ORDIT: Organ Dysfunction in Trauma

A national prospective point prevalence study of multiple organ dysfunction in critical care trauma patients

Full Title	Organ Dysfunction in Trauma: A national prospective point prevalence study
Short Title/Acronym	**ORDIT**
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REC Reference	Scotland A REC: 15/SS/0170
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Principal Investigator	Elaine Cole, Trauma Research Fellow, Queen Mary University of London

GLOSSARY OF TERMS AND ABBREVIATIONS

CI	Chief Investigator
CRF	Case Record Form
CRO	Contract Research Organisation
GAfREC	Governance Arrangements for NHS Research Ethics Committees
JRMO	Joint Research Management Office
MTC	Major Trauma Centre
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial or study
PI	Principal Investigator
REC	Research Ethics Committee
SOP	Standard Operating Procedure
SMG	Study Management Group

INTRODUCTION

Multiple organ dysfunction syndrome (MODS) is a dysfunctional systemic inflammatory response following major tissue trauma causing significant morbidity and in-hospital mortality (1, 2). Recent reports suggest that the incidence of MODS following severe injury is falling and but with significant variation in reported rates (10 - 33%) from Australia, USA and Germany (3-5). Novel therapeutic approaches in early trauma management have increased survival of many people who would previously have died from major haemorrhage (6). Similarly, contemporary trauma systems have resulted in mortality benefits for those who would not have otherwise survived the early post-injury phase (7-9). However this has resulted in greater numbers of severely injured patients admitted to critical care who are at risk of developing MODS (3, 10).

The pattern and temporal trends of contemporary MODS also appear to be changing. Historic studies observed a bimodal pattern of MODS development characterised by 'early' and 'late' organ dysfunction (1, 11). Recent registry data now suggests that the onset of MODS has a multimodal distribution with a peak incidence present within the first 48-72 hours following injury and that this early fulminant MODS has the greatest association with mortality (5, 12). Other studies describe an early onset MODS which is more transient, tending to resolve within four to five days post injury (3, 10). Further, the phenotype of persistent inflammation-immunosuppression catabolism syndrome (PICS) has been described which is characterised by a late, non-resolving MODS lasting more than seven - ten days post injury (12-14).

The definition of MODS lacks an international standard (1, 15) with a number of physiological scoring systems e.g. Sequential Organ Failure Assessment Score (SOFA), Denver Score and Marshall Score (16, 17), used to diagnose the condition following trauma. Once present, MODS has a considerable impact on the patient experience and health costs. Evidence suggests that MODS increases resource use, prolongs critical care and hospital stay, and further complicates longer term patient recovery (3, 4).

From April 2010, inclusive trauma systems were introduced in England and Wales, with

Scotland considering implementation in 2016. An inclusive trauma system is organised to deliver optimum care at the most appropriate facility at the right time (18). Regionalised trauma care is delivered within a specified geographical location, with the most severely injured patients managed in Level 1 hospitals (19), known as Major Trauma Centres (MTCs). These MTC critical care units (or equivalent large hospitals in Scotland) are perfectly positioned to prospectively capture the current situation of MODS for severely injured patients in the UK.

At present there is no specific treatment for MODS, however a greater understanding of the clinical manifestation of post-traumatic MODS in the UK will facilitate enhanced stratification of at-risk populations to improve outcomes, predict resource use, and aid the design of future clinical trials.

STUDY OBJECTIVES

Primary Objective

The primary objective is to investigate the prevalence of MODS in severely injured patients admitted to MTC (or equivalent) critical care units in the UK.

Secondary Objectives

Secondary objectives are to:

- characterise the severity and temporal variation of MODS in critical care trauma patients
- examine the incidence and mode of mortality associated with MODS following trauma
- evaluate the relationship between MODS and length of stay.

Primary Outcome

The primary outcome will be the presence of MODS during the study period. This is defined as a SOFA score of >2 in two or more organ systems.

Secondary Outcomes

Secondary outcomes include in-hospital mortality, ventilator use, organ support, length of critical care stay (levels 3 and 2) and total hospital stay.

METHODOLOGY

Study Design

A one month prospective national point prevalence cohort study of trauma patients ≥16 years admitted to an adult critical care unit which admits trauma patients. For this study, a critical care unit is defined as either an Intensive Care Unit (Level 3 care) or a combined unit of Intensive Care (Level 3 care) and High Dependency Unit (Level 2 care).

Using voluntary convenience sampling, each unit will be invited to participate. Each site will have a nominated study lead and data collector(s) from within the critical care clinical team. Organ injury scoring training will be provided prior to study commencement. Each site will be supported by online information which includes the protocol, guidance/explanatory notes and contact details of the Principal Investigator.

Inclusion Criteria

All consecutive trauma patients (≥16 years of age) admitted to adult critical care from 08.00 on day one of the study to 07.59 on the final day of the in-hospital study period (one month in total) who subsequently provide informed consent to participate. This includes all trauma patients: direct admissions from the Emergency Department, admissions from the operating theatre or from a ward, transfers from other facilities and readmission to critical care.

Exclusion Criteria

- Any inclusion criteria not met
- <16 years old
- Burns only injury

All consecutive trauma patients (≥16 years of age) admitted to adult critical care from 08.00 on day one of the study to 07.59 on the final day of the in-hospital study period (one month in total) will be identified by clinical care staff. The local study investigator will be responsible for data collection, de-identification, data storage and data transfer.

STUDY PROCEDURES

Data will be collected in individual centre critical care units using a paper case record form (CRF). The de-identified data required is already recorded as part of routine clinical care and as part of the Intensive Care National Audit and Research Centre (ICNARC) or Scottish Intensive Care Society Audit Group audits. Organ failure scoring is not usually conducted as part of routine clinical care however it uses parameters that are recorded in routine care by critical care clinical staff on a daily basis. This will be completed for every eligible trauma patient in the critical care unit during the study period. Paper CRFs will be stored within a locked office in each centre only accessible to the centre study lead and data collectors. Each centre will be identified by a numeric code rather than name.

In hospital data collection for each patient:

A Admission variables: age, gender, time and date of traumatic injury, ED admission physiology (base deficit, lactate, systolic blood pressure and GCS), ED admission coagulation (INR), intravenous fluids, blood products and antifibrinolytics administered in first 24 hours post injury.

B Injury variables: mechanism of injury, list of injuries, surgical or interventional radiology episodes and a confirmed list of all injuries.

C Critical care data: date of admission to CCU, admission APACHE score, daily organ failure scores using Sequential Organ Failure Assessment (SOFA), days on organ support (inotropes and renal replacement therapy), ventilator free days, daily highest CRP and lowest lymphocyte counts (all blood taken as part of routine care – fields omitted if not taken by clinical care team). If more than one blood test is taken in a 24 hour period, the worst value will be recorded

D Follow up data: date of in-hospital mortality or date of discharge, critical care and hospital length of stay.

STATISTICAL CONSIDERATIONS

Statistical analysis will be performed using SPSS v21 (IBM Corporation, Armonk, NY, USA). Univariate analysis of variables between two groups will be conducted using unpaired students t-tests or Mann Whitney U tests (for parametric and non-parametric data

respectively). Analysis of more than two groups will be conducted using ANOVA or Kruskal Wallis tests. Percentages or proportions will be analysed using Chi square or Fisher's exact tests. A p value of <0.05 is considered statistically significant for univariate analysis. Multivariate analysis will be used to determine statistically independent relationships between MODS and other variables. Factors achieving significance of p<0.15 in univariate analysis will be entered into the regression models. Multivariate linear regression will be used to analyse continuous dependent variables and binary logistic regression for binary dependent variables. Results of linear regression will be reported as Beta co-efficient with 95% confidence intervals, and for logistic regression adjusted odds ratios (OR) with 95% confidence intervals.

ETHICS

The study has been reviewed and approved at the **Scotland A REC ethics committee (ref: 15/SS/0170),** on 19/02/2016.

DATA HANDLING AND RECORD KEEPING

The Principal Investigator and local collaborators have responsibility to ensure patient anonymity is protected and maintained. They will also ensure their identities are protected from any unauthorised parties. Information regarding study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Scotland Caldicott Guardians, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

Data will be de-identified by the clinical care team. Each centre will maintain a trial file including a protocol, local collaborator delegation log, ethics documentation, national coordination contact details. When all patients have been discharged within each site, the anonymous CRFs will be scanned and sent to the Principal Investigator via an NHS net email account: Elaine.cole1@nhs.net

When the study is complete, the Principal Investigator will ensure that records are to be stored for 20 years as per the Sponsors Research Governance Framework and Trust Policy in the approved repository for long-term storage of local records is the Trust Modern Records Centre.

STUDY LEADERSHIP

The Chief Investigator of the study is Professor Karim Brohi, Centre for Trauma Sciences, Blizard Institute, Queen Mary University of London (QMUL). The study will be coordinated by Elaine Cole, Principal Investigator, Centre for Trauma Sciences, Blizard Institute, QMUL. Both of these investigators hold honorary clinical positions at Barts Health NHS Trust. There will also be a local named collaborator from each participating site. These individuals will comprise the study management group (SMG) and will have the following responsibilities:

To provide leadership for the study within the individual site,

Nominate local data collection personnel,

Act as guarantor for the integrity and quality of the local data,

Communicate with the national coordinator and Principal Investigator.

DISSEMINATION OF RESEARCH FINDINGS:

Data will be written up, presented and disseminated in a timely manner. Elaine Cole will draft the initial scientific report of this study. The main outputs will be research papers for general journals and trauma specialty journals, research abstracts for presentation to national and international meetings and a final report summarising the overall findings. Study collaborators will be named as authors on any publication or report. Findings will be disseminated via the centre for trauma sciences website (www.c4ts.qmul.ac.uk).

REFERENCES

1. Dewar D, Moore FA, Moore EE, Balogh Z. Postinjury multiple organ failure. Injury. 2009 Sep;40(9):912-8. PubMed PMID: 19541301. Epub 2009/06/23. eng.
2. Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC, Sauaia A. A 12-year prospective study of postinjury multiple organ failure: has anything changed? Archives of surgery (Chicago, Ill : 1960). 2005 May;140(5):432-8; discussion 8-40. PubMed PMID: 15897438. Epub 2005/05/18. eng.
3. Dewar DC, Tarrant SM, King KL, Balogh ZJ. Changes in the epidemiology and prediction of multiple-organ failure after injury. The journal of trauma and acute care surgery. 2013 Mar;74(3):774-9. PubMed PMID: 23425734. Epub 2013/02/22. eng.
4. Frohlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: An analysis of 31,154 patients from the TraumaRegister DGU. The journal of trauma and acute care surgery. 2014 Apr;76(4):921-8. PubMed PMID: 24662853. Epub 2014/03/26. eng.

5. Sauaia A, Moore EE, Johnson JL, Chin TL, Banerjee A, Sperry JL, et al. Temporal trends of postinjury multiple-organ failure: Still resource intensive, morbid, and lethal. The journal of trauma and acute care surgery. 2014 Mar;76(3):582-93. PubMed PMID: 24553523. Epub 2014/02/21. eng.
6. Lord JM, Midwinter MJ, Chen YF, Belli A, Brohi K, Kovacs EJ, et al. The systemic immune response to trauma: an overview of pathophysiology and treatment. Lancet. 2014 Oct 18;384(9952):1455-65. PubMed PMID: 25390327. Epub 2014/11/13. eng.
7. Gunst M, Ghaemmaghami V, Gruszecki A, Urban J, Frankel H, Shafi S. Changing epidemiology of trauma deaths leads to a bimodal distribution. Proceedings (Baylor University Medical Center). 2010 Oct;23(4):349-54. PubMed PMID: 20944754. Pubmed Central PMCID: PMC2943446. Epub 2010/10/15. eng.
8. Davenport RA, Tai N, West A, Bouamra O, Aylwin C, Woodford M, et al. A major trauma centre is a specialty hospital not a hospital of specialties. The British journal of surgery. 2010 Jan;97(1):109-17. PubMed PMID: 20013932. Epub 2009/12/17. eng.
9. Twijnstra MJ, Moons KG, Simmermacher RK, Leenen LP. Regional trauma system reduces mortality and changes admission rates: a before and after study. Annals of surgery. 2010 Feb;251(2):339-43. PubMed PMID: 20010086. Epub 2009/12/17. eng.
10. Minei JP, Cuschieri J, Sperry J, Moore EE, West MA, Harbrecht BG, et al. The changing pattern and implications of multiple organ failure after blunt injury with hemorrhagic shock. Critical care medicine. 2012 Apr;40(4):1129-35. PubMed PMID: 22020243. Pubmed Central PMCID: PMC3343366. Epub 2011/10/25. eng.
11. Moore FA, Sauaia A, Moore EE, Haenel JB, Burch JM, Lezotte DC. Postinjury multiple organ failure: a bimodal phenomenon. The Journal of trauma. 1996 Apr;40(4):501-10; discussion 10-2. PubMed PMID: 8614027. Epub 1996/04/01. eng.
12. Gentile LF, Cuenca AG, Efron PA, Ang D, Bihorac A, McKinley BA, et al. Persistent inflammation and immunosuppression: a common syndrome and new horizon for surgical intensive care. The journal of trauma and acute care surgery. 2012 Jun;72(6):1491-501. PubMed PMID: 22695412. Pubmed Central PMCID: PMC3705923. Epub 2012/06/15. eng.
13. Hu D, Ren J, Wang G, Gu G, Chen J, Zhou B, et al. Persistent inflammation-immunosuppression catabolism syndrome, a common manifestation of patients with enterocutaneous fistula in intensive care unit. The journal of trauma and acute care surgery. 2014 Mar;76(3):725-9. PubMed PMID: 24553541. Epub 2014/02/21. eng.
14. Vanzant EL, Lopez CM, Ozrazgat-Baslanti T, Ungaro R, Davis R, Cuenca AG, et al. Persistent inflammation, immunosuppression, and catabolism syndrome after severe blunt trauma. The journal of trauma and acute care surgery. 2014 Jan;76(1):21-9; discussion 9-30. PubMed PMID: 24368353. Epub 2013/12/26. eng.
15. Dewar DC, Balogh ZJ. The epidemiology of multiple-organ failure: a definition controversy. Acta anaesthesiologica Scandinavica. 2011 Feb;55(2):248-9; author reply 9-50. PubMed PMID: 21226867. Epub 2011/01/14. eng.
16. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive care medicine. 1999 Jul;25(7):686-96. PubMed PMID: 10470572. Epub 1999/09/02. eng.

17. Lansink KW, Leenen LP. Do designated trauma systems improve outcome? Current opinion in critical care. 2007 Dec;13(6):686-90. PubMed PMID: 17975391. Epub 2007/11/03. eng.
18. Lansink KW, Gunning AC, Spijkers AT, Leenen LP. Evaluation of trauma care in a mature level I trauma center in the Netherlands: outcomes in a Dutch mature level I trauma center. World journal of surgery. 2013 Oct;37(10):2353-9. PubMed PMID: 23708318. Epub 2013/05/28. eng.