Platelet transfusion versus standard care after acute stroke due to spontaneous cerebral haemorrhage associated with antiplatelet therapy (PATCH): a randomised, open-label, phase 3 trial

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Summary

Background Platelet transfusion after acute spontaneous primary intracerebral haemorrhage in people taking antiplatelet therapy might reduce death or dependence by reducing the extent of the haemorrhage. We aimed to investigate whether platelet transfusion with standard care, compared with standard care alone, reduced death or dependence after intracerebral haemorrhage associated with antiplatelet therapy use.

Methods We did this multicentre, open-label, masked-endpoint, randomised trial at 60 hospitals in the Netherlands, UK, and France. We enrolled adults within 6 h of supratentorial intracerebral haemorrhage symptom onset if they had used antiplatelet therapy for at least 7 days beforehand and had a Glasgow Coma Scale score of at least 8. With use of a secure web-based system that concealed allocation and used biased coin randomisation, study collaborators randomly assigned participants (1:1; stratified by hospital and type of antiplatelet therapy) to receive either standard care or standard care with platelet transfusion within 90 min of diagnostic brain imaging. Participants and local investigators giving interventions were not masked to treatment allocation, but allocation was concealed from outcome assessors and investigators analysing data. The primary outcome was shift towards death or dependence rated on the modified Rankin Scale (mRS) at 3 months, and analysed by ordinal logistic regression, adjusted for stratification variables and the Intracerebral Haemorrhage Score. The primary analysis was done in the intention-to-treat population and safety analyses were done in the intention-to-treat and as-treated populations. This trial is registered with the Netherlands Trial Register, number NTR1303, and is now closed.

Findings Between Feb 4, 2009, and Oct 8, 2015, 41 sites enrolled 190 participants. 97 participants were randomly assigned to platelet transfusion and 93 to standard care. The odds of death or dependence at 3 months were higher in the platelet transfusion group than in the standard care group (adjusted common odds ratio 2·05, 95% CI 1·18–3·56; p=0·0114). 40 (42%) participants who received platelet transfusion had a serious adverse event during their hospital stay, as did 28 (29%) who received standard care. 23 (24%) participants assigned to platelet transfusion and 16 (17%) assigned to standard care died during hospital stay.

Interpretation Platelet transfusion seems inferior to standard care for people taking antiplatelet therapy before intracerebral haemorrhage. Platelet transfusion cannot be recommended for this indication in clinical practice.

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See Online for appendix

Introduction

Haemorrhagic stroke accounts for 11–22% of incident strokes,[1] half of all stroke deaths, and around 42% of the disability-adjusted life-years lost due to stroke (47 million life-years).[2] Spontaneous (non-traumatic) intracerebral haemorrhage caused by cerebral small vessel diseases accounts for two-thirds of haemorrhagic strokes,[3] amounting to more than 2 million incident intracerebral haemorrhages worldwide each year.

Antiplatelet therapy might slightly increase the incidence of intracerebral haemorrhage.[4] In high-income countries, more than a quarter of people who have incident intracerebral haemorrhages were taking antiplatelet therapy.[5] 1 month case fatality after intracerebral haemorrhage is 40%, and people taking antiplatelet therapy beforehand have a 27% (95% CI 10–47) increased odds of death compared with those not taking antithrombotic drugs.[6] Observational analyses suggest that antiplatelet therapy use before intracerebral haemorrhage and reduced platelet activity might worsen the outcome by increasing the risk of early intracerebral haemorrhage volume growth,[7] which is an important determinant of outcome.[8]

Platelet transfusion is used prophylactically and therapeutically in many clinical settings; however, few randomised trials have investigated its effectiveness for

Research in context

Systematic review

Before we initiated the PATCH trial in 2009, a search of ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials (CENTRAL) did not reveal published, ongoing, or planned randomised trials of platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy. On April 1, 2016, we searched MEDLINE (PubMed) from Jan 1, 1950, Embase from Jan 1, 1947; ClinicalTrials.gov, and CENTRAL from Jan 1, 1993, using textwords for platelet transfusion ("platelet" OR "blood platelet" OR "thrombocyte") and the textword "transfusion" and terms for intracerebral haemorrhage and randomised trials, as well as bibliographies of relevant publications, for trials of platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy, irrespective of language of publication. We found one ongoing randomised trial (NCT00699621) and one published randomised trial dissimilar to PATCH of platelet transfusion versus aspirin resumption for aspirin-sensitive people with acute basal ganglia intracerebral haemorrhage undergoing craniotomy.

Added value of this study

This is the only completed randomised trial of people taking antiplatelet therapy who have acute intracerebral haemorrhage to compare the effects of platelet transfusion with standard care on functional outcome. Platelet transfusion seemed inferior to standard care for reducing death or dependence after acute intracerebral haemorrhage in people taking antiplatelet therapy.

Interpretation of all the available evidence

Platelet transfusion seems inferior to standard care after acute intracerebral haemorrhage in people taking antiplatelet therapy. We cannot recommend platelet transfusion for this indication, pending the results of another similar randomised trial.

active bleeding disorders.[9–11] Observational studies have reported variable associations with outcome after platelet transfusion for acute intracerebral haemorrhage in people taking antiplatelet therapy[12–17] and the absence of randomised trials has prevented guidelines from recommending its use.[10,11] However, platelet transfusion is commonly used in emergency departments, stroke units, and neurosurgical settings in people with acute intracerebral haemorrhage associated with antiplatelet therapy use.[18] We did a randomised controlled trial of platelet transfusion in acute intracerebral haemorrhage associated with antiplatelet therapy use, aiming to assess whether platelet transfusion would reduce death or dependence compared to standard care by reducing intracerebral haemorrhage growth.

Methods

Study design and participants

We did a multicentre, randomised, open-label, parallel-group trial at 36 hospitals in the Netherlands, 13 hospitals in the UK, and 11 hospitals in France. The trial was designed and coordinated by the Department of Neurology of the Academic Medical Centre (University of Amsterdam, Netherlands). The trial protocol has been published previously[19] and case report forms are available on the trial website.

For the **PATCH trial website** see http://www.strokeamc.nl/patch

We included patients aged 18 years or older with non-traumatic supratentorial intracerebral haemorrhage confirmed by brain imaging and a Glasgow Coma Scale score of 8–15; in whom platelet transfusion could be initiated within 6 h of symptom onset (or last seen well) and within 90 min of brain imaging; who had been on antiplatelet therapy with a cyclooxygenase (COX) inhibitor (aspirin or carbasalate calcium), adenosine diphosphate (ADP) receptor inhibitor (clopidogrel), or an adenosine-reuptake inhibitor (dipyridamole) for at least 7 days preceding intracerebral haemorrhage; and who had a pre-intracerebral haemorrhage modified Rankin Scale (mRS) score of 0 (no symptoms) or 1 (no significant disability despite symptoms; able to carry out all usual duties and activities). Exclusion criteria were blood on brain imaging suggestive to the treating physician of epidural or subdural haematoma, or an underlying aneurysm or arteriovenous malformation; planned surgical evacuation of intracerebral haemorrhage within 24 h of admission; intraventricular blood more than sedimentation in the posterior horns of the lateral ventricles; previous adverse reaction to platelet transfusion; known use of vitamin K antagonist (unless international normalised ratio ≤1·3) or history of coagulopathy; known thrombocytopenia (lower than 100 cells × 10^9/L); lacking mental capacity by national legal standards before intracerebral haemorrhage; or if death appeared imminent. We did not include participants with infratentorial or large intraventricular haematomas because they are more likely to undergo surgical procedures that might confound the effects of platelet transfusion on outcome. Collaborating clinicians on the delegation log at each hospital site recruited participants, and obtained written informed consent from participants or their legal representatives.

We obtained research ethics committee approval from the Academic Medical Centre ethics committee (MEC08/006) and each participating hospital in the Netherlands; the Scotland A Research Ethics Committee (10/MRE00/36) in the UK; and the Comité de protection des personnes (CPP 12/43, 2012-A00209–34) in France. The trial was monitored by the Clinical Research Unit of the Academic Medical Centre in the Netherlands, the Clinical Research Unit of the Lille University Hospital in France, and the UK trial manager on behalf of The Academic and Clinical Central Office for Research and Development in the UK.

Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive either standard care or platelet transfusion plus standard care. Randomisation was done by investigators via a secure, web-based, computerised randomisation system (TENALEA, Clinical Trial Data Management system; NKIAVL, Amsterdam, The Netherlands) that concealed allocation, and stratified assignment by study hospital and type of pre-intracerebral haemorrhage antiplatelet therapy (COX inhibitor alone, ADP receptor inhibitor alone, COX inhibitor with an adenosine-reuptake inhibitor, or COX inhibitor with an ADP receptor inhibitor). A biased coin randomisation was used, with coin bias factor of three and coin bias threshold of two. Participants and local investigators giving interventions were not masked to treatment allocation, but allocation was concealed to outcome assessors and investigators analysing data.

Procedures

The web-based randomisation system asked investigators to check eligibility criteria and required investigators to record participant age and type of pre-intracerebral haemorrhage antiplatelet therapy. Investigators recorded all other characteristics at the time of enrolment. Stroke severity was scored on the National Institutes of Health Stroke Scale (NIHSS, ranging 0–42, with higher scores indicating more severe stroke). Brain imaging was done at admission with either CT or MRI according to routine clinical practice.

All participants received standard care, which was not defined in the protocol but was assumed to be given according to contemporary European[20] and national guidelines. Leucocyte-depleted platelet transfusions, either buffycoat-derived or collected by apheresis, were supplied by national or regional blood supply organisations, issued by the hospital transfusion laboratory, and administered to participants in the transfusion group according to local hospital protocols for transfusion. The protocol required platelet transfusion to be initiated within 6 h of intracerebral haemorrhage symptom onset and within 90 min of diagnostic brain imaging. Participants taking a COX inhibitor, with or without adenosine-reuptake inhibitor, received one platelet concentrate (equivalent to five donor units), whereas participants taking an ADP receptor inhibitor, with or without another antiplatelet drug, received two platelet concentrates. We chose the different dosages of platelet concentrates based on in-vitro experiments.[21] Investigators recorded whether platelet transfusion started within 3 h or 3–6 h after symptom onset.

Functional outcome scored with the mRS at 3 months (ranging from 0 [no symptoms] to 6 [death]) was rated by a neurologist or research nurse who was not involved in participants' medical treatment. Each country's trial coordinating centre organised collection of the primary outcome so that it could be obtained in participants' first language by either structured telephone interview or face-to-face consultation.

Brain imaging was done at 24 h (plus or minus 3 h) after randomisation with the same technique used for diagnosis. Diagnostic and 24 h brain imaging studies were obtained in Digital Imaging and Communications in Medicine (DICOM) format from trial sites, anonymised, and analysed centrally in Amsterdam. The images were assessed for intracerebral haemorrhage location (deep or lobar) and intraventricular extension. We used an automated planimetric method to segment intracerebral haemorrhage on unenhanced baseline imaging[22] to calculate intracerebral haemorrhage volume in mL; these measurements were manually checked by MIB who was masked to treatment allocation and supervised by one of two independent neuroradiologists (CBM or LFB; not involved in the conduct of the trial and masked to allocation); values were adjusted where necessary.

Investigators recorded the occurrence of any serious adverse events and other safety outcomes that occurred during hospital admission, and also recorded the date and destination of discharge. Safety outcomes were independently verified by research nurses, or the safety committee in France, with use of discharge letters.

Data on paper case report forms were collected at the trial coordinating centre in each country (Amsterdam, Netherlands; Edinburgh, UK; and Lille, France). Good Clinical Practice-compliant internet-based remote data capture was used for entering, managing, and validating data from hospital sites (Oracle Clinical, ORACLE, Redwood Shores, CA, USA.

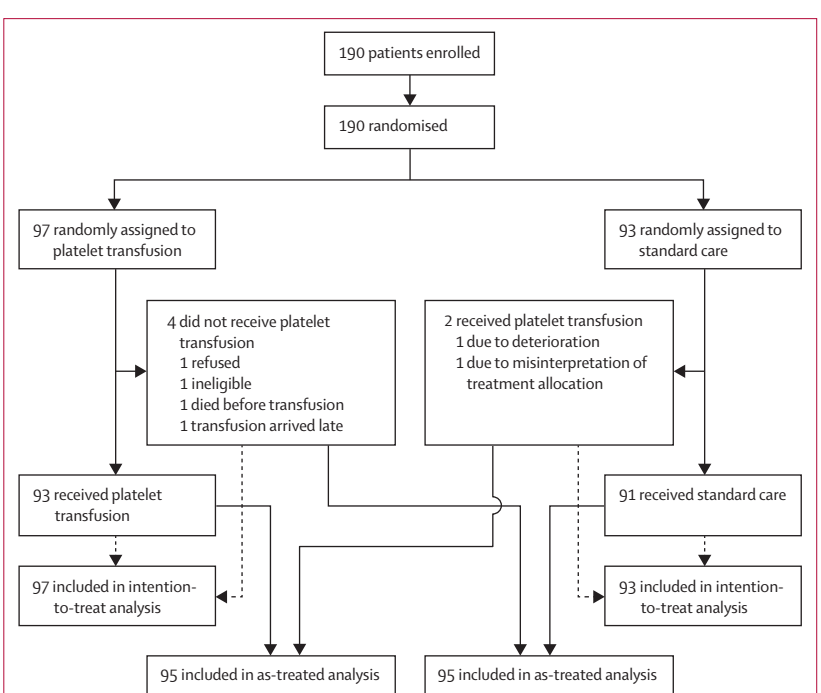

Figure 1: **Trial profile**

Outcomes

The primary endpoint was difference in functional outcome at 3 months after randomisation scored with the mRS. Secondary clinical outcomes at 3 months were survival (mRS score of 1–5), poor outcome defined as an mRS score of 4–6, and poor outcome defined as an mRS score of 3–6. The secondary explanatory outcome was median absolute intracerebral haemorrhage growth in mL after 24 h on brain imaging. Safety outcomes were defined as complications of platelet transfusion (transfusion reactions, thrombotic complications) and for other serious adverse events the treating physician was asked to specify the presumed cause as one of the following: due to complications of intracerebral haemorrhage (enlargement, intraventricular extension, hydrocephalus, oedema, or brain herniation), epileptic seizures, infection (urinary tract or pneumonia), or others that investigators wished to record. We planned a substudy of the spot sign on CT angiography and platelet function testing. We also planned to investigate determinants of poor outcome, functional outcome using the Academic Medical Center (AMC) Linear Disability score, and health economics.

	Platelet transfusion group (n=97)	Standard care group (n=93)
Mean age (years)	74·2 (49–94)	73·5 (40–92)
Men	55 (57%)	57 (61%)
Women	42 (43%)	36 (39%)
Vascular comorbidities		
Ischaemic stroke or TIA	38/94 (40%)	40 (43%)
ICH	4 (4%)	5/92 (5%)
Hypertension	68/94 (72%)	67/92 (73%)
Diabetes mellitus	15 (15%)	17/90 (19%)
Hypercholesterolaemia	46/94 (49%)	40/84 (48%)
Ischaemic heart disease	23/96 (24%)	22/90 (24%)
Peripheral arterial disease	16 (16%)	4/91 (4%)
Coagulation disorder	1/96 (1%)	2/91 (2%)
Antiplatelet therapy pre-ICH*		
COX inhibitor alone	71 (73%)	78 (84%)
COX inhibitor and dipyridamole	18 (19%)	13 (14%)
ADP inhibitor alone	4 (4%)	1 (1%)
COX inhibitor and ADP inhibitor	3 (3%)	1 (1%)
None	1 (1%)	0
Statin therapy pre-ICH	54/96 (56%)	48/92 (52%)
Median GCS score	14 (13–15)	15 (13–15)
Median NIHSS score	12 (7–19)	13 (7–17)
Mean platelet count (×10^9/L)	229 (120–622)	241 (91–461)
Country of inclusion*		
Netherlands (27 centres)	63 (65%)	57 (61%)
France (9 centres)	19 (20%)	20 (22%)
UK (5 centres)	15 (15%)	16 (17%)
ICH location		
Supratentorial deep	62/96 (65%)	70/92 (76%)
Supratentorial lobar	32/96 (33%)	22/92 (24%)
Infratentorial	2/96 (2%)	0
Median ICH volume (mL)	13·1 (5·4–42·4)	8·0 (4·4–25·8)
Intraventricular extension	12/95 (13%)	20/92 (22%)
Median total ICH Score†	1 (0–2)	1 (0–1)
Age >80 years	28 (29%)	34 (37%)
GCS score		
5–12	19 (20%)	11 (12%)
3–4	1 (1%)	0
ICH volume >30 mL	32 (34%)	19 (21%)
Intraventricular extension	12 (13%)	20 (22%)
Infratentorial ICH location	2 (2%)	0

Data are mean (range), n (%), or median (IQR), unless noted otherwise. TIA=transient ischaemic attack. ICH=intracerebral haemorrhage. COX=cyclooxygenase. ADP=adenosine diphosphate. GCS=Glasgow Coma Scale. NIHSS=National Institutes of Health Stroke Scale. *Stratification variable. †3 participants missing in the platelet transfusion group and 2 missing in the standard care group.

Table 1: **Baseline characteristics of the intention-to-treat population**

Statistical analysis

The executive committee agreed on a statistical analysis plan with the trial statistician (RJdH) without knowledge of outcome data and before closing and unmasking the trial database; this statistical analysis plan was submitted in concise format to the Netherlands Trial Register on March 14, 2016, was submitted in full to *Trials* on March 21, 2016, and the trial database was locked and unmasked on March 31, 2016. The statistical analysis plan describes the differences between the protocol and this final report; the principal change was from a fixed dichotomous analysis of the primary outcome (mRS score 4–6 at 3 months) to an ordinal logistic regression analysis of the shift of all categories of the mRS at 3 months, in view of the greater statistical efficiency of this analysis[23] and the hypothesised effect of platelet transfusion to result in a shift on a functional outcome scale by reduction of intracerebral haemorrhage growth. We originally based the target sample size of two groups of 95 participants (total 190) on an estimate of 70% frequency of the primary outcome of death or dependence (defined as mRS 4–6) with standard care,[24] a clinically important 20% absolute reduction of this risk to 50% with platelet transfusion (odds ratio [OR] 0·43), 80% power and a two-sided level of significance of 0·05. However, after the change (and with the same target sample size), power increases to 91% to detect a common OR of 0·43 in an ordinal logistic regression analysis of all pairs of mRS categories, assuming a distribution of the mRS with standard care that is similar to the control group of a recent intracerebral haemorrhage trial.[25]

The primary outcome was the shift of each category in the entire range of the mRS, assuming a common OR analysed by ordinal logistic regression (with adjustment for both the stratification variable of type of pre-intracerebral haemorrhage antiplatelet therapy as well as the Intracerebral Haemorrhage Score as a

For the **statistical analysis plan** see http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1303

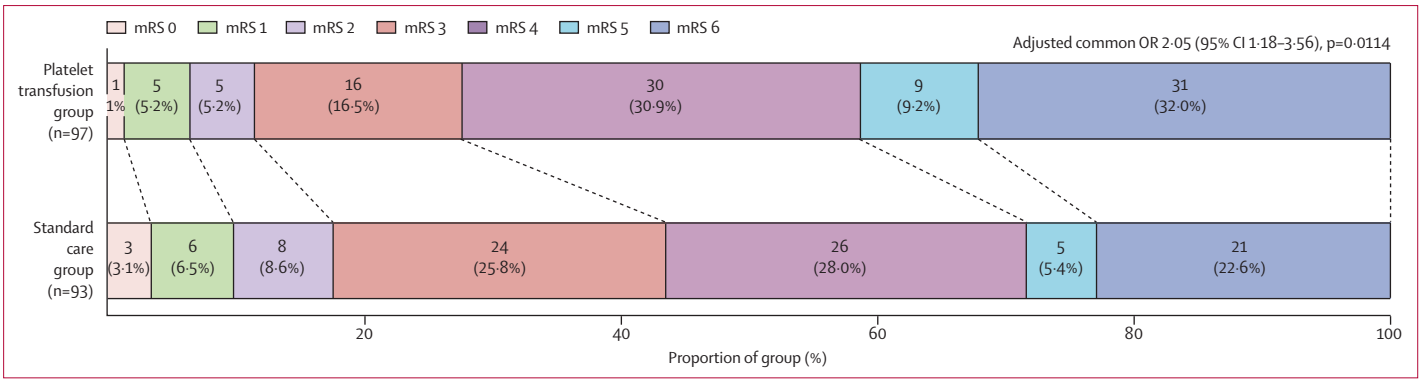

Figure 2: **Distribution of mRS score at 3 months**
mRS=modified Rankin Scale. OR=odds ratio.

predictor of outcome after intracerebral haemorrhage[26]) in the intention-to-treat population. Effect sizes are expressed as ORs with 95% CIs. Baseline characteristics and secondary endpoints were assessed in the intention-to-treat population with no imputation for missing data. Secondary outcomes were compared with the χ^2 test, except for the median difference in intracerebral haemorrhage growth, which was compared with the Mann-Whitney *U* test. Safety outcomes were compared in both the intention-to-treat and the as-treated populations. We used parametric statistics when variables had a normal distribution, and non-parametric statistics when they did not. If zero instances were reported, we added 0·5 to each cell to calculate an OR.

We did three prespecified subgroup analyses of the shift of all categories of the mRS using ordinal regression analyses to test the interaction variable, adjusted for both component variables, for type of antiplatelet therapy regimen pre-intracerebral haemorrhage (single *vs* dual); country of randomisation (Netherlands *vs* France *vs* UK); and trichotomised intracerebral haemorrhage volume at baseline (≤7 mL *vs* >7 to 30 mL *vs* >30 mL) to search for effects in small, medium, and large intracerebral haemorrhages. We did a sensitivity analysis of the effect of platelet transfusion on the primary outcome at hospitals that included at least five participants in which we also adjusted for including centre.

Analyses were done using IBM SPSS statistics version 22 (Cleveland, OH, USA). An independent data monitoring committee (appendix) oversaw the trial and agreed with the termination of the trial when it reached its prespecified sample size in Oct 8, 2015. A separate committee monitored the safety of participants enrolled in France (appendix). The trial is registered with the Netherlands Trial Register, number NTR1303.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data from the trial and had final responsibility for the results and submission for publication.

Results

Between Feb 4, 2009, and Oct 8, 2015, 41 sites enrolled 190 participants (figure 1). 97 participants were randomly assigned to receive standard care with platelet transfusion (platelet transfusion group) and 93 were assigned to standard care without transfusion (standard care group). No participants were lost to follow-up at 3 months and all were included in the final analyses after the last follow-up was completed on Jan 6, 2016.

Baseline characteristics were balanced between groups (table 1), apart from peripheral arterial disease, which was not considered of major prognostic relevance to the primary outcome. 36 (19%) participants had at least one exclusion criterion, 15 (15%) in the platelet transfusion group (12 had intraventricular haemorrhage, two had infratentorial localisation of haematoma, and one was not using antiplatelet therapy) and 21 (23%) in the standard care group (20 had intraventricular haemorrhage and one had thrombocytopenia). Baseline imaging was missing for centralised reading for two participants and intracerebral haemorrhage volume or intraventricular extension could not be measured for five participants because images were degraded by movement artifact.

Four participants assigned to platelet transfusion did not receive it, and two participants assigned to standard

	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95%CI)	p value
Alive at 3 months (survival)	66 (68%)	72 (77%)	0·62 (0·33–1·19)	0·15
mRS score 4–6 at 3 months	70 (72%)	52 (56%)	2·04 (1·12–3·74)	0·0195
mRS score 3–6 at 3 months	86 (89%)	76 (82%)	1·75 (0·77–3·97)	0·18
Median ICH growth at 24 h (mL)*	2·01 (0·32–9·34)	1·16 (0·03–4·42)	..	0·81

Data are n (%) or median (IQR). mRS=modified Rankin Scale. ICH=intracerebral haemorrhage. *n=80 in platelet transfusion group and 73 in standard care group.

Table 2: **Secondary outcomes in the intention-to-treat population**

care received a platelet transfusion (figure 1). Four protocol violations occurred in the platelet transfusion group (two participants did not receive the correct number of platelet concentrates and two received platelet transfusion out of the prespecified time window). Follow-up imaging at 24 h was missing for 17 participants in the platelet transfusion group (three omitted, five died, four imaged >27 h, and five poor quality) and for 20 participants in the control group (nine omitted, four died, two imaged >27 h, and five poor quality).

For the primary outcome, odds of a shift towards death or dependence at 3 months were higher in the platelet transfusion group than in standard care group without adjustment (crude common OR 1·84, 95% CI 1·10–3·08; p=0·0200) and with adjustment (adjusted common OR 2·05, 95% CI 1·18–3·56; p=0·0114; figure 2). In secondary analysis, more participants in the platelet transfusion group had poor outcome with an mRS score of 4–6 at 3 months than did those in the standard care group (table 2). Survival and the proportion of participants with an mRS score of 3–6 at 3 months did not significantly differ between groups; nor did intracerebral haemorrhage growth at 24 h (table 2). The distribution of the mRS was similar in participants who received platelet transfusion within 3 h of symptom onset versus those who received transfusion at 3–6 h (appendix).

40 (42%) participants who received platelet transfusion had a serious adverse event, as did 28 (29%) who received standard care (as-treated population; table 3). Most serious adverse events were intracerebral haemorrhage enlargement or urinary or pulmonary infections. One participant had a minor transfusion reaction. 24 (25%) participants assigned to platelet transfusion and 15 (16%) assigned to standard care died while in hospital. In an analysis of the as-treated population, most adverse events did not differ by group assignment. Serious adverse events due to intracerebral haemorrhage were higher in participants who received platelet transfusion than in those who received standard care (table 3). There was not a significant difference between groups in serious adverse events due to thromboembolism, but four people in the transfusion group had an event versus one in the standard therapy group. Safety outcomes in the intention-to-treat population did not differ between groups.

In the prespecified subgroup analyses, type of antiplatelet therapy, country, and haematoma volume

	Intention-to-treat population			As-treated population		
	Platelet transfusion group (n=97)	Standard care group (n=93)	Odds ratio (95% CI)	Platelet transfusion group (n=95)	Standard care group (n=95)	Odds ratio (95% CI)
Any SAE	41 (42%)	27 (29%)	1·79 (0·98–3·27)	40 (42%)	28 (29%)	1·74 (0·96–3·17)
Any fatal SAE	24 (25%)	15 (16%)	1·71 (0·83–3·51)	23 (24%)	16 (17%)	1·58 (0·77–3·22)
SAE due to ICH	24 (25%)	13 (14%)	2·02 (0·96–4·27)	24 (25%)	13 (14%)	2·13 (1·01–4·50)
ICH enlargement	15 (15%)	13 (14%)	1·13 (0·50–2·52)	15 (16%)	13 (14%)	1·18 (0·53–2·64)
Brain oedema	5 (5%)	0	11·12 (0·61–204·97)	5 (5%)	0	11·61 (0·63–212·94)
Brain herniation	2 (2%)	0	4·90 (0·23–103·33)	2 (2%)	0	5·11 (0·24–107·83)
Intraventricular extension	6 (6%)	0	13·28 (0·74–239·24)	6 (6%)	0	13·87 (0·77–249·82)
Hydrocephalus	3 (3%)	2 (2%)	1·45 (0·24–8·89)	4 (4%)	1 (1%)	4·13 (0·45–37·67)
SAE due to thromboembolism	4 (4%)	1 (1%)	3·96 (0·43–36·08)	4 (4%)	1 (1%)	4·13 (0·45–37·67)
Ischaemic stroke	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
Myocardial infarction	1 (1%)	1 (1%)	0·96 (0·06–15·55)	1 (1%)	1 (1%)	1·00 (0·06–16·23)
Extremity embolism	2 (2%)	0	4·90 (0·23–103·34)	2 (2%)	0	5·11 (0·24–107·81)
Pulmonary embolism	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
SAE due to transfusion						
Non-haemolytic	1 (1%)	0	2·91 (0·12–72·26)	1 (1%)	0	3·03 (0·12–75·37)
Anaphylactic	0	0	..	0	0	..
Acute lung injury	0	0	..	0	0	..
Post-transfusion purpura	0	0	..	0	0	..
Graft-versus-host disease	0	0	..	0	0	..
Transmitted bacterial infection	0	0	..	0	0	..
SAE due to other causes						
Infection (urinary or pulmonary)	14 (14%)	12 (13%)	1·14 (0·50–2·61)	14 (15%)	12 (13%)	1·20 (0·52–2·74)
Epileptic seizures	0	0	..	0	0	..
Other	6 (6%)	5 (5%)	1·16 (0·34–3·94)	7 (7%)	4 (4%)	1·81 (0·51–6·40)

Outcome data are n (%). Participants could have more than one SAE. Some SAEs were deemed to be due to several causes. SAE=serious adverse event. ICH=intracerebral haemorrhage.

Table 3: Safety outcomes occurring during hospital admission in the intention-to-treat and as-treated populations

had no significant interaction with the effect of platelet transfusion versus standard care (figure 3). Platelet transfusion remained inferior to standard care in our sensitivity analysis restricted to hospitals that included at least five participants (n=125; 66%) when the primary outcome was also adjusted for the hospital that included participants (adjusted OR 2·55, 95% CI 1·24–5·24, p=0·0107). In post-hoc analyses, the primary outcome remained unchanged when adjusted for intracerebral haemorrhage volume at baseline (adjusted common OR 1·90, 95% CI 1·08–3·36, p=0·0268) and after excluding the 36 participants who met at least one exclusion criterion (adjusted OR 2·22, 95% CI 1·20–4·09, p=0·0108). Due to insufficient uptake in standard clinical practice we did not perform the planned sub-studies of the spot sign on CT angiography and platelet function testing. We did not investigate causes of poor outcome, functional outcome using the AMC Linear Disability score, or health economics due to insufficient funding.

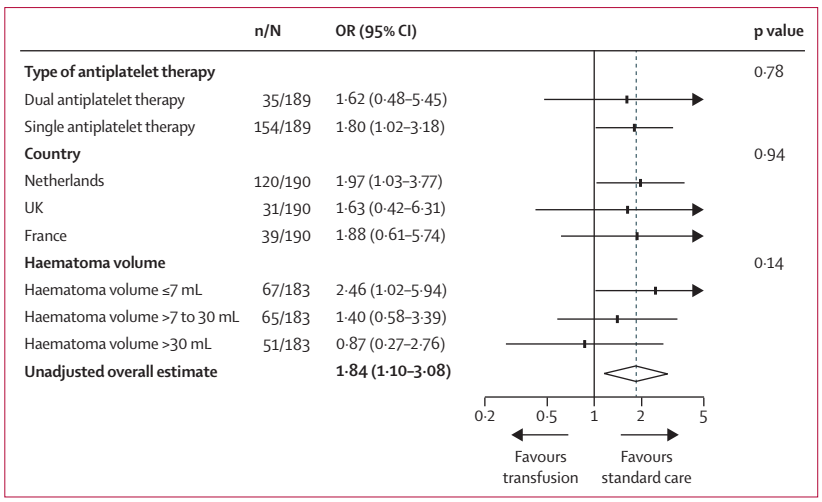

***Figure* 3: Subgroup analyses at 3 months in prespecified subgroups**
mRS=modified Rankin Scale. OR=odds ratio.

Discussion

Our randomised trial of nearly 200 participants shows that platelet transfusion seems to increase the risk of death or dependence in participants who have an acute intracerebral haemorrhage while taking antiplatelet therapy. This effect was consistent in predefined subgroups and remained after adjustment for pre-intracerebral haemorrhage antiplatelet therapy and known prognostic factors. These surprising findings are contrary to our hypothesis that platelet transfusion would reduce intracerebral haemorrhage growth and improve functional outcome, and are not consistent with small observational studies that have found better outcomes associated with the use of platelet transfusion.[12–14]

PATCH is the first randomised trial to investigate the effects of platelet transfusion on acute intracerebral haemorrhage after the use of antiplatelet therapy, and is one of few randomised trials to investigate the effect of platelet transfusion on active bleeding disorders.[9–11,16,17] In this multicentre trial, the effect of platelet transfusion on the primary outcome was consistent in three European countries, supporting the external validity of the trial (although its generalisability to low-income and middle-income countries is unknown). The baseline characteristics and outcomes of the included participants were similar to previous randomised trials for acute intracerebral haemorrhage.[25] Adherence to the assigned treatment was good and clinical follow-up for the primary outcome was complete (figure 1). The trial also achieved its target sample size.

However, the trial has some limitations. The sample size was smaller than in other acute stroke trials, reflecting the lower incidence of acute stroke due to intracerebral haemorrhage, its clinical severity,[5] and the demanding eligibility criteria we used.[27] This small sample size resulted in some chance imbalances in baseline prognostic variables, although their direction of effect was not consistent—ie, some of these imbalances might have biased the platelet transfusion group to a worse outcome and others might have biased it to a better outcome (table 1). Our findings could not be easily explained by chance imbalances in baseline characteristics, although residual confounding due to randomisation imbalances is possible, especially in light of the small sample size. Most of the participants had taken aspirin and relatively few had taken ADP inhibitors, so it is unknown whether the findings are generalisable to the increasing numbers of people who take ADP inhibitors. PATCH investigators were not required to keep screening logs, so the level of bias through selective inclusion is unknown. Furthermore, adherence to antiplatelet therapy for participants was not measured and we relied on information supplied by the participants, caregivers, or medical charts. Too few hospitals were able to test for platelet function to investigate whether function had modified treatment effect, as had been suggested by one observational study.[14] As is often the case in pragmatic trials in emergency settings, a fifth of participants (36 [19%]) met at least one exclusion criterion.[27] In particular, participants with intraventricular extension greater than sedimentation in the posterior horns of the lateral ventricles were included, possibly reflecting difficulty in interpretation of this criterion by clinicians. Because this protocol deviation was not equally distributed between treatment groups, we did a post-hoc sensitivity analysis excluding these participants, in which the findings for the primary outcome remained consistent.

Our findings contrast with the hypothesised mechanism of action of platelet transfusion. We did not find a clear mechanism to explain our findings among the reported safety outcomes (table 3), although there was a non-significant difference in serious adverse events due to thromboembolism and complications of intracerebral

haemorrhage were more common in the platelet transfusion group. Although conjecture, it remains possible that some participants actually had haemorrhagic transformation of infarction rather than intracerebral haemorrhage, or it is possible collateral perfusion around the intracerebral haemorrhage was impaired, resulting in cerebral ischaemia. Platelet transfusion could then increase the risk of thrombosis and result in lesion expansion. In a large observational study, people with thrombotic and prothrombotic disorders such as thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia who received platelet transfusions had increased mortality and myocardial infarction compared with those people who were not transfused.[28] Furthermore, platelets have proinflammatory effects and transfusions might enhance vascular permeability associated with inflammation and platelet consumption. Platelets can also be activated when stored, resulting in increased prothrombotic and inflammatory properties.[29] It is also possible that platelet transfusion might not be beneficial because the absolute increase in intracerebral haemorrhage growth associated with antiplatelet therapy is not large enough to be meaningfully modified by platelet transfusion, or that platelet transfusion is insufficient to reverse the effects of antiplatelet therapy on intracerebral haemorrhage growth. Most effective platelet transfusions are given for prophylaxis of bleeding, often in severe hypoproliferative thrombocytopenia in haematology-oncology participants.[30] The effect of platelet transfusions to stop or reverse ongoing bleeding might be beneficial or deleterious depending on the nature and location of the haemorrhage. These potential effects, combined with some baseline imbalances, could explain the detrimental effect of platelet transfusion in our trial. However, even if platelet transfusion was not harmful, our findings suggest that it is unlikely to be beneficial.

After the findings of the PATCH trial, platelet transfusion cannot be recommended for the treatment of acute intracerebral haemorrhage in people taking antiplatelet therapy because platelet transfusion seemed to worsen their outcome. A similar randomised trial is nearing completion (NCT00699621), and its results are needed to confirm our findings in acute intracerebral haemorrhage. Given the widespread use of platelet transfusion for other acute bleeding disorder despite a shortage of randomised evidence, our findings should lead to further trials so that this potentially hazardous and costly intervention is only used for prophylactic or therapeutic indications when supported by evidence from randomised controlled trials.

Contributors

MIB, CC, and RA-SS coordinated the trial and drafted the manuscript. MIB performed all analyses, supervised by YBR and RJdH. CC and RA-SS obtained funding for the trial and recruited centres and supervised the trial in the UK and France, respectively. KdG was involved in the design of the trial, recruitment of participating centres, and coordinated the trial in the Netherlands. MMK was involved in the design of the trial and coordinated availability of platelet transfusion for Dutch centres. CBM and LFB were involved in the design of the study and supervised the performance of all radiological measurements and interpretation. HAM designed the radiological endpoints and was consulted for all technical aspects of analysing the radiological parameters. He supervised and performed importing of all imaging and automated measurements with interpretation. AB and MV were involved in the original design of the trial and critically reviewed the manuscript. PJN and RJdH were involved in the design of the trial, the statistical analyses involved, and critically reviewed the manuscript. YBR designed the trial, obtained funding, recruited centres, and supervised the entire trial.

Declaration of interests

PJN reports fees for advisory work for Medtronic for atrial fibrillation registration in stroke used for the Academic Medical Center stroke research group. HAM is the cofounder and shareholder of Nico-lab. All other authors declare no competing interests.

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