A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.

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<td>bmjopen-2011-000588</td>
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<td>08-Nov-2011</td>
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<tr>
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Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

Forest Plot platelet Transfusion.wmf
A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.

Key Words: intracranial haemorrhage, platelet transfusion

Word Count: 2451

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ABSTRACT

Objectives
The administration of platelet transfusions is becoming standard practice in some Trauma centres for both spontaneous and traumatic antiplatelet associated intracranial haemorrhage. The aim of this study was to perform a meta-analysis to determine the effect on survival in the cohort of patients who have received a platelet transfusion compared to those who have not in antiplatelet associated intracranial haemorrhage (traumatic or spontaneous).

Design
The Medline database was searched using the Pubmed interface. The following search terms were used: 1. Head injury AND antiplatelet agents. 2. Intracranial haemorrhage AND platelet transfusion. Case control and nested case control studies comparing the cohort who were given platelet transfusions against the cohort who had not were included in the meta-analysis.

Results
218 abstracts were obtained from the Head Injury AND antiplatelet agents search. Four papers were accepted into the study. 222 abstracts were obtained from the intracranial haemorrhage AND platelet transfusion search. Two were accepted into the study. Two of the six studies were in patients with spontaneous intracranial haemorrhage. The remaining four studies were in patients with traumatic intracranial haemorrhage. Significant heterogeneity was present between the studies; \( I^2 = 58.276 \). The Random effects model was therefore the preferred model, this produced a pooled odds ratio for survival of 0.773 (95% CI: 0.414 – 1.442).

Conclusions
The results of this meta-analysis has shown, based upon six small studies that there was no clear benefit in terms of survival in the administration of a platelet transfusion to patients with antiplatelet associated intracranial haemorrhage.
INTRODUCTION

Antiplatelet agents, in particular Aspirin and Clopidogrel are both associated with a small risk of intracranial haemorrhage. He et al,[1] in 1998 performed a meta-analysis of 16 clinical trials and showed that aspirin treatment was associated with an absolute risk increase of haemorrhagic stroke of 12 events per 10,000 persons (95% CI: 5-20; P<0.001). With regard to traumatic intracranial haemorrhage early studies in this field (Mack et al, [2]. Spektor et al,[3]. Jones et al,[4]) failed to demonstrate antiplatelet agents as a risk factor for intracranial haemorrhage in patients with blunt head trauma. Fabbri et al,[5] in 2010 undertook a cohort study looking at predictors for intracranial haemorrhage on a database of 14,288 head injury patients. These authors found using multivariate logistic regression that the combination of age over 65 years and the use of antiplatelet agents statistically increased the risk of intracranial haemorrhage in their model. Preinjury use of antiplatelet agents alone was found to have an odds ratio of 1.2 (95% CI: 0.9 -1.7, p=0.202). Thus it may well be that the combination of increased age plus use of antiplatelet agents rather than antiplatelet agents in isolation increases the risk of traumatic intracranial haemorrhage (TICH) as suggested by Fabbri et al,[5].

McMillan et al,[6] proposed a protocol for the administration of a platelet transfusion in patients with traumatic intracranial haemorrhage who were on preinjury antiplatelet agents. The authors however admit in their own review that the evidence for this approach is lacking. A systematic review by Beshay et al,[7] provided an overview of the pharmacology of antiplatelet agents in the setting of intracranial haemorrhage. Cambell et al in 2010,[8] also provided a protocol for correcting platelet dysfunction in antiplatelet associated intracranial haemorrhage. These authors also recognised that the current evidence for this approach is limited. The administration of platelet transfusions has become standard practice in some trauma centres for traumatic antiplatelet associated intracranial haemorrhage. The aim of this study was to determine by meta-analysis the impact of a platelet transfusion on survival in patients on preinjury antiplatelet agents who sustain an intracranial hemorrhage (either spontaneous or traumatic).
METHODS

The Medline database was searched using the Pubmed interface. The following search terms were used:-

1. Head injury AND antiplatelet agents.
2. Intracranial haemorrhage AND platelet transfusion. Case control and nested case control studies comparing the cohort who were given platelet transfusions against the cohort who had not were included in the meta-analysis. The search strategy was run several times during the development of the paper in order to ensure that all of the relevant papers were captured up to the date of submission. The final run was performed on 10 August 2011.

Selection criteria was broadly based upon MOOSE,[9] methodology. Inclusion criteria were 1. Case control studies comparing mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who received a platelet transfusion versus mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who did not receive a platelet transfusion. No lower limit was placed on the size of the study groups in either the case control or nested case control studies. 2. Cohort studies with a nested case control group comparing mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who received a platelet transfusion versus mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who did not receive a platelet transfusion. 3. Case control studies or nested case control studies comparing mortality rates of adult patients on antiplatelet agents with spontaneous intracranial haemorrhage who received a platelet transfusion versus mortality rates of adult patients on antiplatelet agents with spontaneous intracranial haemorrhage who did not receive a platelet transfusion. No lower limit was placed on the size of the study groups in either the case control or nested case control studies. Appraisal of the full papers was made by both authors. All relevant studies had a Jadad score,[10] of zero in view of the fact that they were non randomised case control studies.

Heterogeneity between studies was performed using the Q test and the I² test. Statistical analysis was performed using Comprehensive Meta-analysis version 2 (meta-analysis.com; Biostat Inc, NJ 07631, NJ, USA). Articles were eligible for inclusion from
any language provided that they were published in peer reviewed journals. Year range: 1950 to the current year (August, 2011). Exclusion criteria: 1. Case control or cohort studies which did not separate out antiplatelet agents from warfarin anticoagulation or from other potential clotting abnormalities. 3. Case control or nested case control studies in patients with intracranial haemorrhage from thrombocytopaenia. All of the abstracts and full papers reviewed were in English language and therefore problems with translation were not encountered. Abstracts from proceedings were not included in the search strategy neither was a search for unpublished data performed. Contact was not made with authors of any of the studies, the data was extracted directly either from the abstract or the full text.
RESULTS

218 citations were obtained using the search terms *Head Injury AND antiplatelet* agents. Twenty-seven abstracts were reviewed for relevance and from these twenty-four papers were reviewed in full. Four papers were accepted into the study. Forty-six citations were obtained using the search terms *Head Injury AND Platelet Transfusion*. Five relevant abstracts were identified; after deduplication no new abstracts were obtained. 222 citations were obtained using the search terms *intracranial haemorrhage AND platelet transfusion*. Deduplication produced four new abstracts which were reviewed as full papers. Two were accepted into the study. Two of the six studies included in this meta-analysis were case controlled studies in patients with spontaneous intracranial haemorrhage, the remaining four studies were in patients with traumatic intracranial haemorrhage. Cross referencing produced no further studies.

Significant heterogeneity was present between the studies; $I^2 = 58.276$ Therefore the Random effects model was the preferred model, this produced a pooled odds ratio for survival of 0.773 (95% CI: 0.414 – 1.442). The Fixed effects model was also evaluated and this was found to produce a similar results (common odds ratio for survival: 0.798; 95% CI: 0.559 – 1.139). The Forest plot is shown in Figure 1.

**Figure 1**
An overview of the six studies is provided below in order to identify reasons for heterogeneity or possible confounding factors. A comparison of the studies by age, mean GCS and mortality rates are provided in Tables 1, 2 and 3 respectively. The study by Washington et al.[11] was a retrospective cohort study. The inclusion criteria were isolated head injuries with a GCS ≥ 13 and intracranial haemorrhage on CT in patients on preinjury antiplatelet therapy. A comparison was made between the group who had received a platelet transfusion with the group who did not. Administration of the platelet transfusion was administered at the discretion of the attending surgeon. Primary outcome measures were neurological decline, Glasgow Outcome Scale, surgical intervention and mortality.

Table 1: Comparison Of Studies By Mean Age

<table>
<thead>
<tr>
<th>Author</th>
<th>Transfused Group</th>
<th>Control Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington et al.</td>
<td>74.3 ± 11.7</td>
<td>75.4 ± 12.3</td>
<td>.63</td>
</tr>
<tr>
<td>Ducruet et al.</td>
<td>73.2 ± 10.1</td>
<td>71.7 ± 13.5</td>
<td>.597</td>
</tr>
<tr>
<td>Creutzfeldt et al.</td>
<td>70</td>
<td>71</td>
<td>.65</td>
</tr>
<tr>
<td>Downey et al.</td>
<td>77.4</td>
<td>73.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>87.2 ± 10.5</td>
<td>76.8 ± 9.9</td>
<td>.473</td>
</tr>
<tr>
<td>Fortuna et al.</td>
<td>73 ± 2</td>
<td>68 ± 1</td>
<td>.02</td>
</tr>
</tbody>
</table>
### Table 2: Comparison Of Studies By Mean GCS

<table>
<thead>
<tr>
<th>Author</th>
<th>Transfused Group</th>
<th>Control Group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington et al</td>
<td>14.8</td>
<td>14.8</td>
<td>0.52</td>
</tr>
<tr>
<td>Ducruet et al.</td>
<td>11.8 ± 3.8</td>
<td>11.8 ± 3.7</td>
<td>0.992</td>
</tr>
<tr>
<td>Creutzfeldt et al</td>
<td>13*</td>
<td>11*</td>
<td>0.10</td>
</tr>
<tr>
<td>Downey et al.</td>
<td>NQ**</td>
<td>NQ**</td>
<td>0.96</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>13.5 ± 3.0</td>
<td>13.7 ± 2.8</td>
<td>0.676</td>
</tr>
<tr>
<td>Fortuna et al.</td>
<td>11 ± 1</td>
<td>13 ± 0.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Mean GCS value calculated by Batchelor et al.
$ p value Wilcoxon’s test calculated by Washington et al.
*Median first GCS score
** NQ: mean values not quoted only p value given

### Table 3: Mortality Rates for The Five Studies

<table>
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<tr>
<th>Author</th>
<th>Transfused Group</th>
<th>Control Group</th>
</tr>
</thead>
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</tr>
<tr>
<td>Ducruet et al.</td>
<td>12.9%</td>
<td>6.5%</td>
</tr>
<tr>
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<tr>
<td>Downey et al.</td>
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<tr>
<td>Ivascu et al.</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td>Fortuna et al.</td>
<td>30%</td>
<td>16%</td>
</tr>
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</table>
The study by Ducruet et al,[12] was a retrospective case control study of patients with primary intracerebral haemorrhage. The primary outcome measure was to detect a 25% difference in haematoma expansion from the CT on admission between the platelet transfused group and the non transfused group. Other outcome parameters were the modified Rankin Score on discharge, mortality rate and the rate of systemic complications. The study by Creutzfeldt et al,[13] was a retrospective cohort study. All patients had spontaneous rather than traumatic intracranial haemorrhage, Patients with an INR greater than 1.5 were excluded. A comparison was made between the group who had received a platelet transfusion with the group who did not. The primary outcome measure was hospital death. Secondary outcome measure was favourable outcome. The study by Downey et al,[14] was a retrospective case control study comparing patients with traumatic brain injury on preinjury antplatelet agents who received a platelet transfusion against patient with traumatic brain injury on antiplatelet agents who did not receive a platelet transfusion. Primary outcome measure was mortality. Secondary outcome measure was length of hospital stay. The study by Ivascu et al,[15] was a retrospective cohort study of patients on preinjury antiplatelet agents with traumatic intracranial haemorrhage, patients were 50 years of age or older. A comparison was made between the group who had received a platelet transfusion with the group who did not. The primary outcome measure was mortality. The Fortuna study,[16] was a retrospective review of patients over the age of 49 years with blunt head trauma who were taking either preinjury warfarin, clopidogrel or aspirin. The data from the study indicates that patients on antiplatelet agents were not taking warfarin as well. Data was available to compare the group of patients who received platelet transfusion therapy against the group of patients who did not. The primary outcome measure was mortality.
DISCUSSION

Six studies were identified for the meta-analysis, two studies evaluating patients with spontaneous intracranial haemorrhage and four with traumatic intracranial haemorrhage. Interestingly the two studies evaluating platelet transfusions in patients with spontaneous intracranial haemorrhage both showed a slight benefit although due to the small size of the studies neither reached statistical significance. All four trauma studies showed no additional benefit for the administration of a platelet transfusion. Due to the small number of published studies to date the spontaneous cohort was combined with the traumatic cohort.

The Ducruet study,[12] was well controlled with regard to age (p=0.597) and mean GCS (p=0.992). The indications for giving a platelet transfusion were not available to the investigators, although the assumption was that a platelet transfusion was given at the discretion of the attending physician. The mortality rate in the treatment group was half that in the non treatment group however due to the small numbers (4/31 versus 2/35) the result did not reach statistical significance. The Creutzfeldt study,[13] was well controlled for age and median GCS. The indications for using a platelet transfusion were also not available to the investigating authors. The mortality rate in the control group was quite high in comparison to the other studies. Due to the small size of the study the difference in the mortality rate between the study group and the control group did reach statistical significance.

The study by Downey et al,[14] was well controlled with respect to the presenting GCS (p=0.96) but not with respect to age. Patients who received a platelet transfusion were older than the control group (p=0.001). Thirty-one patients received a platelet transfusion at the discretion of the attending surgeon at one center. At the second study center 135 patients received a platelet transfusion as part of a routine procedure if the PFA-100 screening test showed evidence of platelet dysfunction. There was little difference in mortality between the control group and the treatment group.
The Ivascu study,[15] was reasonably well controlled with regard to age and presenting GCS. Patients received a platelet transfusion at the discretion of the attending surgeon. The Injury Severity Score was slightly higher in the transfusion group than in the control group (23.4 versus 20.3; p = 0.183). This may be the explanation for the sizeable difference in the mortality between the two groups with the higher mortality being in the transfusion group (28% versus 13%; p = 0.064). The Fortuna study,[16] was poorly controlled for age and GCS, a platelet transfusion was given at the discretion of the attending surgeon. The patients receiving platelet transfusion were generally older (p=0.02) and had more severe disease as demonstrated by the lower GCS at presentation (p= 0.004). As a consequence patients in the platelet transfusion group had a higher mortality than those in the group which did not receive a platelet transfusion.

Mortality rate is a relatively crude indicator of platelet transfusion effect in this clinical setting. Cerebral haematoma size, haematoma progression and outcome scores are more sensitive markers. The only outcome measure common to all six studies was mortality which is the principle reason for choosing this clinical marker. With regard to spontaneous intracranial haemorrhage three important papers relevant to this subject need to be discussed. Sansing et al,[17] undertook a retrospective cohort study on 282 patients with spontaneous intracranial haemorrhage, 70 patients were on antiplatelet medication. The authors found no difference between the antiplatelet medication group and the no antiplatelet group with regard to volume of intracranial haemorrhage on CT, haematoma growth or outcome score. Naidech et al,[18] performed a cohort study on 68 patients with spontaneous intracranial haemorrhage who were either on antiplatelet agents or had laboratory evidence of reduced platelet function. A platelet transfusion was administered in 16 patients at the discretion of the attending physician. The authors found that there was no difference in the modified Rankin Scale at 14 days, 28 days and 3 months between the transfused group and the non transfused group. Naidech,[19] et al in 2011 published their findings from a prospective cohort study on 45 patients with spontaneous intracranial haemorrhage and reduced platelet activity The cohort was divided into high risk for haemorrhage growth grade and non high risk patients for
haemorrhage growth. High risk patients received a CT and platelet transfusion within 12 hours of symptom onset. Non high risk patients received a CT and platelet transfusion after 12 hours. The authors found that for the high risk group platelet transfusion within 12 hours resulted in smaller haemorrhage size and better outcome (modified Rankin Score) compared to the cohort of patients who received a platelet transfusion after 12 hours. Further work is required in some of these areas, in particular to clarify the effect of preinjury antiplatelet agents on haematoma size and progression.

Conclusions

The small size of the studies none of which were powered to demonstrate a difference in survival clearly means that no firm conclusions can be draw from this meta-analysis. Except for the study by Downey et al.[14] platelet transfusion in the remaining studies were given at the discretion of the attending surgeon. Despite this limitation there was reasonable matching between the treatment groups and the control groups. The relative importance of this subject however has prompted a multiple centre randomised control trial based in the Netherlands, The PATCH study,[20] in order to address the potential efficacy of platelet transfusion in patients with antiplatelet associated intracranial haemorrhage. The end points of the study are safety of platelet transfusion and haematoma progression.
ADDITIONAL INFORMATION

Contributorship Statement

Mr Batchelor reviewed all the abstracts, reviewed all the full papers, performed the statistical analysis and wrote the paper.

Collaborator

Dr Alan Grayson was involved in the early stages of the search strategy and reviewed some of the abstracts.

Competing Interests

There are no competing interests.

Data sharing Information

There is no additional data available

Funding Statement.

This research received no specific grant from any agency in the public, commercial or not-for-profit sectors.
ARTICLE SUMMARY

Article Focus

The aim of this meta-analysis was to determine the impact on survival of a platelet transfusion in patients on preinjury antiplatelet agents with:-

- traumatic intracranial haemorrhage following blunt head trauma
- spontaneous intracranial haemorrhage

Key Messages

- Six studies were found to be suitable for the meta-analysis. (Two studies for spontaneous intracranial haemorrhage, the remaining four were traumatic intracranial haemorrhage).
- The pooled odds ratio showed no benefit in survival following a platelet transfusion (OR =0.773 (95% CI: 0.414 – 1.442).

Strengths and Limitations

- The studies were small, unpowered and not randomised
- Mortality is a relatively crude marker of effect in the cohort of patients with either spontaneous or traumatic haemorrhage.
REFERENCES


**LEGENDS**

**Figure 1: Forest Plot For The Six Studies**

(Random Effects Model)
MOOSE Checklist

A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.

Author List

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Consultant In Emergency Medicine

Co-author: Alan Grayson MB ChB
Specialist Registrar in Emergency Medicine

Name and address for correspondence.

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<td>Trauma centres in North America in particular are administering platelet transfusions to patients with antiplatelet related intracranial haemorrhage (both spontaneous and traumatic). The current evidence for this approach however has not been fully evaluated.</td>
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<td>Platelet transfusion decreases mortality in antiplatelet associated intracranial haemorrhage.</td>
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<td>√ Description of study outcomes</td>
<td>Mortality rates from intracranial haemorrhage</td>
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<tr>
<td>√ Type of exposure or intervention used</td>
<td>Platelet transfusion</td>
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<td>√ Type of study designs used</td>
<td>We included case-control studies and cohort studies,</td>
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<td>√ Study population</td>
<td>Traumatic or spontaneous intracranial haemorrhage in adults.</td>
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<td>We did not employ any search software.</td>
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<td>√ Use of hand searching</td>
<td>We hand-searched bibliographies of retrieved papers for additional references,</td>
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<td>√ List of citations located and those</td>
<td>Details of the literature search process are outlined in the results section ( page 6). The citation list is available upon request</td>
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<td>Detailed inclusion and exclusion criteria were described.</td>
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<td>appropriateness of studies assembled for assessing the hypothesis to be tested</td>
<td>in the methods section.</td>
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<tr>
<td>√ <strong>Rationale for the selection and coding of data</strong></td>
<td>Data extracted from each of the studies provided mortality rates for patients with intracranial haemorrhage with or without a platelet transfusion.</td>
</tr>
<tr>
<td>√ <strong>Assessment of confounding</strong></td>
<td>Potential confounding variables were identified and tabulated. p values for potential confounding variables were given in the appropriate tables</td>
</tr>
<tr>
<td>√ <strong>Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results</strong></td>
<td>Only six studies were identified where a comparison was made between the platelet transfusion group and the none transfusion. All of the studies were low quality, no randomization. Transfusion was given at the discretion of the attending surgeon except in one study where it was dependent on the platelet activity. All papers reviewed in full where relevant had a Jadad score of 0.</td>
</tr>
<tr>
<td>√ <strong>Assessment of heterogeneity</strong></td>
<td>Heterogeneity of the studies were explored within two types of study designs using Cochrane’s Q test of heterogeneity and $I^2$ statistic that provides the relative amount of variance of the summary effect due to the between-study heterogeneity.</td>
</tr>
<tr>
<td>√ <strong>Description of statistical methods in sufficient detail to be replicated</strong></td>
<td>The number of deaths in the treatment group were compared to the number of deaths in the non treatment groups using both the Fixed effect and Random effect models.</td>
</tr>
<tr>
<td>√ <strong>Provision of appropriate tables and graphics</strong></td>
<td>We included the Forest plot and three addition Tables for a comparison of Mean Age, Mean GCS and Mortality rates between the 2 groups.</td>
</tr>
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</table>

**Reporting of results should include**

<p>| √ <strong>Graph summarizing individual study estimates and overall estimate</strong> | Figure 1 |
| √ <strong>Table giving descriptive information for each study included</strong> | Table 1,2,3 |
| √ <strong>Indication of statistical uncertainty of findings</strong> | 95% confidence intervals were presented with all summary estimates, $I^2$ values and results of sensitivity analyses |</p>
<table>
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<tr>
<td>√ Quantitative assessment of bias</td>
<td>The main source of potential bias is due to the fact that the more severely injured or affected patients may have received the transfusion. Therefore a comparison was may between groups with regard to mortality rates and mean GCS</td>
</tr>
<tr>
<td>√ Justification for exclusion</td>
<td>We excluded studies that included other preinjury clotting abnormalities such as warfarin</td>
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<td>√ Assessment of quality of included studies</td>
<td>We discussed the fact that all studies were of low quality.</td>
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<th>Reporting of conclusions should include</th>
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<td>√ Consideration of alternative explanations for observed results</td>
<td>We discussed the potential lack of effect of the platelet transfusion may be due to the low quality of the studies rather than a lack of treatment effect.</td>
</tr>
<tr>
<td>√ Generalization of the conclusions</td>
<td>Further studies are required to establish whether platelet transfusions are beneficial in this cohort of patients</td>
</tr>
<tr>
<td>√ Guidelines for future research</td>
<td>We recommend future studies on the effect of haematoma size, haematoma growth and other outcome measures.</td>
</tr>
<tr>
<td>√ Disclosure of funding source</td>
<td>No separate funding was necessary for the undertaking of this systematic review.</td>
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A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.
TITLE

A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.

Key Words: intracranial haemorrhage, platelet transfusion

Word Count: 3437

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ABSTRACT

Objectives

The aim of this study was to evaluate by meta-analysis the current level of evidence in order to establish the impact of a platelet transfusion on survival in patients on preinjury antiplatelet agents who sustain an intracranial hemorrhage (either spontaneous or traumatic).

Design

This was a meta-analysis, the Medline database was searched using the PubMed interface and the Ovid interface. CINAHL and EMBASE databases were also searched. The search was performed to identify RCT’s, case controlled studies or nested case controlled studies comparing the outcome (death or survival) of patients with intracranial haemorrhage and preinjury antiplatelet agents who received a platelet transfusion against a similar cohort of patients who did not receive a platelet transfusion.

Results

Four hundred and ninety-nine citations were obtained from the PubMed search. Thirty-one full articles were reviewed from 34 abstracts. Six studies were found suitable for the meta-analysis. No randomised controlled studies were identified. Two of the six studies were in patients with spontaneous intracranial haemorrhage. The remaining four studies were in patients with traumatic intracranial haemorrhage. Significant heterogeneity was present between the studies; \( I^2 = 58.276 \). The Random effects model was therefore the preferred model, this produced a pooled odds ratio for survival of 0.773 (95% CI: 0.414 – 1.442).

Conclusions

The results of this meta-analysis has shown, based upon six small studies that there was no clear benefit in terms of survival in the administration of a platelet transfusion to patients with antiplatelet associated intracranial haemorrhage. Further work is required in order to establish any potential benefit in the administration of a platelet transfusion in patients with spontaneous or traumatic intracranial haemorrhage who were on preinjury antiplatelet agents.

There is no trial or study registration number for this meta-analysis.
INTRODUCTION

Antiplatelet agents, in particular Aspirin and Clopidogrel are an essential component of treatment and prophylaxis for both cardiovascular disease and cerebrovascular; however they are both associated with a small risk of intracranial haemorrhage. He et al,[1] in 1998 performed a meta-analysis of 16 clinical trials and showed that aspirin treatment was associated with an absolute risk increase of haemorrhagic stroke of 12 events per 10,000 persons (95% CI: 5-20; P<0.001). With regard to traumatic intracranial haemorrhage early studies in this field (Mack et al, [2]. Spektor et al,[3]. Jones et al,[4]) failed to demonstrate antiplatelet agents as a risk factor for intracranial haemorrhage in patients with blunt head trauma. Fabbri et al,[5] in 2010 undertook a cohort study looking at predictors for intracranial haemorrhage on a database of 14,288 head injury patients. These authors found using multivariate logistic regression that the combination of age over 65 years and the use of antiplatelet agents statistically increased the risk of intracranial haemorrhage in their model. Preinjury use of antiplatelet agents alone was found to have an odds ratio of 1.2 (95% CI: 0.9 - 1.7, p=0.202). Thus it may well be that the combination of increased age plus use of antiplatelet agents rather than antiplatelet agents in isolation increases the risk of traumatic intracranial haemorrhage (TICH) as suggested by Fabbri et al,[5].

McMillan et al,[6] proposed a protocol for the administration of a platelet transfusion in patients with traumatic intracranial haemorrhage who were on preinjury antiplatelet agents. The authors however admit in their own review that the evidence for this approach is lacking. A systematic review by Beshay et al,[7] provided an overview of the pharmacology of antiplatelet agents in the setting of intracranial haemorrhage. Cambell et al in 2010,[8] also provided a protocol for correcting platelet dysfunction in antiplatelet associated intracranial haemorrhage. These authors also recognised that the current evidence for this approach is limited. The administration of platelet transfusions is practiced in some trauma centres for traumatic antiplatelet associated intracranial haemorrhage. The aim of this study was to evaluate by meta-analysis the current level of evidence in order to establish the impact of a platelet transfusion on survival in patients on preinjury antiplatelet agents who sustain an intracranial hemorrhage (either spontaneous or traumatic).
METHODS

The MEDLINE database was searched using the Pubmed interface. The following search terms were used: - 1. **Head injury AND antiplatelet agents.** 2. **Intracranial haemorrhage AND platelet transfusion.** Case control and nested case control studies comparing the cohort who were given platelet transfusions against the cohort who had not were included in the meta-analysis. The search strategy was run several times during the development of the paper in order to ensure that all of the relevant papers were captured up to the date of submission. The final Pubmed search was performed on 30 November 2011. The Athens website was also utilised to search the UK MEDLINE database, EMBASE and CINAHL databases. The search was performed on the 30th November. A full review of the search strategy is provided in appendix 1. No limits were placed on the search using either the Pubmed portal or the Athens portal with regard to year range, age range or language. Thirdly, a search for randomised controlled trials was performed using the Cochrane database. A full review of the search strategy is provided in appendix 1.

Selection criteria was broadly based upon MOOSE,[9] methodology. Inclusion criteria were 1. Randomised controlled trials comparing patients with aspirin related intracranial haemorrhage (spontaneous or traumatic) who were treated with a platelet transfusion compared to patients with aspirin related intracranial haemorrhage who were not treated with a platelet transfusion. 2. Case control studies comparing mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who received a platelet transfusion versus mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who did not receive a platelet transfusion. No lower limit was placed on the size of the study groups in either the case control or nested case control studies. 3. Cohort studies with a nested case control group comparing mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who received a platelet transfusion versus mortality rates of adult head injury patients on antiplatelet agents (with intracranial haemorrhage) who did not receive a platelet transfusion. 4. Case control studies or nested case control studies comparing mortality rates of adult patients on antiplatelet agents with spontaneous intracranial haemorrhage who received a platelet transfusion versus mortality rates of adult patients on antiplatelet agents with spontaneous intracranial haemorrhage who did not receive a
platelet transfusion. No lower limit was placed on the size of the study groups in either the case control or nested case control studies. Appraisal of the abstract titles for relevance was made by John Batchelor and Alan Grayson. All full papers were reviewed by John Batchelor and Alan Grayson.

Articles were eligible for inclusion from any language provided that they were published in peer reviewed journals. Exclusion criteria: 1. Case control or cohort studies where patient transfusion was used to correct a generalised coagulopathy. 2. Case control or nested case control studies in patients with intracranial haemorrhage from thrombocytopenia. All of the abstracts and full papers reviewed were in English language and therefore problems with translation were not encountered. Abstracts from proceedings were not included in the search strategy neither was a search for unpublished data performed. Contact was not made with authors of any of the studies, the data was extracted directly either from the abstract or the full text.

Statistical analysis was performed using Comprehensive Meta-analysis version 2 (meta-analysis.com; Biostat Inc, NJ 07631, NJ, USA). Forest plots were produced for the studies with respect to mortality. Heterogeneity between studies was performed using the I² test.
RESULTS

Six studies were identified which were found to be suitable for the meta-analysis. Two studies were case controlled studies in patients with spontaneous intracranial haemorrhage, the remaining four studies were in patients with traumatic intracranial haemorrhage. No completed randomised controlled trials were identified. The inclusion and exclusion PRISMA flow diagram is shown in Figure 1. A more detailed summary of the results of the search strategy is shown in appendix 1.

Figure 1

Characteristics Of Included Studies

Washington and his group,[10] from Missouri retrospectively reviewed 1,101 patients presenting to their level one trauma centre over a two year period with minor traumatic brain injury (GCS >= 13). Of these, 321 had traumatic ICH and 113 (35.2%) were on pre-injury antiplatelet agents. The two groups were similar at baseline in terms of age and presenting GCS. Primary outcome measures were neurological decline, Glasgow Outcome Scale, surgical intervention and mortality. Platelet transfusion was given according to physician discretion, introducing a risk of bias. The transfused group had a higher Marshall score, reflecting a larger haematoma volume (20.6 +/- 26.5 v 8.2 +/- 13.7; p = 0.02), at presentation. There was a significantly more patients in the transfused group taking clopidogrel compared to the non transfused group (52% versus 20%, p = 0.0005). They found no statistically significant difference in outcome between the groups; they did find a trend towards significance for medical decline (defined a priori as an increase in the delivered level of monitoring or intervention because of cardiac, pulmonary or renal decline). Mortality rates were not significant between the two groups (2/44 (5%) versus 0/64 (0%)). They did however find that of all the traumatic brain injury (TBI) patients included, any patient receiving a transfusion (n=65; 20%) had a significantly higher
mortality (6% v 0%; p<0.0001) and odds ratio of medical decline (5.8; 95% CI 1.2 to 28.2).

The study by Ducruet et al,[11] was a retrospective cohort study of 66 patients admitted to a neurological ICU with a primary intracranial haemorrhage (ICH) whilst on antiplatelet agents. 105 of 121 patients were on aspirin alone, 11 of 121 patients were taking aspirin and clopidogrel. Of the remaining 5 patients patients 2 were on dipyridamole and the final 3 not specified. Of these, 35 (53.8%) received a platelet transfusion. The primary outcome measure was to detect a 25% difference in haematoma expansion from the CT on admission between the platelet transfused group and the non transfused group. Other outcome parameters were the modified Rankin Score on discharge, mortality rate and the rate of systemic complications The indications for giving a platelet transfusion were not available to the investigators, although the assumption was that a platelet transfusion was given at the discretion of the attending physician. This may introduce an element of bias into the study and is to the detriment of the paper. The groups were well matched with regard to age (p=0.597) and mean GCS (p=0.992). The mortality rate in the treatment group was half that in the non treatment group however due to the small numbers (2/35 (5.7%) versus 4/31 (12.9%)), the result did not reach statistical significance. They also noted no statistical significance in either initial or final haematoma volume (initial volume (ml) 30.9 +/- 28.3 vs 27.7 +/- 25.4, p=0.63; final volume 33.9 +/-32.6 vs 33.1 +/- 30.8, p=0.92), length of stay or discharge modified Rankin score (4.1 +/- 1.3 vs 4.5 +/- 0.9). The study did suggest a trend towards increased mortality (23.1% versus 6.1%; p=0.10) and haematoma expansion (35.7% versus 11.8%; p=0.034) in patients taking clopidogrel rather than those taking aspirin alone.

The Creutzfeldt study,[12] was a single-centre, retrospective study of 368 consecutive patients with spontaneous ICH over two years admitted to a primary stroke centre. Of these, 121 (31.3%) were taking antiplatelet agents (aspirin 105, clopidogrel 3, aspirin + clopidogrel 11, aspirin + dipyridamole 2). The primary
outcome measure was hospital death. Secondary outcome measure was favorable outcome. This study was again well matched for age (70 versus 71; p=0.65); however, median GCS (13 (9-15) versus 11 (6.5-14); p=0.1) was lower at presentation, suggesting that some of the group not receiving a platelet transfusion were deemed unsalvageable and palliation was the preferred treatment pathway, as reflected by the increased Do Not Attempt Resuscitation order frequency (34% versus 44%). The indications for using a platelet transfusion were also not available to the investigating authors and again, it must be assumed that this was given at the discretion of the attending physician with the caveats described above. The mortality rate in the control group (38%) was quite high in comparison to the other studies. In the patients who died in the intervention group, all 14 died because of withdrawal of treatment, presumably due to futility of continued management. Due to the small size of the study the difference in the mortality rate between the study group and the control group did reach statistical significance (p=0.17).

The study by Downey et al,[13] was a retrospective review over 4 years in two Level 1 trauma centres. They identified 328 patients over 50 with TBI on preinjury antiplatelet therapy of whom 166 (50.6%) received platelet transfusion. Primary outcome measure was mortality. Secondary outcome measure was length of hospital stay. The two groups were well matched with respect to the presenting GCS (p=0.96) but not with respect to age. Patients who received a platelet transfusion were older than the control group (p=0.001). This may reflect the increased prevalence of cardiovascular and cerebrovascular disease in a more elderly population. Thirty-one patients received a platelet transfusion at the discretion of the attending surgeon at one center. At the second study center 135 patients received a platelet transfusion as part of a routine procedure if the PFA-100 screening test showed evidence of platelet dysfunction. There was little difference in mortality between the treatment group and the control group (17.5% versus 16.7%). Additional confounders include the higher rates of both warfarin use (89% versus 80%; p=0.038) and clopidogrel use (45% versus 14%; p<0.001). Unfortunately, the data as described do not allow separation of these
two groups. The warfarin group had an increased mortality (27.5% versus 15.2%; p=0.032); the clopidogrel group did not (15.5% versus 17.7%; p=0.62), which contradicts the findings of the later study by Creutzfeldt et al.[12].

The Ivascu study,[14] was a retrospective review of a trauma registry over a five year period of patients with ICH who were taking preinjury antiplatelet agents. In total 109 patients were identified; 61 patients were on aspirin, 17 patients were on clopidogrel and 31 patients were on both. Of these 109 patients, 40 (36.7%) were given a platelet transfusion, again at the discretion of the attending physician. The primary outcome measure was mortality. The patients in this study were reasonably well matched with regard to age (p=0.593) and presenting GCS (p=0.332). The Injury Severity Score was slightly higher in the transfusion group than in the control group (23.4 +/- 9.8 vs 20.3 +/- 6.7; p = 0.183). This may be the explanation for the sizeable difference in the mortality between the two groups with the higher mortality being in the transfusion group (27.5% versus 13.0%; p = 0.064), as may also explain the increased proportion in the transfusion group operated upon compared to the non transfused group (9/40 {22.5%} versus 8/69 {11.5%}); p=0.137).

The Fortuna study,[15] was a retrospective review of patients with TBI aged over 50 years in a single, tertiary, Level 1 trauma centre. They identified 521 patients fitting these criteria, but acknowledge that they did exclude patients in whom the medical records were incomplete. Of the 521 patients, 166 were taking preinjury antiplatelet and anticoagulant therapy. 126 patients were taking antiplatelet agents (17 clopidogrel, 91 aspirin and 18 were taking both), 29 patients were taking warfarin and 11 patients “other” unspecified medication. 66 (39.8%) of these 166 patients received a platelet transfusion during their stay. Patients receiving a platelet transfusion were older (73 +/- 2 versus 69 +/- 1; p=0.02), had a lower initial GCS (11 +/-1 versus 13 +/- 0.2; p=0.004), a higher initial ISS (28 +/- 1 versus 24 +/- 1; p=0.001) and a longer length of stay (12 +/- 2 versus 7 +/- 0.4 days; p=0.007); all of these may have contributed to the higher mortality (20/66; 30.3%) compared to those in the group which did not receive a
platelet transfusion (16/100; 16%). As with many of the preceding papers, the platelets were given at the discretion of the attending physician.

A comparison of the studies by age, mean GCS and mortality rates are provided in Tables 1, 2 and 3 respectively.

Table 1: Comparison Of Studies By Mean Age

<table>
<thead>
<tr>
<th>Author</th>
<th>Transfused Group Mean Age</th>
<th>Control Group Mean Age</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Washington et al.</td>
<td>74.3 ± 11.7</td>
<td>75.4 ± 12.3</td>
<td>.63</td>
</tr>
<tr>
<td>Ducruet et al.</td>
<td>73.2 ± 10.1</td>
<td>71.7 ± 13.5</td>
<td>.597</td>
</tr>
<tr>
<td>Creutzfeldt et al.</td>
<td>70</td>
<td>71</td>
<td>.65</td>
</tr>
<tr>
<td>Downey et al.</td>
<td>77.4</td>
<td>73.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>87.2 ± 10.5</td>
<td>76.8 ± 9.9</td>
<td>.473</td>
</tr>
<tr>
<td>Fortuna et al.</td>
<td>73 ± 2</td>
<td>68 ± 1</td>
<td>.02</td>
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</tbody>
</table>
Table 2: Comparison Of Studies By Mean GCS

<table>
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<th>Transfused Group</th>
<th>Control Group</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td>Washington et al</td>
<td>14.8@</td>
<td>14.8</td>
<td>0.52$</td>
</tr>
<tr>
<td>Ducruet et al.</td>
<td>11.8 ± 3.8</td>
<td>11.8 ± 3.7</td>
<td>0.992</td>
</tr>
<tr>
<td>Creutzfeldt et al.</td>
<td>13*</td>
<td>11*</td>
<td>0.10</td>
</tr>
<tr>
<td>Downey et al.</td>
<td>NQ**</td>
<td>NQ**</td>
<td>0.96</td>
</tr>
<tr>
<td>Ivascu et al.</td>
<td>13.5 ± 3.0</td>
<td>13.7 ± 2.8</td>
<td>0.676</td>
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<tr>
<td>Fortuna et al.</td>
<td>11 ± 1</td>
<td>13 ± 0.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

@ Mean GCS value calculated by Batchelor et al.
$ p value Wilcoxon’s test calculated by Washington et al.
* Median first GCS score
** NQ: mean values not quoted only p value given

Table 3: Mortality Rates for The Six Studies

<table>
<thead>
<tr>
<th>Author</th>
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<th>Control Group</th>
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<tr>
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<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Ducruet et al.</td>
<td>12.9%</td>
<td>6.5%</td>
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<tr>
<td>Creutzfeldt et al.</td>
<td>26%</td>
<td>38%</td>
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<tr>
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<td>17.5%</td>
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<td>Ivascu et al.</td>
<td>28%</td>
<td>13%</td>
</tr>
<tr>
<td>Fortuna et al.</td>
<td>30%</td>
<td>16%</td>
</tr>
</tbody>
</table>
Meta-analysis Data

Forest plots were produced for the mortality rates in the intervention (transfusion) and control groups (Figure 2). Separate Forest plots were produced for traumatic and spontaneous ICH. These are included as Figures 3 and 4. Significant heterogeneity was present between the six studies; $I^2 = 58.276$ therefore the Random effects model was the preferred model, this produced a pooled odds ratio for survival of 0.773 (95% CI: 0.414 – 1.442). The Fixed effects model was also evaluated and this was found to produce a similar results (common odds ratio for survival: 0.798; 95% CI: 0.559 – 1.139). The Fixed Effect model for the spontaneous only group produced a pooled odds ratio of 1.825 (95% CI: 0.892 – 3.744). The Fixed Effect model for the trauma only group produced a pooled odds ratio of 0.609 (95% CI: 0.404 – 0.917).
DISCUSSION

Six studies were identified for the meta-analysis, two studies evaluating patients with spontaneous intracranial haemorrhage and four with traumatic intracranial haemorrhage. Combining the data from all studies, there was no evidence of benefit, with a trend towards decreased survival in patients selected for a platelet transfusion. The low numbers of participants in each study makes and also the differing pathophysiology of traumatic ICH and spontaneous ICH makes any clear conclusions prohibitive.

When the data for traumatic ICH is extracted separately, platelet transfusions appear to have a negative effect on survival 0.609 (95% CI: 0.404 – 0.917). The paper by Downey et al.[13] had the greatest weight in the meta-analysis data, because of its greater numbers. The paper by Downey et al.[13] was judged by both authors to be the weakest due to differing protocols followed on either site (treatment at physician discretion versus treatment according to platelet function. If this paper is removed, the risk of survival from platelet transfusion decreases further (OR 0.387; 95% CI 0.216 – 0.694); how much weight can be given to this due to the reduction of patient numbers by 46% is unclear. The fact that platelet transfusions were given at the discretion of the attending surgeon does add significant bias into the meta-analysis. Although the studies were reasonably controlled with respect to presenting GCS other factors such as increased haematoma volume or associated co-morbidity may have contributed to the worse outcome in the platelet transfusion group rather than the platelet transfusion itself. There may be a caveat for transfusing patients on antiplatelet agents who have sustained a traumatic ICH, although further work is required in this area.

Conversely, patients with spontaneous ICH showed a trend towards benefit from platelet transfusion (OR 1.825; 95% CI 0.892 – 3.734). This was despite the small study numbers and allocation of patients at physician discretion, possibly introducing a positive bias in terms of both severity and therefore presumed survivability. With the assumption that patients considered more likely to
survive were more likely to be given a platelet transfusion and vice versa. A
subgroup analysis Ducruet et al,[11] also showed that in the subgroup of patients
on clopidogrel there was an increased mortality and an increase in haematoma
expansion.

With regard to spontaneous intracranial haemorrhage three important papers
relevant to this subject need to be discussed. Sansing et al,[16] undertook a
retrospective cohort study on 282 patients with spontaneous intracranial
haemorrhage, 70 patients were on antiplatelet medication. The authors found no
difference between the antiplatelet medication group and the no antiplatelet
group with regard to volume of intracranial haemorrhage on CT, haematoma
growth or outcome score. Naidech et al,[17] performed a cohort study on 68
patients with spontaneous intracranial haemorrhage who were either on
antiplatelet agents or had laboratory evidence of reduced platelet function. A
platelet transfusion was administered in 16 patients at the discretion of the
attending physician. The authors found that there was no difference in the
modified Rankin Scale at 14 days, 28 days and 3 months between the transfused
group and the non transfused group. Naidech,[18] et al in 2011 published their
findings from a prospective cohort study on 45 patients with spontaneous
intracranial haemorrhage and reduced platelet activity. The cohort was divided
into high risk for haemorrhage growth grade and non high risk patients for
haemorrhage growth. High risk patients received a CT and platelet transfusion
within 12 hours of symptom onset. Non high risk patients received a CT and
platelet transfusion after 12 hours. The authors found that for the high risk group
platelet transfusion within 12 hours resulted in smaller haemorrhage size and
better outcome (modified Rankin Score) compared to the cohort of patients who
received a platelet transfusion after 12 hours. Further work is required in some
of these areas, in particular to clarify the effect of preinjury antiplatelet agents on
haematoma size and progression.

With regard to the traumatic ICH cohort a relevant paper was published by
Bachelani et al,[19] in 2011. Theses authors performed a nested case control
study comparing aspirin associated traumatic intracranial haemorrhage against a
ccontrol group of non aspirin associated intracranial haemorrhage. The Aspirin
Response test (ART;VerifyNow) was performed on all patients. Patients with an
ART < 550 received a platelet transfusion. Eleven patients in the non aspirin
ccontrol group (n=48) had an ART evidence of platelet inhibition and
consequently received a platelet transfusion. Two patients in the aspirin group (n
= 36) had no ART evidence of platelet inhibition and therefore did not receive a
platelet transfusion. The data was therefore not suitable for this met-analysis.
Bachelani at al,[19] however found no difference in mortality between the
aspirin group and the non aspirin group.

Conclusions
The small size of the six studies none of which were powered to demonstrate a
difference in survival clearly means that no firm conclusions can be draw from this
meta-analysis. Except for the study by Downey et al,[13] platelet transfusion in the
remaining studies were given at the discretion of the attending surgeon. The current
low level of evidence has prompted a multiple centre randomised control trial based
in the Netherlands, The PATCH study,[20] in order to address the potential efficacy
of platelet transfusion in patients with antiplatelet associated intracranial
haemorrhage. The end points of the study are safety of platelet transfusion and
haematoma progression. Further work is clearly required on this subject so that the
efficacy of platelet transfusion in spontaneous or traumatic ICH can be fully
evaluated.
ADDITIONAL INFORMATION

Contributorship Statement

Mr Batchelor reviewed all the abstracts, reviewed all the full papers, performed the statistical analysis and wrote the paper.

Dr Grayson also reviewed all the abstract titles for relevance. Dr Grayson also reviewed the papers selected for the meta-analysis and undertook a substantial part in the preparation of the revised manuscript.

Acknowledgements

The authors would like to thank Katherine Wylie Senior Informaticist, Department of Emergency Medicine, Manchester Royal Infirmary, for her assistance with the Cochrane Search

Competing Interests

There are no competing interests.

Data sharing Information

There is no additional data available

Funding Statement.

This research received no specific grant from any agency in the public, commercial or not-for-profit sectors.
ARTICLE SUMMARY

Article Focus

The aim of this meta-analysis was to determine the impact on survival of a platelet transfusion in patients on preinjury antiplatelet agents with:

• traumatic intracranial haemorrhage following blunt head trauma

• spontaneous intracranial haemorrhage

Key Messages

• Six studies were found to be suitable for the meta-analysis. (Two studies for spontaneous intracranial haemorrhage, the remaining four were traumatic intracranial haemorrhage).

• The pooled odds ratio showed no benefit in survival following a platelet transfusion (OR = 0.773 (95% CI: 0.414 – 1.442).

Strengths and Limitations

• The studies were small, unpowered and not randomised

• Mortality is a relatively crude marker of effect in the cohort of patients with either spontaneous or traumatic haemorrhage.

• Significant bias may have been introduced in view of the fact that in all but one study the platelet transfusions were given at the discretion of the attending physician.
REFERENCES


Assessment of platelet transfusion for reversal of aspirin after traumatic brain injury.


20. de Gans K, de Haan RJ, Majoie CB et al. Patch Study: platelet transfusion in cerebral haemorrhage; study protocol for a multicentre, randomised, control trial. Web Page address for study protocol:  [http://biomedcentral.com/1471-2377/10/19](http://biomedcentral.com/1471-2377/10/19)
LEGENDS

Figure 1: The PRISMA Flow Diagram

Figure 2: The Forrest Plot For The Six Studies. Random Effect Model.

Figure 3: Forest Plot For The Two Spontaneous ICH Studies. Fixed Effects Model.

Figure 4: Forest Plot For The Four Traumatic ICH Studies. Fixed Effects Model.
PRISMA Flow Diagram

Pubmed Website Portal
499 citations in total (see also appendix 1)
De-duplication of 10 abstracts

34 Potentially Relevant Abstracts

31 Full Articles were reviewed

Six articles were suitable for the meta-analysis.
1. Washington et al. 2011
2. Ducruet et al. 2010
5. Ivascu et al. 2008
6. Fortuna et al. 2008

Athens Website Portal
MEDLINE, EMBASE, CINAHL
399 Citations in total
De-duplication 179
220 unique citations
22 Relevant abstracts
De-duplication with Pubmed search: 2 abstracts
Neither RCT, case control nor nested case control studies.

Cochrane Library Searched For Clinical Trials; 45 citations identified. None Relevant.

25 articles were rejected. Neither RCT, case control nor nested case control studies.
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Favours Survival
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<td>Downey et al. 2009</td>
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<tr>
<td>Ivascu et al. 2008</td>
<td>0.395</td>
<td>0.148</td>
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<td>Fortuna et al. 2008</td>
<td>0.408</td>
<td>0.194</td>
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<tr>
<td></td>
<td>0.609</td>
<td>0.404</td>
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</tbody>
</table>

Favours Death  
Favours Survival
### Appendix 1

**Results Of The Pubmed Search (November 2011, Week 4)**

<table>
<thead>
<tr>
<th>Key Words</th>
<th>Citations</th>
<th>RA*</th>
<th>Dup#</th>
<th>FP~</th>
<th>Accept</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head Injury AND Antiplatelet Agents</td>
<td>223</td>
<td>27</td>
<td>0</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td>Head Injury AND Platelet Transfusion</td>
<td>47</td>
<td>5</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intracranial Haemorrhage AND PT*</td>
<td>229</td>
<td>12</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>

RA* Relevant Abstract Titles  # Duplications compared to first search  ~ Full paper review

*Platelet Transfusion

**Databases Searched Using The Athens Web Interface**

(November 2011, Week 4)

<table>
<thead>
<tr>
<th>Databases Searched</th>
<th>Key Words</th>
<th>Citations</th>
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<tbody>
<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Platelet Transfusion AND intracranial haemorrhage</td>
<td>52</td>
</tr>
<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Platelet Transfusion AND Head Injury</td>
<td>26</td>
</tr>
<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Platelet Transfusion AND Stroke</td>
<td>114</td>
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<tr>
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<td>Platelet Transfusion AND cerebrovascular accident</td>
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<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Platelet Transfusion AND antiplatelet agents</td>
<td>75</td>
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<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Head Injury AND antiplatelet Agents</td>
<td>24</td>
</tr>
<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Head Injury AND Aspirin</td>
<td>66</td>
</tr>
<tr>
<td>MEDLINE, CINAHL, EMBASE</td>
<td>Head Injury AND Clopidogrel</td>
<td>37</td>
</tr>
</tbody>
</table>

**SUMMARY:** 399 Citations. De-duplication of 179. Total of 220 unique citations.

The Cochrane Database of clinical trials generated 45 unique studies non were relevant to this meta-analysis

**The Cochrane Library Issue 11 of 12, Nov 2011**

(MeSH descriptor **Intracranial Hemorrhages** explode all trees) AND (MeSH descriptor Platelet Transfusion/adverse effects/methods

OR MeSH descriptor **Platelet Aggregation Inhibitors/therapeutic use**

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
From the 220 unique citations de-duplication with the Pubmed search identified 2 new abstracts. Both of these were abstracts from proceedings. Neither were therefore eligible for inclusion. Additionally neither were suitable for the meta-analysis.

Cross Referencing generated no new articles.
MOOSE Checklist

A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet associated intracranial haemorrhage.

Author List

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Consultant In Emergency Medicine

Co-author: Alan Grayson MB ChB
Specialist Registrar in Emergency Medicine

Name and address for correspondence.

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Manchester Royal Infirmary.
Tel: 0161 276 6984  Fax: 0161 276 8538
e-mail: johnbatchelor@msn.com
<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief description of how the criteria were handled in the meta-analysis</th>
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</thead>
<tbody>
<tr>
<td>Reporting of background should include</td>
<td></td>
</tr>
<tr>
<td>√ Problem definition</td>
<td>Some Trauma centres in North America in particular are administering platelet transfusions to patients with antiplatelet related intracranial haemorrhage (both spontaneous and traumatic). The current evidence for this approach however has not been fully evaluated.</td>
</tr>
<tr>
<td>√ Hypothesis statement</td>
<td>Platelet transfusion decreases mortality in antiplatelet associated intracranial haemorrhage.</td>
</tr>
<tr>
<td>√ Description of study outcomes</td>
<td>Mortality rates from intracranial haemorrhage</td>
</tr>
<tr>
<td>√ Type of exposure or intervention used</td>
<td>Platelet transfusion</td>
</tr>
<tr>
<td>√ Type of study designs used</td>
<td>We included case-control studies and cohort studies,</td>
</tr>
<tr>
<td>√ Study population</td>
<td>Traumatic or spontaneous intracranial haemorrhage in adults.</td>
</tr>
<tr>
<td>Reporting of search strategy should include</td>
<td></td>
</tr>
<tr>
<td>√ Qualifications of searchers</td>
<td>The credentials of the two investigators JSB and AG are indicated in the author list.</td>
</tr>
</tbody>
</table>
appropriateness of studies assembled for assessing the hypothesis to be tested in the methods section.

Rationale for the selection and coding of data

Data extracted from each of the studies provided mortality rates for patients with intracranial haemorrhage with or without a platelet transfusion.

Assessment of confounding

Potential confounding variables were identified and tabulated. p values for potential confounding variables were given in the appropriate tables.

Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results

Only six studies were identified where a comparison was made between the platelet transfusion group and the none transfusion. All of the studies were low quality, no randomization. Transfusion was given at the discretion of the attending surgeon except in one study where it was dependent on the platelet activity. No formal scoring was used in this meta-analysis.

Assessment of heterogeneity

Heterogeneity of the studies were explored within two types of study designs using the I^2 statistic which provides the relative amount of variance of the summary effect due to the between-study heterogeneity.

Description of statistical methods in sufficient detail to be replicated

The number of deaths in the treatment group were compared to the number of deaths in the non treatment groups using both the Fixed effect and Random effect models.

Provision of appropriate tables and graphics

We included three Forest plots (one for all 6 studies, one for the spontaneous study group and one for the trauma study group) and three addition Tables for a comparison of Mean Age, Mean GCS and Mortality rates between the 2 groups.

Reporting of results should include

Graph summarizing individual study estimates and overall estimate

Figure 2

Table giving descriptive information for each study included

Table 1,2,3

Indication of statistical uncertainty of findings

95% confidence intervals were presented with all summary estimates, I^2 values and results of sensitivity analyses

Reporting of discussion should include
| √ | Quantitative assessment of bias | The main source of potential bias is due to the fact that the more severely injured or affected patients may have received the transfusion. Therefore a comparison was may between groups with regard to mortality rates and mean GCS |
| √ | Justification for exclusion | We excluded studies that included coagulation abnormalities in general where platelet transfusion may have been required. |
| √ | Assessment of quality of included studies | We discussed the fact that all studies were of low quality. |

**Reporting of conclusions should include**

| √ | Consideration of alternative explanations for observed results | We discussed the potential lack of effect of the platelet transfusion may be due to the low quality of the studies rather than a lack of treatment effect. |
| √ | Generalization of the conclusions | Further studies are required to establish whether platelet transfusions are beneficial in this cohort of patients |
| √ | Guidelines for future research | We recommend future studies on the effect of haematoma size, haematoma growth and other outcome measures. |
| √ | Disclosure of funding source | No separate funding was necessary for the undertaking of this systematic review. |
A meta-analysis to determine the effect on survival of platelet transfusions in patients with either spontaneous or traumatic antiplatelet medication-associated intracranial haemorrhage

John S Batchelor and Alan Grayson

BMJ Open 2012 2:
doi: 10.1136/bmjopen-2011-000588

Updated information and services can be found at:
http://bmjopen.bmj.com/content/2/2/e000588

These include:

Supplementary Material
Supplementary material can be found at:
http://bmjopen.bmj.com/content/suppl/2012/04/10/bmjopen-2011-000588.DC1

References
This article cites 20 articles, 3 of which you can access for free at:
http://bmjopen.bmj.com/content/2/2/e000588#BIBL

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Articles on similar topics can be found in the following collections

- Emergency medicine (308)
- Haematology (incl blood transfusion) (57)
- Neurology (433)

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