Heparin versus citrate anticoagulation for continuous renal replacement therapy in intensive care: the RRAM observational study

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Declared competing interests of authors: Peter J Watkinson was the Chief Medical Officer for Sensyne Health plc (Oxford, UK) and holds shares in the company, and has received grant funding from the National Institute for Health Research (NIHR), Wellcome Trust and Sensyne Health plc outside the submitted work. He was also a member of the NIHR Health Technology Assessment (HTA) European Economic and Social Committee (EESC) Methods Group, NIHR HTA EESC Panel and the NIHR, HTA Programme, Prioritisation Committee and methods group: Hospital based care (B), previously HTA Elective and Emergency Specialist Care Panel (April 2015–November 2019) and NIHR Invention for Innovation Product Development Awards Panel (2018–present). Lui Forni has received grant funding from Baxter International Inc. (Deerfield, IL, USA) outside the submitted work. Fergus Caskey has received honoraria from Baxter International Inc. outside the submitted work. Kathryn M Rowan was a member of the NIHR Health and Social Care Delivery Research Board (2014–19). J Duncan Young was a consultant advisor for the NIHR Efficacy and Mechanism Evaluation (EME) programme and a member of the NIHR EME Funding Committee, NIHR EME Sub-Group Remit Check and NIHR EME Strategy Advisory Committee during the conduct of the study (October 2012–December 2019).

Published February 2022
DOI: 10.3310/ZXHI9396

Scientific summary

The RRAM observational study

Health Technology Assessment 2022; Vol. 26: No. 13
DOI: 10.3310/ZXHI9396

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Scientific summary

Background

Acute kidney injury is common in critically ill patients being treated in an intensive care unit. In the UK, approximately 50% of all patients admitted to an intensive care unit have acute kidney injury and 10% of all admitted patients require renal replacement therapy, which aims to prevent harm from electrolyte and metabolic disturbances as well as fluid overload. The vast majority (> 95%) of these patients receive continuous renal replacement therapy, which requires anticoagulation in both the blood and the machine to prevent clotting. Over the last decade, conventional systemic heparin anticoagulation has started to be replaced by regional citrate anticoagulation for continuous renal replacement therapy, which has gone from being rarely used to being used in > 50% of ICUs. However, this shift towards regional citrate anticoagulation for continuous renal replacement therapy is occurring with little comparative evidence of safety or longer-term clinical effectiveness and cost-effectiveness.

Aims and objectives

Aim

The aim of the Renal Replacement Anticoagulant Management (RRAM) study was to evaluate the clinical and health economic impacts of moving from systemic heparin anticoagulation to regional citrate anticoagulation for continuous renal replacement therapy in patients treated by non-specialist intensive care units in England and Wales.

Objectives

The RRAM study addressed the following objectives:

- investigate the benefits, risks and costs of regional citrate anticoagulation compared with systemic heparin anticoagulation
- compare the long-term development of end-stage renal disease between regional citrate anticoagulation and systemic heparin anticoagulation
- establish efficient research techniques that, if successful, could be used to track the effects of any change in critical care practice occurring in intensive care units in England and Wales over a reasonably short timescale.

Methods

Study design and governance

The RRAM study was an observational comparative effectiveness study utilising existing data sources to address the clinical effectiveness and cost-effectiveness of the change to regional citrate anticoagulation for continuous renal replacement therapy in UK intensive care units. We received approvals from the South Central – Oxford B Research Ethics Committee, Health Research Authority and Confidentiality Advisory Group for the use of identifiable patient data without consent under Section 251 of the NHS Act 2006 (Great Britain. *National Health Service Act 2006*. Chapter 41, Part 13, Patient Information, Section 251. London: The Stationery Office; 2006.). The National Institute for Health Research convened a majority independent Study Steering Committee. The trial was sponsored by the Intensive Care National Audit & Research Centre and co-ordinated by the Intensive Care National Audit & Research Centre Clinical Trials Unit.

Interventions

Patients who received regional citrate anticoagulation for continuous renal replacement therapy (exposure)

Patients receiving continuous renal replacement therapy in an intensive care unit after the date on which the intensive care unit completed the transition from systemic heparin anticoagulation to regional citrate anticoagulation.

Patients who received systemic heparin anticoagulation for continuous renal replacement therapy (comparator)

Patients receiving continuous renal replacement therapy in an intensive care unit before the date on which the intensive care unit indicates that it started to transition from systemic heparin anticoagulation to regional citrate anticoagulation, or patients receiving continuous renal replacement therapy in an intensive care unit that had not transitioned to regional citrate anticoagulation.

Inclusion and exclusion criteria

Patients were eligible for inclusion if they:

- were aged $\geq$ 16 years
- had been admitted to an adult general intensive care unit in England or Wales participating in the Intensive Care National Audit & Research Centre Case Mix Programme between 1 April 2009 and 31 March 2017
- had received continuous renal replacement therapy in an intensive care unit, identified by the recording of renal support, as defined by the Critical Care Minimum Data set on at least 1 calendar day during the intensive care unit stay.

Patients were excluded if they:

- had pre-existing end-stage renal disease, identified by the recording of a requirement for chronic renal replacement therapy for end-stage renal disease in the Intensive Care National Audit & Research Centre Case Mix Programme data set
- had been admitted to an intensive care unit after kidney or multiorgan (including kidney) transplantation
- had been admitted to an intensive care unit with acute hepatic failure.

Outcomes

Primary effectiveness outcome

The primary effectiveness outcome was all-cause mortality 90 days after the first intensive care unit admission in which continuous renal replacement therapy was received.

Primary economic outcome

The primary economic outcome was incremental net monetary benefit gained at 1 year at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year associated with a change from systemic heparin anticoagulation to regional citrate anticoagulation during continuous renal replacement therapy.

Secondary outcomes

The secondary outcomes were:

- all-cause mortality at hospital discharge, 30 days and 1 year after intensive care unit admission
- days of renal, cardiovascular and advanced respiratory support while in an intensive care unit
- bleeding episodes during intensive care unit stay
- thromboembolic episodes occurring within 90 days after ultimate hospital discharge
- intensive care unit and hospital length of stay
- development of new, treated end-stage renal disease at 1 year after intensive care unit admission
- estimated lifetime incremental net benefit associated with a change from systemic heparin anticoagulation to regional citrate anticoagulation during continuous renal replacement therapy.

Data sources and linkage

Clinical effectiveness

We identified a cohort of patients who received continuous renal replacement therapy for acute kidney injury in an intensive care unit in England or Wales between 1 April 2009 and 31 March 2017 from the Intensive Care National Audit & Research Centre Case Mix Programme national clinical audit database. NHS Digital, acting as a 'trusted third party', used NHS numbers to link individual patient data with the UK Renal Registry, Hospital Episode Statistics (for England) and Civil Registrations data sets. To obtain data on patients admitted to hospitals in Wales, we undertook data linkage between Intensive Care National Audit & Research Centre Case Mix Programme and Patient Episodes Database for Wales data separately following a similar methodology, with the NHS Wales Informatics Service acting as a trusted third party. These data were combined with a survey of anticoagulation practices for continuous renal replacement therapy in intensive care units in England and Wales participating in the Intensive Care National Audit & Research Centre Case Mix Programme to separate the cohort into systemic heparin anticoagulation and regional citrate anticoagulation groups according to the mode of anticoagulation in use at the time of their admission to intensive care.

Health economics and quality of life

Micro-costing task analysis

We conducted a micro-costing task analysis of continuous renal replacement therapy using systemic heparin anticoagulation and regional citrate anticoagulation at eight intensive care units that were selected to represent different anticoagulation modes and manufacturer systems. At each site we conducted a cognitive 'walk-through' with clinicians that included a hierarchical task analysis of the set-up and running of continuous renal replacement therapy, which allowed for staff time and consumables for each task to be estimated.

Continuous renal replacement therapy system set-up time and frequency

Continuous renal replacement therapy system set-up time and the frequency of system failures were estimated from anonymised electronically held individual patient data from the Post-Intensive Care Risk-Adjusted Alerting and Monitoring study and from the electronic clinical information system for patients treated in Oxford, UK, during 2015–17.

Intensive care unit, hospital and longer-term costs

Unit costs of intensive care unit/hospital length of stay and dialysis were obtained from *NHS Reference Costs 2017–18* [Department of Health and Social Care (DHSC). *NHS Reference Costs 2017–18*. London: DHSC; 2018]calculated as a total cost per patient to 1 year following the index intensive care unit admission. The cost of renal replacement therapy for end-stage renal disease was also estimated for patients identified from the UK Renal Registry as having end-stage renal disease treated using renal replacement therapy, dependent on the mode of renal replacement therapy and time to transplant, where applicable.

Health-related quality of life and quality-adjusted life-years

EuroQol-3 Dimensions, three-level version, health-related quality-of-life data for patients at 3 months and 1 year after intensive care unit discharge were obtained from the 8000-patient UK Intensive Care Outcome Network study [(Young D, Barber V, Harrison D, Watkinson P. The effect of postal questionnaire burden on response rate and answer patterns following admission to intensive care: a randomised controlled trial. *BMC Med Res Methodol* 2017;**17**:49.)]. Eligible patients meeting the inclusion criteria were identified and divided into quartiles of age. Averaged EuroQol-3 Dimensions, three-level version-based utility weights were calculated by quartile at 3 months and 1 year, and these were used as the measure of health-related quality of life. All patients developing end-stage renal disease and requiring dialysis were assigned an appropriate utility weight based on European norms from the date of first renal replacement therapy for end-stage renal disease forward. Health-related quality of life data at 3 months and 1 year were then combined with the survival data to calculate quality-adjusted life-years at 1 year.

Data analysis

Clinical effectiveness

To assess clinical effectiveness, we conducted an analysis of individual patient data following techniques based on interrupted time series analysis, where the interruption corresponds to the change from systemic heparin anticoagulation to regional citrate anticoagulation for continuous renal replacement therapy. Random-effects multilevel generalised linear models (patients nested within intensive care units) were used to estimate the intensive care unit-level effect of transitioning to regional citrate anticoagulation on trends in patient-level outcomes. Logistic models were used for binary outcomes and linear models were used for continuous outcomes. The study includes periods both before and after the switch from systemic heparin anticoagulation to regional citrate anticoagulation in individual intensive care units and a comparator group of intensive care units that did not change anticoagulation mode. The primary impact model for the effect of the change from systemic heparin anticoagulation to regional citrate anticoagulation allowed for a change in both level and slope. Results of the regression models are reported as the odds ratio (or, for continuous outcomes, difference in means), with 95% confidence interval for the change in level, and the odds ratio per year (or difference in means per year), with 95% confidence interval for the change in slope associated with the change from systemic heparin anticoagulation to regional citrate anticoagulation.

Cost-effectiveness

The cost-effectiveness analysis reports the mean (with 95% confidence interval) incremental costs and quality-adjusted life-years at 1 year associated with a change from systemic heparin anticoagulation to regional citrate anticoagulation for continuous renal replacement therapy, overall and for prespecified subgroups. Incremental net monetary benefit at 1 year associated with a change from systemic heparin anticoagulation to regional citrate anticoagulation was estimated, valuing incremental quality-adjusted life-years in accordance with a National Institute for Health and Care Excellence-recommended willingness-to-pay threshold for a quality-adjusted life-year gain (£20,000) and by subtracting the incremental costs. The incremental net monetary benefit calculation assumed no correlation between costs and quality-adjusted life-years; a single-level, bivariate, seemingly unrelated regression model for costs and quality-adjusted life-years indicated that the impact of not accounting for correlation would be small and conservative (≈ 3% increase in standard error of incremental net monetary benefit). The cost-effectiveness analysis projected lifetime cost-effectiveness by encapsulating the relative effects of the alternative strategies on long-term survival and health-related quality of life, combining extrapolations from the patient survival data with external evidence on long-term survival and health-related quality of life. Lifetime costs were projected by applying morbidity costs associated with use of dialysis for end-stage renal disease over the lifetime. 'Best case' analysis was defined by basing costs on the site providing the lowest per-patient cost for continuous renal replacement therapy with regional citrate anticoagulation and the site with the highest per-patient cost for continuous renal replacement therapy with systemic heparin anticoagulation. 'Worst case' analysis was defined using the reverse situation.

Results

Survey of anticoagulant practice

In September 2018, 200 adult general intensive care units in England and Wales were identified as participating in the Intensive Care National Audit & Research Centre Case Mix Programme. Between September 2018 and March 2019, 188 of these intensive care units completed the online survey, a response rate of 94%. Among these, 182 (96.8%) reported using continuous renal replacement therapy, 111 (61%) of which reported changing from systemic heparin anticoagulation to regional citrate anticoagulation. Out of the 182 intensive care units that reported using continuous renal replacement therapy, 181 (99.5%) contributed data for at least one patient to the study cohort. A total of 175 (96.7%) intensive care units contributed patients for the period that systemic heparin anticoagulation was in use (hereafter referred to as the systemic heparin anticoagulation group)

and 63 (34.8%) contributed patients for the period that regional citrate anticoagulation was in use (hereafter referred to as the regional citrate anticoagulation group). A total of 57 intensive care units contributed patients to both systemic heparin and regional citrate anticoagulation groups.

Clinical effectiveness

Cohort identification

We identified 99,945 admissions to adult general intensive care units in the Intensive Care National Audit & Research Centre Case Mix Programme between 1 April 2009 and 31 March 2017 that met the inclusion criteria. Using NHS numbers, we linked records in Hospital Episode Statistics (for England) ($n = 89{,}463$ admissions), Patient Episodes Data for Wales ($n = 7087$), UK Renal Registry ($n = 7391$) and Civil Registrations (Deaths) ($n = 67{,}844$) data sets. After applying exclusions, 69,001 patients were included in the analyses: 60,416 (87.6%) were treated in an intensive care unit while systemic heparin anticoagulation was in use and 8585 (12.4%) were treated after the intensive care unit had completed the switch to regional citrate anticoagulation.

Primary outcome

Unadjusted mortality at 90 days following the index admission to intensive care unit was 53.3% among the systemic heparin anticoagulation group and 54.0% among the regional citrate anticoagulation group. There were no significant trends over time for 90-day mortality during either the systemic heparin or regional citrate anticoagulation periods (odds ratio 1.00, 95% confidence interval 0.99 to 1.01, and odds ratio 1.00, 95% confidence interval 0.96 to 1.04, respectively). When modelled, the change to regional citrate anticoagulation was not associated with a step increase in 90-day mortality (odds ratio 0.98, 95% confidence interval 0.89 to 1.08).

Secondary outcomes

The change to regional citrate anticoagulation was associated with step increases in the number of days of renal support (difference in means per year 0.53 days, 95% confidence interval 0.28 to 0.79 days), advanced cardiovascular support (difference in means per year 0.23 days, 95% confidence interval 0.09 to 0.38 days) and advanced respiratory support (difference in means 0.53 days, 95% confidence interval 0.03 to 1.03 days). The change to regional citrate anticoagulation was associated with a step change increase in intensive care unit length of stay (difference in means 0.86 days, 95% confidence interval 0.24 to 1.49 days) but not subsequent days in hospital or total hospital length of stay. When adjusting for patient covariates, the change to regional citrate anticoagulation was associated with a non-significant decrease in bleeding episodes (odds ratio 0.90, 95% confidence interval 0.76 to 1.06).

Cost-effectiveness

Primary outcome

For the primary cost-effectiveness analysis at 1 year, the transition to regional citrate anticoagulation was associated with an estimated step change of £2456 (95% confidence interval £999 to £3912). Benefits in terms of quality-adjusted life-years at 1 year were estimated to be negligible and stable over time. The resulting estimated incremental net monetary benefit at 1 year associated with a change to regional citrate anticoagulation was −£2376 (95% confidence interval −£3841 to −£911). The estimated likelihood of cost-effectiveness at 1 year with a willingness-to-pay threshold of £20,000 per quality-adjusted life-year was less than 0.1%.

Secondary outcomes

The change to regional citrate anticoagulation was associated with an estimated lifetime incremental net monetary benefit of −£724 (95% confidence interval −£9446 to £7997), with an estimated likelihood of cost-effectiveness of 44% at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year, increasing to 78% at a willingness-to-pay threshold of £100,000 per quality-adjusted life-year.

Subgroup analyses

Clinical effectiveness and cost-effectiveness analyses were consistent among the prespecified subgroup of patients meeting Sepsis-3 criteria during the first 24 hours of admission to an intensive care unit.

Conclusions

Our study indicates that the introduction of regional citrate anticoagulation to intensive care units in the NHS has not improved outcomes for patients, but has substantially increased costs for the hospitals caring for them. Importantly, our study demonstrates the possibilities of tracking the effects of changes in intensive care unit practice in England and Wales at scale across routinely collected databases. Our findings strongly support the need to do this for other significant changes in practice, provided that the methodological issues identified can be overcome.

Recommendations for research

Recommendation 1

Our study demonstrates the possibilities of tracking the effects of changes in intensive care unit practice in England and Wales at scale across routinely collected databases. Our findings strongly support the need to do this for other significant changes in practice. Therefore, there is a need to identify and prioritise other changes in clinical practice for similar evaluation.

Recommendation 2

Methodological research is required to better understand the most appropriate ways of measuring and testing the effects of real-world changes in clinical practice, in intensive care units and other providers of health-care services, such as how to interpret information about step-changes in the context of associated changes in trend; if and how to allow for non-linearity in trends; and the potential implications of misspecification of trend shape parameters for interpretation of step changes. Given that most such analyses are likely to be based on routinely collected administrative data and patient registries, the potential implications of trends in data quality or linkage quality need to be understood and appropriate methods for handling these developed.

Trial registration

This trial is registered as ClinicalTrials.gov NCT03545750.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 26, No. 13. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 16/111/136. The contractual start date was in April 2018. The draft report began editorial review in February 2020 and was accepted for publication in July 2020. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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