Intracranial haemorrhage in thrombocytopenic haematology patients. A nested case-control study. The InCiTe Study Protocol.

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004199
Article Type:	Protocol
Date Submitted by the Author:	08-Oct-2013
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Primary Subject Heading:	Haematology (incl blood transfusion)
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	Bleeding disorders & coagulopathies < HAEMATOLOGY, Bone marrow transplantation < HAEMATOLOGY, Leukaemia < HAEMATOLOGY, Blood bank & transfusion medicine < HAEMATOLOGY

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Running title: ICH in haematology patients case-control protocol

Key words: Intra-cranial haemorrhage; haematological malignancies; thrombocytopenia; case-control study; protocol

Word Count:; abstract 300; main text 3,542

Study Registration

ISRCTN05026912 (prospective registration)

NIHR Portfolio (UKCRN ID 10712)

Ethics

Oxford Research Ethics Committee B (10/H0605/78)

External Peer Review

British Society of Blood and Marrow Transplantation Scientific Committee (CTCP 10-02)

Abstract

Introduction

Intra-cranial haemorrhage (ICH) is one of the most serious side-effects of severe thrombocytopenia in haematology patients. ICH is rare, but can have devastating consequences (death or major morbidity). It is unknown why some patients with severe thrombocytopenia bleed and others do not.

Study Aims

Primary aim is to identify risk factors for ICH in patients with haematological malignancies. Secondary aims are to identify short-term outcomes for these patients at 30 days (major morbidity and mortality) and produce a more accurate estimate of ICH incidence in this population. This information is key to identifying means to improve treatment and quality of care.

Methods/Analysis

This is a UK-wide case-control study of ICH nested within a 4 year prospective surveillance study set up specifically for the case-control study. Each case will be matched to one control. Cases will be adult haematology patients (≥ 16 yrs) who have had any type or severity of ICH who are receiving, about to receive or have just received myeloablative chemotherapy (defined as chemotherapy expected to cause a significant thrombocytopenia <50x 10^9/L for >5 days) or a haemopoietic stem cell transplant. Only patients being treated with curative intent will be included. Controls will be patients who fulfil the same inclusion criteria as cases (apart from ICH) and were treated at the same hospital immediately before the index case. Cases and controls will be matched to type of treatment (myeloblative chemotherapy or haemopoietic stem cell transplant). Hospitals across the UK will participate in a monthly e-mail reporting strategy (started June 2011), as to whether a case of ICH occurred during the preceding calendar

month. Case and control forms will be sent to any hospital reporting an eligible case. Conditional logistic regression will be used to calculate odds ratios. Denominator data for incidence estimates will use national registry data.

Article Summary

Article focus

- Intra-cranial haemorrhage
- Study design

Key Messages

- Case-control study will examine risk factors for intra-cranial haemorrhage in patients with haematological malignancies

Strengths and limitations

- Case-control studies are an efficient way of studying rare outcomes
- Nested case-control design mimimises selection bias
- UK-wide study
- Data on exposures based on data from medical records. This minimises recall bias but risk that data may not have been recorded

Introduction

To advance the quality of care for haematology patients (when they are receiving intensive chemotherapy) it is important to gain a greater understanding of the risk factors for life-threatening haemorrhage. This case-control study concentrates on intra-cranial haemorrhage (ICH) because it is the most serious type of bleed caused by significant thrombocytopenia. If an ICH does not cause death it may lead to significant long-term morbidity. However, this

complication of severe thrombocytopenia (defined as a platelet count ≤ 50 x 10^9/L) is rare, its exact incidence is uncertain and predisposing risk factors are unknown.

There have been many case reports in the literature of ICH in patients with haematological disorders but there has been no previous attempt to prospectively study ICH within this patient group and assess whether there are any common factors that predispose patients to this serious side-effect.

Prophylactic platelet transfusions are used to prevent patients with severe thrombocytopenia developing a life-threatening haemorrhage. The use of platelet transfusions in patients with haematological disorders accounts for a large proportion (59%) of all platelets issued in the UK [1]. In patients with haematological malignancies, platelets issued to prevent thrombocytopenic bleeding account for up to 69% of all platelets issued to that patient population [2 3]. Platelet transfusions are not without risk and therefore a reliable marker of a patient's bleeding risk needs to be sought. A number of recently completed studies have highlighted our lack of knowledge regarding risk factors and incidence of severe and life-threatening haemorrhage [4-7].

The morning platelet count has been used, up to now, to indicate when a patient requires prophylactic platelet transfusions. The consensus outlined in BCSH guidelines on platelet transfusions was that patients should receive a platelet transfusion when the platelet count is <10 x 10^9/L unless there are other risk factors for haemorrhage such as sepsis, concurrent use of antibiotics or other abnormalities of haemostasis [8]. A patient's morning platelet count has been shown to be a poor predictor of haemorrhage [9]. In a recent study the rate of bleeding was similar over a broad range of platelet counts (6 to 80 x 10^9/L) [5]. This is unsurprising as a patient's platelet count indicates only the presence of a specific number of platelets within the circulation, but does not give any information on the functional activity of these platelets, nor

does it provide any information on the other factors that affect the formation of a clot. Why some patients with severe thrombocytopenia bleed and others do not is therefore unknown.

Rare complications in haematological disorders are difficult to study and in consequence are often under-researched; our understanding of them is poor; and any interventions used in current clinical practice are rarely based on robust evidence. Routine sources of information are limited or unreliable [10], and comprehensive studies of uncommon haematological conditions require a large collaboration to identify relatively small numbers of patients. A case-control study nested within a prospective surveillance study will overcome many of these problems. This type of study design has been used successfully to study rare disorders in other patient groups, but this is the first time this study design has been used in haematology patients [11 12].

A systematic review of the literature (2000 to 2010) found that cases of ICH in haematology patients have been very poorly reported [13]. Data about postulated risk factors from this systematic review and from known risk factors for ICH in the general population will be collected in this study.

Study Objectives

Primary Objective

What factors (e.g. age, type of haematological disease, treatment, infection) are associated with an increased risk of developing an ICH?

Secondary Objectives

Objective 1: What is the incidence of ICH in thrombocytopenic haematology patients?

Objective 2: What are the short-term outcomes for these patients (e.g. death within 30 days of haemorrhage, persistent neurological deficit)?

Study Design

This is a case-control study nested within a prospective surveillance system.

The study aims to collect anonymous data about haematological patients who have had an ICH while undergoing intensive chemotherapy or a stem cell transplant. This information is key to identifying means to improve treatment and quality of care.

The British Paediatric Surveillance Unit (BPSU) and UK Obstetric Surveillance System (UKOSS) have developed a reliable and straightforward methodology to study uncommon disorders of childhood and pregnancy. BPSU surveys have been used to inform national screening committee decisions on antenatal screening [14]. Information will be collected through doctors and specialist nurses in hospitals throughout the UK. An information collection system will be developed for this study and will be based a similar systems in obstetrics (UKOSS). Assistance in the development of this system will be via the British Society of Blood and Marrow Transplantation (BSBMT) and advice from UKOSS. Once this system is in place it could also be used for future studies of rare disorders and complications within haematology that are difficult to study via any other method.

Recruitment

Patients will be identified through a new haematological surveillance system (Haematology Active Surveillance System) “HASS”, which is based on similar obstetric (UKOSS) and paediatric surveillance systems (BPSU), to study rare haematological disorders.

Case Identification

This anonymous descriptive, case-control study will be conducted through a monthly case-collection scheme. Each hospital with a haematology department caring for patients with acute leukaemia or transplant patients will identify at least four individuals (representing haematologists, specialist nurses, and transplant co-ordinators) to report to HASS.

The individuals will be identified via BSBMT (principal transplant consultant and transplant co-ordinator, specialist nurse) and individuals associated with AML-16 trial or other current MRC (medical research council) leukaemia trials for non-transplant cases (principal investigator for the current leukaemia trials at each centre and research nurses associated with the trials).

Every month, the four nominated individuals will be sent a report card (in an e-mail format). They will be asked to complete a simple Yes/No tick box indicating if any cases have occurred in the previous month (Fig 1.). We expect that the majority of cards each month will be "No cases" because ICH is a rare event. "No cases" responses are extremely important because they allow us to confirm the number of haematology patients in the denominator cohort.

Control Identification

In order to perform the case-control study, HASS will also collect anonymised information on control patients. Clinicians who report a case will also be asked to identify an appropriate control patient and complete a similar data collection form from their case notes.

Study Participants

Cases: All adult patients (≥ 16 yrs of age) who have an ICH while receiving or about to receive myeloablative chemotherapy (expected to cause a significant thrombocytopenia < 50 x 10^9/L for > 5 days) or a stem cell transplant within the study period (1st May 2011 to 30th April 2015). Only patients being treated or about to be treated with curative intent will be included (this includes patients who present with an ICH at initial diagnosis or relapse and who would have been treated with curative intent if they had not had an ICH). All types and severities of intra-cranial haemorrhage will be included.

Controls: Are patients that fulfil the same inclusion criteria as cases (apart from the presence of ICH) and were treated immediately before the index case. Cases will be matched to type of treatment (chemotherapy or haemopoietic stem cell transplantation).

This methodology has been used by UKOSS successfully in previous studies and has been shown to produce a comparison group similar in characteristics to the population as a whole.

Data Collection

On receiving a case report, the central team will dispatch case and control data collection forms to the clinician. The data collection forms will seek additional information on risk factors in both cases and controls, and the management and outcome of the ICH. Cases and controls will be allocated a central HASS identification number. No names, addresses, dates of birth, hospital numbers or NHS numbers will be sought. Respondents will only be asked to record the unique HASS identification number in order to facilitate elimination of duplicates.

If the completed forms are not received back by the central team after four weeks, a written reminder will be sent out. If there is still no response after a further four weeks, a further set of forms will be sent to the centre (to ensure that non-return is not due to the forms going missing) and the clinician will be contacted by telephone. After a further four weeks the clinician will receive a further written reminder and telephone call.

All information will be anonymous and will be completed from the patient's case notes. The studies thus only involve the provision of information after the acute event has occurred. The patients' management will not be changed in any way by inclusion of their data in the study, and patients will not be contacted at any point by the central research team or by local collaborating clinicians. All the data requested in the case and control forms are data that are routinely recorded within patients' medical records.

The response rate from reporting clinicians will be monitored throughout the course of the study, as part of the routine operation of HASS. A three-monthly newsletter will be produced to inform all of the reporting clinicians of response rate to the study, and number of cases reported.

Rationale for questions to be asked within the data collection form

Clinical Factors associated with increased risk of ICH in the general population

Age: The risk of ICH increases with age. In a systematic review of the literature a RR of ICH 1.97 for every 10yr increase in age (95% CI 1.79 to 2.17)[15]. In a pooled prospective study of over 21000 individuals there was a RR 2.06 for every 10yr increase in age (95% CI 1.76 to 2.51)[16].

Sex: Some studies have shown a significantly higher rate of ICH in men. RR in general population male vs. female for ICH 3.73 (95% CI 3.28 to 4.25)[15]. No difference was seen in *Sturgeon et al (2007)[16]*.

Ethnic Origin: Young and middle-aged blacks have a substantially higher risk of sub-arachnoid (SAH) or intra-cerebral haemorrhage than whites of a similar age [2.1 x risk of SAH (95% CI 1.3 to 3.6); 1.4 x risk of intra-cerebral haemorrhage (95% CI 0.9 to 2.1) [17]*: In Sturgeon et al study* RR 2.56 (95% CI 1.8 to 3.65) [16]].

Smoker: Current smoker RR 1.31 (95% CI 1.09 to 1.58)[15] (*Ariesen et al, 2003).* No difference seen in *Sturgeon et al (2007)[16]*.

Hypertension:. Patients with systolic blood pressure (BP) ≥ 160mmHg or diastolic BP ≥110mmHg RR 5.55 (95% CI 3.07 to 10.0) [16]. In Ariesen et al study 2003 RR 3.68 (95% CI 2.52 to 5.38) [15].

Diabetes: In Ariesen et al study 2003 RR 1.3 (95% CI 1.02 to 1.67) [15]. No difference seen in *Sturgeon et al (2007) [16].*

Site of haemorrhage: Site of haemorrhage is a predictor of functional outcome in general population [18]. In a recent study, poor outcomes after ICH in AML patients were associated with four independent risk factors, three of which were associated with the site of the

haemorrhage. Brainstem haemorrhage (P = 0.001), sub-arachnoid haemorrhage (SAH) (P = 0.017), and extra-dural haemorrhage (EDH) (P = 0.014) [19].

Volume of haemorrhage: In the general population the volume of the haematoma is one of the most important predictors of mortality and functional outcome after ICH [18 20 21].

Glasgow coma scale (GCS) at time of haemorrhage: In the general population this was another important predictor of functional outcome. FUNC score GCS < 9 much worse outcome [18].

Clinical Factors associated with haemorrhage in haematology patients

A recent history of severe bleeding: In a review of almost 3,000 thrombocytopenic adult patients, over a 10-year period, Friedmann showed a significant relationship between a history of recent bleeding (within the previous five days) and occurrence of significant haemorrhage (OR 6.72; 95% CI, 5.53 to 8.18) [9].

Uraemia: In Friedmann's study, uraemia (defined as blood urea nitrogen > 50 mg/dL which equals urea > 17.9 mmol/l) was associated with an increased risk of bleeding (OR 1.64; 95% CI, 1.40 to 1.92) [9].

Recent bone marrow transplantation: In Friedmann's study a recent bone marrow transplant (under 100 days) was associated with an increased risk of bleeding (OR 1.32; 95% CI, 1.22 to 1.43) [9].

Hypoalbuminaemia: In Friedmann's study, hypoalbuminaemia (defined as a serum albumin of 2.0 gm/dL or lower) was associated with an increased risk of bleeding (OR 1.54; 95% CI, 1.33 to 1.79) [9].

Acute Graft vs. Host Disease (GvHD): In a single centre retrospective study of 622 allogeneic transplant patients over a 20 year period 21 cases of ICH were identified. A multivariate analysis with logistic regression identified acute GVHD as the only factor that significantly influenced ICH

occurrence [22]. In a single centre randomised controlled trial of platelet transfusions, (n = 159, of which 41 had allogeneic transplants) GvHD of any grade was associated with an increased risk of haemorrhage on univariate analysis (OR 2.8; 95% C.I. 1.2 to 8.2) [23].

Veno-occlusive disease (VOD): Najima and Zumberg also showed a possible association of VOD of any grade with an increased risk of haemorrhage, although the confidence intervals were very wide (Hazard ratio 2.63 (95% CI 0.77 to 9.00) (Najima *et al*, 2009)[22]; (OR 4.4; 95% CI 0.6 to 27.8) (Zumberg *et al*, 2002)[23].

Fever: In Webert's retrospective analysis [24] of Rebulla's data [25] the presence of an elevated body temperature increased the risk of mild bleeding (grade I & II) by 52% (RR 1.52; 95% CI (1.25 to 1.85); p< 0.005) The presence of an elevated body temperature increased the risk of clinically significant bleeding (grade II - IV) by 87% (RR 1.87; 95% CI (1.40 to 2.49); p< 0.005) For clinically significant bleeding the risk of bleeding increased as the temperature increased. Risk of bleeding increased significantly when the patient's body temperature was between:

38-38.4 (RR 2.43; 95% CI (1.0 to 5.90); p< 0.05); and >38.5 (RR 3.95; 95% CI (1.90 to 8.20); p=0.0001). In a previous small study 9 out of 13 patients who bled were febrile at the time of haemorrhage. However, this study was performed when aspirin was still used as an anti-pyretic [26 27].

Use of amphotericin: Therapeutic use of amphotericin B is associated with decreased expression of glycoprotein Ib on the surface of stored platelets [28]. This may induce a platelet function defect. In Zumberg's study usage of amphotericin B was associated with an increased risk of bleeding (OR 3.8; 95% CI 1.3 to 10.5) [23].

Use of antibiotics: Beta lactam antibiotics have been associated with platelet dysfunction [29 30].

Laboratory factors associated with haemorrhage:

CRP: Inflammation has been shown to induce severe haemorrhage in thrombocytopenic mice [31].

Prothrombin Time: Prolonged PT was associated with a poorer outcome after ICH in AML patients ($P < 0.001$) [19].

Haemoglobin: A low haematocrit has been shown to be associated with an increased risk of bleeding [32-34].

Persistent Thrombocytopenia: Platelets have been shown to provide an endothelial supportive function by plugging gaps in the endothelium of otherwise intact blood vessels. Animal studies have shown that thrombocytopenia is associated with the gradual thinning of the vessel wall endothelium over time, and that, if thrombocytopenia persists, gaps gradually occur between adjacent endothelial cells [35-37]. This thinning and fenestration of the endothelium is accompanied with on-going and increased use of circulating platelets to prevent the loss of red blood cells (RBCs) through these gaps. In a study of 1402 bone marrow transplant (BMT) patients very low platelet counts were significantly associated with bleeding post BMT. The risk of bleeding in a patient with 3 to 7 (out of 7) days of platelet counts $<10 \times 10^9$/l in the week preceding the haemorrhage was 40 to 60% higher than a patient with 0 to 2 days with low platelet counts. However, only 8.6% of patients who bled had such profound thrombocytopenia prior to the bleeding episode. In most cases, bleeding episodes started with platelet counts $>20 \times 10^9$/l [38 39].

Definition of End of Study/Study Power

The study will be completed at the end of four years if a sufficient number of cases have been reported to allow detection of an odds ratio (OR) of 2.0 with 80% power at a 5% significance level for the risk factors of fever, amphotericin B usage and antibiotic usage. This will require a

minimum of 136 cases (for the variables stated above); using the incidence data of these variables from previous studies [9 40]. We had originally planned the study length to provide sufficient cases and controls to detect with 80% power at the 5% level an OR of 2.5 for a range of analyses of associated factors. This would have required a minimum of 78 cases using the incidence data referred to above. An interim review of this study by an expert epidemiologist advised that the study should remain open for longer than the planned two year period. This was because the majority of odds ratios (OR) identified from previous studies of ICH in the general population detected significant OR for individual factors of between1.5 to 2 [9 15-17 19 22-24]. Our original minimum study number would have been insufficient to detect an OR of 2 with sufficient power.

The true incidence of ICH is unknown and there are a wide range of estimates from the literature, from 0.5% to 6.9% [5 22 25 41-43]. The study initially expected that the true estimate was between 1 to 2%, with a prediction of 120 to 240 cases within a 2 year period. This was an overestimate of the number of cases actually reported once the study had started and the study duration has therefore been extended to four years after a review of initial recruitment by the study management group.

Denominator Data

One of the secondary objectives is to determine the incidence of ICH in patients with a haematological malignancy or receiving a stem cell transplant. According to the BSBMT registry there were 2,939 transplants performed in 2008. All stem cell transplants performed in the UK have to be reported via BSBMT to the European Group for Blood and Bone Marrow Transplantation (EBMT). We will be able to obtain accurate denominator data via BSBMT for transplant patients.

Accurate denominator data for patients with acute leukaemia will be obtained via a variety of sources including numbers recruited to (Medical Research Council) MRC acute leukaemia trials over the designated time period. The majority of patients diagnosed with leukaemia in the UK are recruited to an acute leukaemia trial.

Analysis

Descriptive information will be presented as frequencies or proportions with confidence intervals.

Odds ratios with 95% confidence intervals will be calculated and adjusted for confounders and effect modifiers using conditional logistic regression.

Incidence rates will be calculated with 95% confidence intervals. See preceding section regarding denominator data. If the true incidence of ICH is 0.5%, then an accurate estimate of incidence will be obtainable with 60 cases from a study population of approximately 12,000 (transplant patients (approximately 6,000 cases over 2 years) and non-transplant patients (approximately 6,000 cases over 2 years) combined).This would provide an estimate of the incidence of ICH of 0.5% with a 95% confidence interval (CI) of 0.39% to 0.64%. An estimate of incidence will not use data from the whole four year study period. This is because fewer hospitals had been recruited and were actively participating in the study's first year.

Consent

It will not be practicable to obtain consent for data collection from individual patients, as this would prevent the achievement of one of the objectives of the study, namely to document the number of patients who suffer from this complication in the UK. Accurate measurement of incidence requires documentation of all cases occurring in the UK.

The National Information Governance Board (formerly Patient Information Advisory Group (PIAG)) considers that organisations seeking to use patient information for research purposes without consent should seek anonymised or pseudo-anonymised data only and not any personally identifiable information.

Accordingly, this study will not collect names, addresses, postcodes, dates of birth, hospital numbers or NHS numbers in order to maintain patient confidentiality. Collection of data in this way in the absence of consent is unlikely to cause significant harm.

Data Security

The security of all data will be maintained by storage on NHS Blood and Transplant's secure network, accessible only by the key researchers and responsible members of NHSBT who may require access to data to ensure compliance with regulations. Access by any other individuals for the purposes of any other study will only be allowed after a successful application to a Research Ethics Committee.

Dissemination of Study Information

The study has been prospectively registered on the Clinical Trials website www.controlled-trials.com (ISRCTN05026912).

The data from this study will be analysed and the results published as soon as possible in a scientific journal after study completion. The information will be published and distributed to all participating clinicians; it will also be available on the HASS website as well as being presented at scientific meetings.

Authors' contributions

LJE devised the study. MFM and SJS contributed to the development of the idea. DC provided statistical support in development of the protocol. LJE reviewed the literature and wrote the draft of the manuscript. DC, MFM, and SJS critically reviewed the paper. All authors approved the submitted version.

Acknowledgements

Prof Marion Knight director of UKOSS for help and advice on setting up a case-control study within a prospective surveillance system.

British Society of Blood and Marrow Transplantation for their support and adoption of this study on to their portfolio (BSBMT Ref: CTCP 10-02).

MRC Acute Myeloid Leukaemia Trials Team for assistance in providing initial contact details for ask hospitals to participate.

Peer Review

The study protocol was externally peer reviewed by the British Society of Blood and Marrow Transplantation Scientific Committee before being adopted on to their portfolio.

Funding

NHS Blood and Transplant Trust Fund (TF 018)

Competing Interests

Authors have no competing interests to declare

Funding statement

This work was supported by NHS Blood and Transplant Trust Fund grant number TF018.

This is an NIHR portfolio adopted study (UKCRN ID 10712), and has received support from NIHR funded staff across the UK.

Competing Interests

The authors have no competing interests to declare

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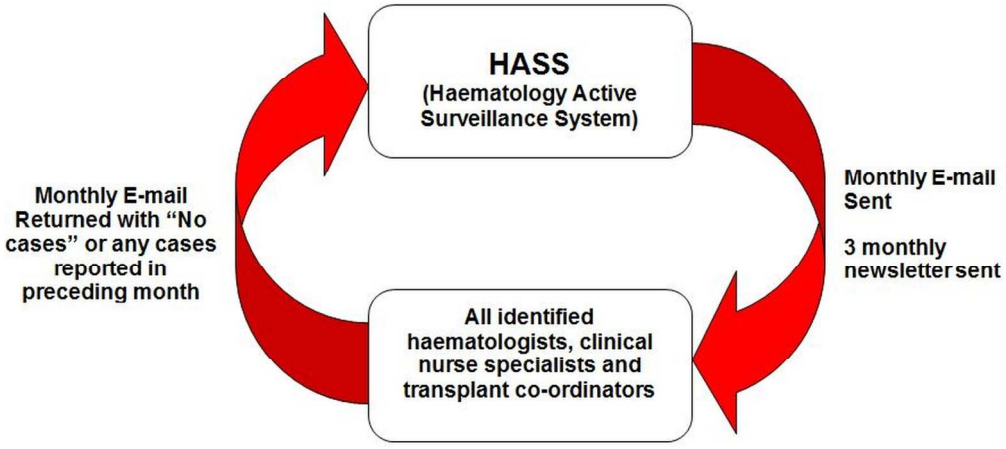

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