA trial was a pragmatic, multicentre, Bayesian, open-label, group-sequential, parallel-group randomised controlled trial comparing standard care plus REBOA versus standard care in patients with exsanguinating haemorrhage in the emergency room. The study included an elicitation exercise, an embedded mixed-methods process evaluation and a health economic evaluation.

The primary clinical outcome was 90-day mortality (defined as death within 90 days of injury, before or after discharge from hospital).

Secondary clinical outcomes included 3-, 6- and 24-hour mortality, in-hospital mortality, 6-month mortality, length of stay (in hospital and intensive care unit), 24-hour blood product use, need for haemorrhage control procedures (operation or angioembolisation), time to commencement of haemorrhage control procedure, complications/safety data and functional outcome [measured using the extended Glasgow Outcome Scale (GOS-E)] at discharge.

Economic outcomes were 6-month (within trial) and lifetime (modelled) UK NHS perspective costs, life-years and quality-adjusted life-years (QALYs) [calculated using EuroQol Group's 5-dimension health status 5-level questionnaire (EQ-5D-5L)], 6-month quality of life (measured using EQ-5D-5L).

Methods

Trauma patients were recruited in 16 UK major trauma centres. Trauma patients aged (or believed to be aged) 16 years or older, with confirmed or suspected life-threatening torso haemorrhage thought to be amenable to adjunctive treatment with REBOA were eligible. Women known (or thought to be) pregnant and those with injuries deemed unsurvivable were excluded.

The trauma team leader assessed the patients for eligibility. Patients who were eligible for inclusion in the trial were incapacitated and unable to give consent at the time of eligibility assessment and randomisation. There was also not sufficient time to consult a surrogate decision-maker, or even an independent medical practitioner, for advice about including the patient. Enrolment therefore took place without prior consent following Research Ethics Committee approval for this approach. Consent for continuing participation (i.e. data collection) was sought by a member of the UK-REBOA trial team once patients were no longer in a critical condition (defined as being cared for in a ward area rather than an intensive care unit or high-dependency unit) or from a personal (or nominated professional) consultee.

The trauma team leader enrolled the participant using a dedicated, secure website, available on a handheld device (smartphone, tablet) or desktop computer which is linked directly to the 24-hour

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randomisation system at the Centre for Healthcare Randomised Trials, based in the Health Services Research Unit, University of Aberdeen. Patients were randomised into one of the two intervention arms, in a 1 : 1 allocation ratio, in randomly generated blocks of two or four.

Standard care: Patients allocated to the control group received 'standard care', as expected in a specialist major trauma centre. Such treatment typically included intubation, blood transfusion including blood products in a 1 : 1 : 1 ratio, interventions such as tourniquet application, and early operative or endovascular haemorrhage control. Treatment could also have included open aortic occlusion of the thoracic or abdominal aorta.

Standard care plus REBOA: Patients allocated to this arm of the trial additionally received the technique of endovascular aortic occlusion, for the purpose of resuscitation, as part of an overall treatment strategy. The addition of REBOA to current standard care was intended to provide earlier, temporary haemorrhage control, to facilitate transfer to an operating theatre or interventional radiology suite for definitive haemostasis. The trial sought to evaluate the *technique* of REBOA rather than a specific brand of device, and therefore permitted the use of any licensed occlusion balloon, and did not prescribe or mandate a particular product. The trial had an integrated training programme to ensure familiarity with the REBOA procedure.

In patients who had been randomised to the standard care plus REBOA arm of the trial, clinicians could decide not to insert the balloon occlusion device if: the patient's haemodynamic status improved (as a result of other resuscitative measures), if they were deemed to no longer have life-threatening torso haemorrhage requiring adjunctive treatment with REBOA; they deteriorated (to the point of imminent death); or there was technical difficulty in obtaining arterial access, and it was felt that operative control of haemorrhage could be obtained more quickly.

The data collection strategy for the UK-REBOA trial was designed to minimise the burden on participants and clinicians, and for the avoidance of duplication. The randomisation system collected balloon inflation/deflation times. The trial drew on routinely collected data, primarily from the Trauma Audit and Research Network (TARN) registry which includes demographic, injury, treatment and outcome data (including the GOS-E and EQ-5D-5L). Mortality and hospital resource use data were also sought from NHS Digital.

The main analysis was based on the intention-to-treat principle. There were two planned interim analyses of survival and a final analysis of all outcomes after follow-up was complete. Baseline and follow-up data were summarised using descriptive statistics and graphical summaries. Treatment effects are presented with 95% credible intervals for the primary and secondary outcomes.

Elicitation exercise

An elicitation exercise involving 20 subject matter experts (12 emergency medicine physicians, 3 pre-hospital care doctors, 4 surgeons and 1 intensivist) was undertaken to derive prior probability distributions to help contextualise the interpretation for the primary and secondary outcomes of the trial. Subject matter experts, on average, estimated in-hospital and 90-day mortality in this patient group, without the use of REBOA, to be in excess of 50%. Mortality at earlier time points (6 and 24 hours) was estimated to be closer to 25%. The elicited data, and the resulting prior probability distributions, indicate that the experts, on average, had a favourable opinion of REBOA, that is they expect the addition of REBOA to standard care to improve mortality at all time points.

Clinical results

Sixteen recruitment sites were opened in a staggered manner. Recruitment commenced in October 2017, was halted in March 2020 due to COVID-19, and restarted in July 2020. The second interim analysis (including 80 participants) triggered one of the pre-specified stopping rules, and recruitment closed in March 2022, by which time 90 participants had been recruited.

Forty-four participants were randomised to standard care (2 of whom did receive REBOA) and 46 were randomised to standard care plus REBOA (19 of whom had the catheter inserted and balloon inserted and the remaining 27 progressed to different time points along this pathway). The groups were well-matched in terms of age, gender, comorbidities, mechanism of injury and injury severity. In the standard care arm, the median age was 39 years (interquartile range 30–56 years) and 77% were male. In the standard care plus REBOA arm, the median age was 46 years (interquartile range 33–62) and 61% were male. The median Injury Severity Score in both arms was 41 (interquartile range 29–50), with the majority classed as having very severe injury.

Of the 46 patients allocated to standard care plus REBOA treatment, 25 (54%) died within 90 days. Of the 43 standard care patients for whom primary outcome data are available, 18 (42%) died within 90 days. Using the minimally informative prior, the odds of 90-day mortality were 1.58 for patients allocated to the standard care plus REBOA arm (95% credible interval 0.72 to 3.52). The posterior probability of an odds ratio > 1 (i.e. that REBOA was harmful) was 86.9%. The direction of the estimate did not change when an enthusiastic (the elicited) prior was used or when the estimate was adjusted for baseline characteristics. For the secondary outcomes (3-, 6- and 24-hour mortality), the posterior probability that REBOA was harmful was higher than for the primary outcome. Additional analyses to account for intercurrent events did not change the direction of the estimate for mortality at 3, 6 and 24 hours, at 90 days or 6 months, or in-hospital mortality.

Death due to haemorrhage was more common in the standard care plus REBOA group than in the standard care group. The mean number of days spent in intensive care and in hospital were lower in the standard care plus REBOA group compared to the standard care group, partly because of the higher number of earlier deaths in the standard care plus REBOA arm.

There were no serious adverse device effects.

Health economics

We costed individual components of resources and summed these to generate a total cost for the whole initial hospitalisation admission period. Total NHS resource use for the index hospitalisation was obtained from patient-level data in TARN and the key resource use variables for costing included time of arrival, time of emergency department departure, time of first operation, time of death/discharge, number and type of operative procedures and volume of blood transfusions that were required. Secondary care contacts and episodes of care that were commenced between the date of discharge from the index hospitalisation through 6 months post randomisation were sourced, where available, through linkage of patient records to the Hospital Episode Statistics database. All costs are reported from a UK NHS perspective in Great British pounds (GBP) (year 2020-1).

Quality of life was measured using the EQ-5D-5L prior to patient's discharge from their index hospitalisation and at 6 months post admission. EQ-5D-5L asks respondents to report any problems on a given day across five dimensions of mobility, self-care, usual activities, anxiety/depression and pain. The data were available from TARN and supplemented with data collected by the local trial teams. EQ-5D-5L data were cross-walked to the 3L version and valued using UK general population preference tariffs. Baseline utility was set equal to the unconscious state (−0.402) and utility following death was

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set to 0. QALYs were calculated using an area under the curve approach assuming linear extrapolation between time points.

From the within-trial health economic analysis, participants in the standard care plus REBOA arm of the study incurred lower costs {index hospital admission: mean cost £57,384 [standard deviation (SD) £62,863]} compared to those in standard care [mean cost £116,064 (SD £128,957)]. Lower costs in the standard care plus REBOA arm of the study were mainly due to lower use of hospital resources (length of stay, etc.) due to the competing risk of death (i.e. a higher number of deaths in the REBOA plus standard care group). Similarly, life-years accrued and QALYs over 6 months post randomisation were also lower in standard care plus REBOA compared to standard care due to a greater proportion of trial participants dying, with mortality also occurring earlier in the follow-up period for the REBOA arm. The mean life-years gained in the standard care plus REBOA arm was 0.232 (SD 0.247) compared to 0.305 (SD 0.236) in the standard care arm.

When modelled over a full lifetime horizon, standard care plus REBOA is less costly (probability 99%), due to the competing risk of mortality but is also substantially less effective in terms of QALYs accrued over a lifetime horizon (probability 91%). The findings are robust to a range of scenario analyses undertaken, with the probability of standard care being the optimal treatment strategy ranging from 66% to 81% at a threshold value of a QALY = £50,000.

Process evaluation

The process evaluation was conducted in two phases; both phases involved interviews with clinical and research staff based at recruitment sites. Phase 1 was designed to identify barriers during trial initial and set-up; Phase 2 focused on exploring barriers and facilitators of recruitment into the trial and intervention delivery. A behavioural framework was used in Phase 2 to direct analysis and generate solutions designed to enhance trial practices, which included regular online meetings between the principal investigators from each site, updates to training materials and delivery, and e-mail/Twitter feedback on recruitment activity.

Conclusions

This is the first randomised trial ever to be conducted examining the potential clinical effectiveness of REBOA for the management of exsanguinating haemorrhage. All the analyses conducted suggest with high probability that a strategy of standard care plus REBOA is harmful.

Implications for health care: The continuing use of REBOA, at least in the UK in-hospital setting, should be re-evaluated.

Implications for research: The role (if any) of REBOA in the pre-hospital setting remains unclear. Further research to clarify its potential (or not) may be required.

Trial registration

This trial is registered as ISRCTN16184981.

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