CHAPTER 4

Systematic review and meta-analysis: Is pre-injury antiplatelet therapy associated with traumatic intracranial hemorrhage?

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ABSTRACT

The objective of this systematic review and meta-analysis is to evaluate whether the pre-injury use of antiplatelet therapy (APT) is associated with increased risk of traumatic intracranial hemorrhage (tICH) on CT scan. Pubmed, Medline, Embase, Cochrane Central, reference lists and national guidelines on traumatic brain injury were used as data sources.

Eligible studies were cohort studies and case-control studies that assessed the relationship between APT and tICH. Studies without control group were not included. The primary outcome of interest was tICH on CT. Two reviewers independently selected studies, assessed methodological quality and extracted outcome data.

This search resulted in ten eligible studies with 20,247 patients with head injury that were included in the meta-analysis. The use of APT in head injury patients was associated with significant increased risk of tICH compared to control (odds ratio 1.87, 95% confidence interval 1.27 to 2.74). There was significant heterogeneity in the studies (I^2 84%), although almost all showed an association between APT use and tICH. This association could not be established for patients on aspirin monotherapy. When considering only patients with mild traumatic brain injury (mTBI) the odds ratio is 2.72 (95% CI 1.92-3.85). The results were robust to sensitivity analysis on study quality.

In conclusion APT in head injury patients is associated with increased risk of tICH, this association is most relevant in patients with mTBI. Whether this association is the result of a causal relationship, and whether this relationship also exists for patients on aspirin monotherapy cannot be established with the current review and meta-analysis.

Introduction

Traumatic brain injury is a major cause for morbidity and mortality worldwide.[1,2] Approximately 5% of emergency department (ED) visits are because of traumatic brain injury (TBI), and in the United States there are approximately 2.5 million TBI related ED visits annually.[1,3] For patients with severe (GCS 3-8) or moderate TBI (GCS 9-12) intracranial complications are frequent and a CT head is indicated in all patients.[4] In contrast, for patients with mild TBI (GCS 13-15) intracranial complications are infrequent (< 10%), and rarely require neurosurgical intervention (< 1%).[5] Nonetheless intracranial complications after head injury do occur and are potentially life threatening. To enhance efficiency without compromising on patient safety various decision rules and guidelines have been developed to identify patients with increased risk of intracranial complications.[4-9]

Whereas many decision rules and guidelines consider the use of vitamin K antagonists (e.g. warfarin) as risk factor for intracranial complications after minor head injury, antiplatelet therapy (APT) is not generally considered to be an independent risk factor for intracranial complications after minor head injury.[4-9] Recent publications however raised the question whether APT increases the risk of brain injury after head trauma.[10-20] Both the American ACEP (American College of Emergency Physicians) clinical policy on this subject as the British NICE (National Institute for Health and Care Excellence) guidelines stressed the need for research on this subject and the Scandinavian guidelines included antiplatelet therapy as a risk factor.[4,9,21] With the ageing population and hence the increasing use of aspirin, ticagrelor, clopidogrel and other antiplatelets the need to establish whether the pre-injury use of APT is associated with traumatic intracranial hemorrhage (tICH) becomes more and more urgent.[1,22]

This meta-analysis aims to quantitatively assess the available data from various studies regarding direct (< 24h) tICH on CT following head injury in relationship to APT use.

Methods

Identification of studies

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) to conduct our review and meta-analysis and also adhered to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[23,24] A search of the databases Pubmed, Medline, Embase, Cochrane Central from inception to 29-09-2015 was made. The following combinations of search terms were used to search all databases: head trauma; brain injury; cerebral injury; brain trauma; cerebral trauma; brain contusion; cerebral contusion; brain concussion; cerebral concussion; anticoagulant; antithrombotic; platelet aggregation inhibitor; vitamin K antagonist; carbasalate calcium; aspirin; acetylsalicylic acid; clopidogrel; ticagrelor; dipyridamole; prasugrel; marcoumar; phenprocoumon; acenocoumarol; noac; doac; apixaban; rivaroxaban; dabigatran; heparin; enoxaparin nadroparin.

We also searched the most important relevant guidelines for references and we searched the reference list of appropriate studies.[4,8,9,21]

Selection criteria, data extraction, quality assessment

We included retrospective as well as prospective observational cohort studies and case-control studies that evaluated the relationship between (any type of) APT use and tICH following head injury on CT in an ED setting. Studies without control group or studies outside the ED were excluded. Studies that only included patients with tICH were also excluded. Severity of the brain injury was no selection criteria for inclusion of the study. The main outcome measure was tICH on head-CT, other outcome measures of interest were neurosurgical intervention and mortality within six months, for studies to be eligible we had to be able to extract data on at least one of these outcomes. No limits were placed on characteristics of participants, date of publication or language of publication.

Three authors (CB, TT, AR) selected articles and extracted data; each step in selection and data extraction was done independently by two of these authors. Any disagreements were resolved by discussion and consensus. We extracted data regarding: study design, study location, sample sizes, characteristics of participants (including age and GCS), intervention (type of APT), control group, outcome measure, measures of effect (including Odds Ratio) and quality of methods. Methodological quality of the studies was assessed independently by two authors (CB, TT, AR) with the Newcastle-Ottawa assessment scale (NOS).[25] Any disagreements were resolved by discussion and consensus. The NOS consists of three components assessing the

studies on selection (four items), comparability (one item) and exposure (three items). Each item is scored with a maximum of one star, except the item comparability, that could be scored two stars; therefore a maximum of nine stars can be scored. We rated studies as low risk of bias if they received nine stars, moderate risk of bias if they received seven or eight stars and high risk of bias if they received less than seven stars.

Several attempts were made to contact all authors of included studies for additional information. The review was registered in the PROSPERO register as number CRD42015025458.

Statistical analysis

The pooled odds ratio and 95% confidence interval were calculated for the relationship between APT use and tICH. Pre-specified subgroup analyses were performed for severity of TBI (GCS > 13 or GCS ≥ 13), type of APT (aspirin; clopidogrel; other) and type of control group (no medication; warfarin). A random effects model was used.

We evaluated heterogeneity with the I^2 test, which represents the proportion of variability not explained by chance alone. The likelihood of publication bias was assessed graphically with a funnel plot.[26]

All analyses were made with RevMan (version 5.3) from The Cochrane Collaboration (2014).

Results

Study selection

The search of Pubmed, Medline, Embase and Cochrane Central returned 831, 1099, 2480, 117 results respectively. After correction for duplicates 3193 articles remained. After selection on title and abstract 3165 articles were excluded, leaving 28 articles. These 28 articles were analyzed in more detail to assess suitability. After this assessment another 17 articles were excluded, leaving eleven articles. Of these eleven articles two were based on the same study results, these results were only used once for this meta-analysis (Figure 1).[15,16]

Study characteristics

Ten studies (eleven publications) with a total of 20,247 participants met the inclusion criteria.[10-20] One study is a retrospective case-control study, the nine other study are cohort studies.[13] Eight cohort studies have a retrospective design and one has a prospective design. All studies are published in English since 2003, and conducted in three different Western countries in level I and II trauma centers (Table 1). Four studies looked specifically at the use of clopidogrel.[13-16, 20] One study assessed specifically the use of aspirin [18]. All other studies included different types and combinations of APT's.[10-12,17,19] The control groups consisted of TBI-patients without (a type of) APT; in the study by Nishijima and in the study by Brewer the control group were TBI-patients on warfarin therapy. The age of included patients and severity of trauma varied between studies as is outlined in Table 1.

Risk of bias within studies

Using the NOS, one study was rated as low risk of bias, while seven studies were rated as moderate risk of bias and two studies were rated as high risk of bias. The NOS ratings are included in Table 1.

In the study by Cull et al selection bias was a major concern. The study included only patients registered in the trauma registry. This trauma registry only includes patients admitted to the hospital.[27] Admitted TBI-patients are not a random selection of all ED TBI patients and both tICH and the use of APT in itself can be reasons for hospital admission. The effect of the possible bias is reflected in the fact that the APT group had relatively less patients with severe TBI compared to the non-APT group (4.7% versus 10.2%) hence the APT-group might not be comparable with the non-APT group.

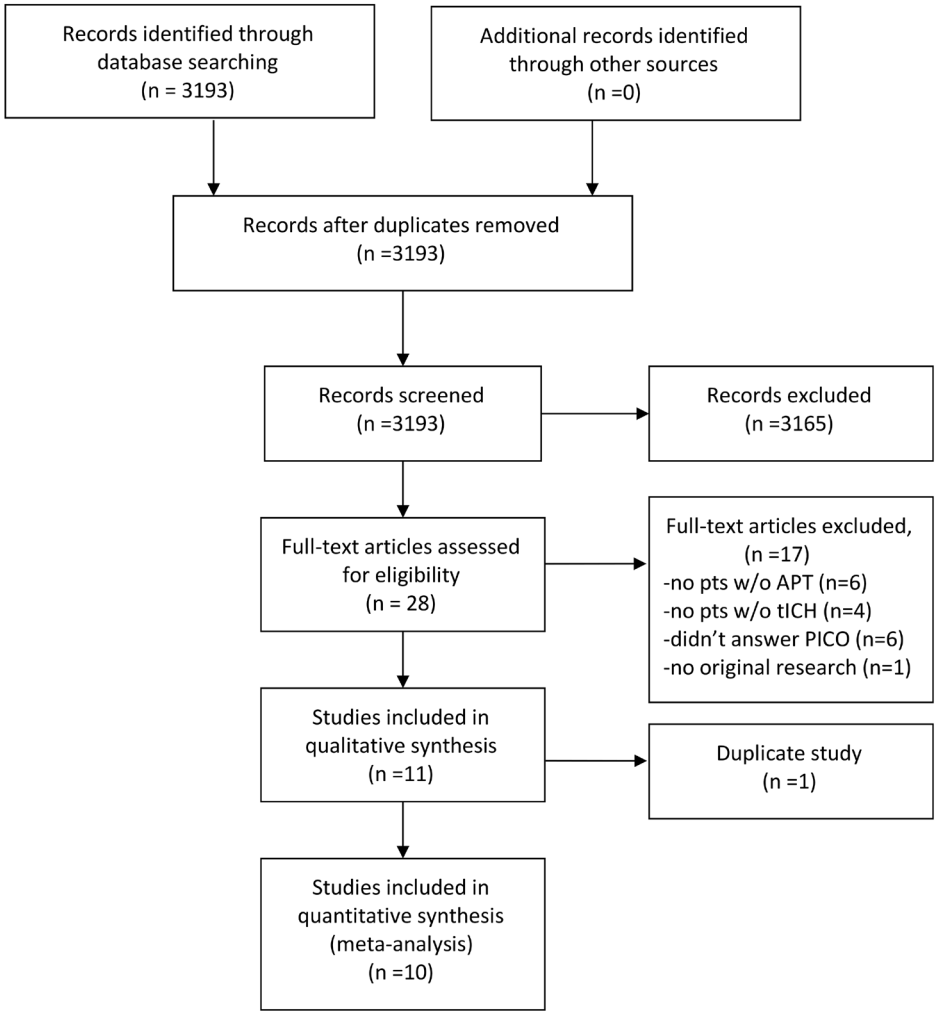

Figure 1

Flow diagram of included studies

Bias in the studies by Ahmed and Dunham encompassed the same selection bias as the study by Cull (admitted patients only) besides this comparability between groups (GCS, age) was not reported in the manuscripts, although we did get this information from the Dunham study group.

Table 1. included studies

Source	Design	Setting	Single/ Multicentre	Country	Age	GCS
Ahmed 2015	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>17	3-15
Brewer 2011	Retrospective cohort	ED, level II	Singlecentre	U.S.A.	>17	15
Cull 2015	Retrospective cohort	ED, level I	Multicentre	U.S.A.	>40	3-15
Dunham 2014	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>59	3-15
Fabbri 2010	Retrospective cohort	ED, level I	Singlecentre	Italy	>9	14.15
Jones 2006	Retrospective case-control	ED, level II	Singlecentre	U.S.A.	>50	3-15
Levine 2013	Retrospective cohort	ED, level I	Singlecentre	U.S.A.	>14	15
Nishijima 2012	Prospective cohort	ED, level I/II	Multicentre	U.S.A.	>17	3-15
Riccardi 2013	Retrospective cohort	ED, level II	Singlecentre	Italy	>65	15
Spektor 2003	Retrospective cohort	ED, level I	Multicentre	Israel	>59	9-15

* Patients with concomitant VKA and ASA use were excluded from analysis (Brewer 21 patients, Nishijima 107 patients)

In the study by Brewer selection bias was also a major concern, the study only included trauma registry patients. This trauma registry only included patients admitted to or consulted by the trauma service [20]. These patients likely suffered from greater overall trauma compared to the non-trauma registry patients as stated by the authors. No information regarding comparability between groups was reported.

The most important bias in the study by Fabbri was detection bias, as only in 63.3% of patients a CT scan was made.

The case-control study by Jones had very limited information in the manuscript and we were not able to get in contact with the authors. The study included both patients with head injury as patients without head injury and patients were matched for age, sex, mechanism of injury and Injury Severity Score. Because patients were

No of pts	APT	Control	Selection	Compari-bility	Outcome	Risk of bias
163	clopidogrel, ASA	No APT	**	**	***	Moderate risk
141*	clopidogrel	VKA	**	*	***	High risk
1547	clopidogrel, ASA	No APT/VKA	**	**	***	Moderate risk
148	clopidogrel, ASA	No APT/VKA	**	**	***	Moderate risk
14228	ASA, ticlopidine, indobufen	No APT	****	**	**	Moderate risk
86†	clopidogrel	No clopidogrel	-	*	**	High risk
658	clopidogrel	No clopidogrel/ VKA	***	**	***	Moderate risk
1064*	clopidogrel	VKA	****	**	***	Low risk
2149	clopidogrel, ASA, ticlopidine	No APT/VKA	****	*	***	Moderate risk
231	ASA	No APT/VKA	**	**	***	Moderate risk

† Not all patients sustained a head trauma, patients without head trauma were excluded from analysis (40 patients)

not matched for GCS and no information is provided regarding GCS we do not know if the groups are comparable in this regard, GCS is known to be the most important predictor of tICH.[5,6]

In the retrospective study by Levine only patients that underwent a CT-head were included, this may have caused selection bias.

The study by Nishijima is the only prospective trial in this review, it was generally well set up, unfortunately patients on clopidogrel were only compared to warfarin and not to a control group without antithrombotic medication. This may underestimate the risk of clopidogrel as warfarin is generally regarded as a risk factor for tICH.[4,8,9]

The study by Riccardi did not report comparability of baseline characteristics between the APT group and the non-APT group.

Finally in the study by Spektor it was not clear from the manuscript in which way the selection of patients was done and if consecutive patients were included.

Outcomes

Combining all data for a summary OR we found an increased risk for tICH in patients with APT versus patients without APT. The overall OR was 1.87 (95% CI 1.27-2.74) (Table 2, Figure 2)

Risk of bias across studies

Strong evidence of heterogeneity (I^2 84%) was observed. To explore this heterogeneity a funnel plot was drawn, which showed only minor asymmetry with no indication for publication bias. (Supplementary Figure 1)

Additional analysis

Based on the risk of bias a sensitivity analysis was performed, excluding all studies with a high risk of bias. The odds ratio for APT as a risk factor for the development of intracranial traumatic complications was 2.02 (95% CI 1.33-3.08; I^2 87%) for the low-intermediate risk of bias studies. We also performed a sensitivity analysis excluding the study by Spektor, which only included patients with aspirin use. The result of that analysis was an OR of 2.02 (95% CI 1.35-3.03; I^2 85%). Finally we did a sensitivity analysis that only included studies with patients with mild TBI (GCS 13-15), which resulted in an OR of 2.72 (95% CI 1.92-3.85; I^2 53%).

Table 2. study outcomes

Source	tICH APT-group	tICH non-APT-group
Ahmed (2015)	35/52 (67.3%)	56/111 (50.5%)
Brewer (2011)	15/36 (41.7%)	23/84 (27.4%)
Cull (2015)	198/422 (46.9%)	504/1125 (44.8%)
Dunham (2014)	35/76 (46.1%)	23/72 (31.9%)
Fabbri (2010)	180/1366 (13.2%)	700/12862 (5.4%)
Jones (2006)	9/25 (36.0%)	10/21 (47.6%)
Levine (2013)	3/10 (30%)	14/648 (2.2%)
Nishijima (2012)	29/252 (11.5%)	36/705 (5.1%)
Riccardi (2013)	22/617 (3.6%)	25/1532 (1.6%)
Spektor (2003)	27/110 (24.5%)	31/121 (25.6%)

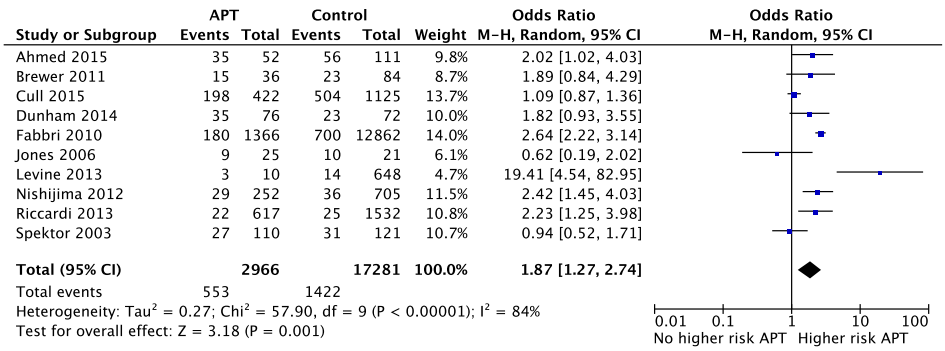

Figure 2

Forrest plot of included studies.

Discussion

We conducted a systematic review and meta-analysis of the literature to assess the association between the use of APT and tICH.

Evidence from the nine available studies suggests that pre-injury APT use is associated with an increased incidence of tICH. However, this conclusion should be interpreted with caution given the high heterogeneity and methodological flaws of several included studies in this review. To our knowledge the current meta-analysis is the only quantitative analysis of pooled data on this topic.

The use of APT seems to be most relevant in patients with mild TBI, it is in these patients that APT use may direct the clinical decision whether to scan or admit the patient or not.

Important to mention, but outside the scope of this review, there are indications that patients on APT not only have a higher risk of tICH, but those with tICH also do have a higher risk of unfavorable outcome.[13,28-32]

Studies comparing APT and VKA therapy are limited, the limited studies available mainly included patients with clopidogrel and patients with warfarin therapy.[15,16,20] These studies do not show that the tICH risk associated with clopidogrel use is lower than that associated with warfarin use. Hence it could be advisable to use the same guidelines for scanning and disposition for clopidogrel therapy as apply for VKA therapy in (mild) TBI patients. Whether this is also advisable for other antiplatelet therapy cannot be answered based on the current review.

Another consideration, which is also outside the scope of this review, is whether routine administration of platelets in patients with tICH and APT is useful. There is only low quality evidence from observational studies, and the results of these studies are contradictory.[31-36] Both a systematic review and a recent guideline by the AABB (formerly American Association of Blood Banks) conclude that there is insufficient evidence to recommend for or against platelet transfusion in patients with tICH while receiving APT.[37,38] Routine administration of platelets in TBI patients receiving APT without evidence of hemorrhage on CT does not seem to be indicated.[38]

Limitations

This review and meta-analysis has a number of limitations and the results of this review should be interpreted in the light of these limitations. First, the patient population, APT use, control group and outcome definitions are not the same across studies. This resulted in significant heterogeneity across studies. Second, the overall quality of the included studies was low. All the original studies were observational studies and almost all studies had a retrospective design with consequently a higher risk of bias. Especially selection bias was a concern in many of the included studies. Because of the design of the studies it is impossible to establish a causal relationship of APT use and the risk of tICH. Confounding, as in any meta-analysis of observational studies, may introduce considerable bias. Another limitation is that in this review APT is considered as a group, it is unlikely however that all different antiplatelet medications will have the same risk of tICH, there were insufficient studies on different antiplatelet medications to specify the risk of different APT's. Especially for patients on low-dose aspirin monotherapy it is uncertain if the risk for tICH is increased, the only included study that assessed aspirin as risk factor for tICH did not find an increased risk. Finally although tICH is generally regarded as important in the disposition and treatment of TBI patients, this is in fact a surrogate outcome for mortality and morbidity following TBI.

Clinical implications

Considering the observed association between APT use and tICH, APT use should be considered as a potential risk factor for tICH in future guidelines regarding (mild) TBI. Whether patients on low-dose aspirin monotherapy do have an increased risk of tICH as well cannot be concluded based on the current review and meta-analysis because of limited literature.

Conclusions

Although the estimates of the association between APT and tICH are clinically relevant, they are still somewhat preliminary and do not prove that APT use increases the risk of tICH. Additional prospective studies are needed to confirm and quantify findings further. These studies could also give an indication whether a causal relationship between APT and tICH is probable, and explore the risks of different types of APT's.

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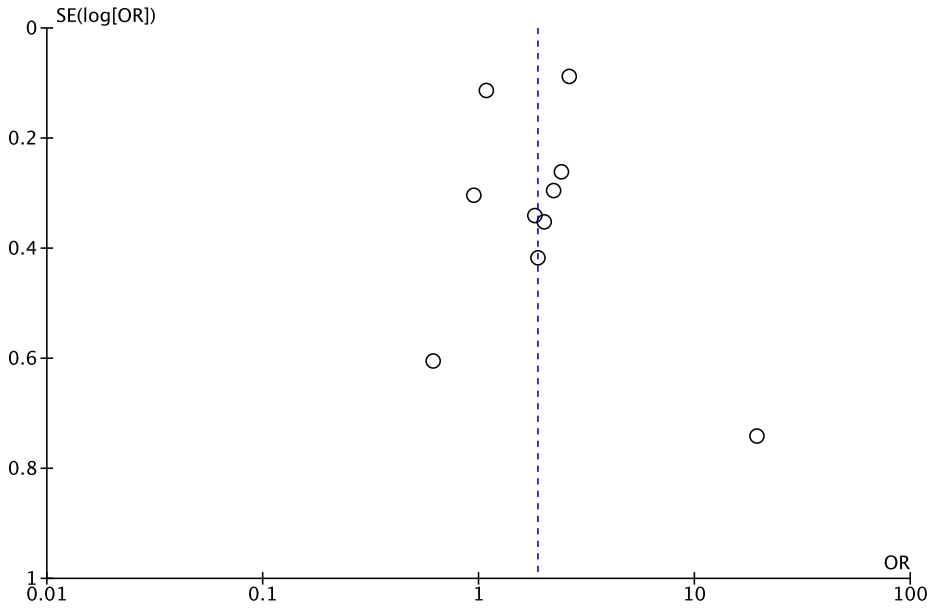
Supplementary Material



Supplementary Figure 1.

Funnel plot of included studies.