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Clinical Review

RISK OF DELAYED INTRACRANIAL HEMORRHAGE IN ANTICOAGULATED PATIENTS WITH MILD TRAUMATIC BRAIN INJURY: SYSTEMATIC REVIEW AND META-ANALYSIS

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□ **Abstract—Background: Delayed intracranial hemorrhage is a potential complication of head trauma in anticoagulated patients. Objective: Our aim was to use a systematic review and meta-analysis to determine the risk of delayed intracranial hemorrhage 24 h after head trauma in patients who have a normal initial brain computed tomography (CT) scan but took vitamin K antagonist before injury. Methods: EMBASE, Medline, and Cochrane Library were searched using controlled vocabulary and keywords. Retrospective and prospective observational studies were included. Outcomes included positive CT scan 24 h post-trauma, need for surgical intervention, or death. Pooled risk was estimated with logit proportion in a random effect model with 95% confidence intervals (CIs). Results: Seven publications were identified encompassing 1,594 patients that were rescanned after a normal first head scan. For these patients, the pooled estimate of the incidence of intracranial hemorrhage on the second CT scan 24 h later was 0.60% (95% CI 0–1.2%) and the resulting risk of neurosurgical intervention or death was 0.13% (95% CI 0.02–0.45%). Conclusions: The present study is the first published meta-analysis estimating the risk of delayed intracranial hemorrhage 24 h after head trauma in patients anticoagulated with vitamin K antagonist and normal initial CT scan. In most situations, a repeat CT scan in the emergency department 24 h later is not necessary if the first CT scan is normal. Special care may be required for patients with serious mechanism of injury, patients showing signs of neurologic deterioration, and patients presenting with excessive anticoagulation or receiving antiplatelet co-medication.**

□ **Keywords—traumatic brain injury; delayed intracranial hemorrhage; anticoagulation therapy; coagulopathy; vitamin K antagonist**

INTRODUCTION

Traumatic brain injury represents a major health and socioeconomic problem in high-income countries, where it is the leading cause of morbidity and mortality among young individuals, with an incidence of 100–300 per 100,000 (1,2). These commonly seen injuries in the emergency department (ED) require rapid diagnosis and proper management in order to improve patient outcomes (3). The initial evaluation of patients includes computed tomography (CT) scans of the brain to quickly

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determine the type and extent of injury as well as to select the optimal management strategy (4,5). The role of the first CT scan, as well as supplemental ones in cases of rapid neurologic deterioration, is well accepted (6). However, the importance of repeated scans for anticoagulated patients suffering from a mild traumatic brain injury with a normal initial head CT scan is not clearly established in current guidelines.

Several studies suggest that anticoagulated patients are exposed to an increased risk of intracranial hemorrhage (ICH) after head trauma (7–10). In addition, usage of oral anticoagulants is rapidly increasing in the elderly population (11,12). With the anticipated growth of this population and the increasing number of head injury patients seen in the ED, the clinical dilemmas surrounding these patients become increasingly relevant. Among elderly patients suffering a fall, long-term anticoagulation has been shown to not only increase the incidence of ICH when compared to those not taking anticoagulant, but also to increase the mortality of those suffering an ICH (13,14).

Delayed ICH is a potential complication of head trauma in anticoagulated patients after an initial normal head CT scan. Although clinical decision rules exist to help determine which patients suffering from a head injury require a head CT scan, these rules do not apply to anticoagulated patients. Some guidelines suggest that all anticoagulated patients with head injury should undergo strict observation during the first 24 h and have a control CT before discharge (15–18). Recent National Institute for Health and Care Excellence guidelines now propose secondary scans at delays ranging from 7 days up to 1 month (19). However, these recommendations are not based on studies looking at the prevalence of delayed ICH. Other guidelines rather propose to proceed with community follow-up in cases of mild traumatic brain injury (20).

The aim of this study was to conduct a systematic review and meta-analysis to estimate the 24-h risk of delayed ICH in anticoagulated patients with mild traumatic brain injury and normal initial brain CT, considering the wide range of reported incidence of delayed ICH (0–11% using confidence interval [CI]) and that no meta-analysis has ever been published on this specific topic.

METHODS

The methodological approach followed for this systematic review and meta-analysis was based upon the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) methodology and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 statement (21,22).

Search Strategy

EMBASE, MEDLINE, and Cochrane Library were searched using controlled vocabulary and keywords without language or date limitations. Search terms were as follows for our MEDLINE strategy: ((((hemorrhage [MeSH Terms] OR intracranial hemorrhage[MeSH Terms] OR brain hemorrhage[MeSH Terms] OR delayed bleeding[Title/Abstract] OR delayed hemorrha*[Title/Abstract])) AND ((tbi[Title/Abstract] OR traumatic brain injury[Title/Abstract] OR craniocerebral trauma [MeSH Terms] OR brain injury, chronic[MeSH Terms] OR brain injuries[MeSH Terms]))) AND ((coumadins [MeSH Terms] OR warfarin[MeSH Terms] OR anticoagulants[MeSH Terms])). A similar but specific strategy was used for EMBASE. We also searched the grey literature with the following databases using the same keywords: OpenSIGLE, New York Academy of Medicine (Grey Literature Collection), Greylit.org, and Google Scholar. All database searches were done under the guidance of an information specialist. Attempts were made to contact authors of all selected manuscripts to ensure data content and complete cases of missing information. References from eligible studies were also screened for other relevant publications.

Identification of Studies

Studies retained for our systematic review were: randomized controlled trials, prospective or retrospective cohort studies, case-control studies, or cross-sectional studies. To be included, studies had to focus mainly on patients with mild traumatic brain injury (see Figure 1 for definition by Carroll et al.), who used vitamin K antagonist before injury, who were scanned on hospital presentation, and whose initial scan was normal (23). Delayed ICH was

> **"MTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of MTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury."**

Figure 1. Operational definition of mild traumatic brain injury (MTBI) as recommended by The World Health Organization (WHO) Collaborating Centre Task Force on Mild Traumatic Brain Injury in Carroll et al. (23).

defined as any intracranial bleeding detected on the subsequent CT scan. Studies were included only if the secondary CT scan was performed within 24 h of initial investigation.

Studies were independently screened for inclusion by three physicians (JMC, FB, and ML), with the requirement of a unanimous selection. All selected publications were then fully read by the two reviewers (JMC and MM) for inclusion. Disagreement was resolved by consensus among authors.

Outcomes

For this systematic review and meta-analysis, any sign of bleeding on the subsequent CT scan was considered as an event for the primary outcome. Neurosurgical intervention and death were considered as secondary outcomes.

Data Collection and Processing

Data from the selected publications were extracted by two authors (JMC and MM) using an adapted standardized data extraction form derived from Reljic et al. (24). All disagreements during this stage were resolved by consensus with the help of a third author (RD).

The following study characteristics were recorded in all cases: study design, patients characteristics (international normalized ratio [INR], age, sex), inclusion and exclusion criteria, antiplatelet therapy co-medication, mechanism of injury, number of patients, time of first and second head CT scans, bleeding description, and outcomes. Study authors were contacted for precisions when data could not be extracted from the original full text without ambiguity, or in cases of conference abstracts without full text publication. Studies with unresolved uncertainties were excluded.

Two authors independently assessed the study risk of bias (JMC, MM). Each study was evaluated using the Newcastle-Ottawa Scale to assess the quality of cohort studies in meta-analyses (25). This tool was developed to assess the quality of non-randomized studies based on their design, content, and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results. With this system, studies are judged on three broad perspectives. In the selection category (maximum of four stars), studies received points if the cohort was representative (meaning the same type of patients who are typically kept for a 24-h observation period in the ED), if data were confirmed through secured records, and if there was a confirmation that the outcome was not present at the start of the study. There was also a point for a control cohort, which none of the studies included. A maximum of two stars was awarded in the comparability category. The first star was given if the study controlled for the most important factor, INR in our case. The second star could be awarded if significant secondary factors were considered (antiplatelet co-medication, age, mechanism of injury). Three stars were awarded in the outcome category if the outcome assessments were blinded or obtained from linked records, if the follow-up period was long enough (at least 24 h), and if all subjects were accounted for at the end of the study (<10% of lost to follow-up). All studies were kept regardless of their quality. Their evaluation is reported in the Results section.

Patients' Inclusion Criteria

In the selected studies, the data concerning a patient were extracted for analysis if: the patient was using vitamin K antagonist before injury, was victim of a mild traumatic brain injury, had a normal initial head scan on presentation, and was subsequently rescanned within 24 h. The 24 h cutoff is important because it represents the guidelines recommended observation period. Furthermore, looking at delayed ICH in patients for up to 1 month after the initial evaluation is not realistic or practical, plus it is impossible to exclude the possibility of a second traumatic incident causing a new ICH. Thus, our study population is exclusively composed of patients with an initially normal brain scan who were subsequently rescanned within 24 h.

Primary Data Analysis

The proportion of patients with delayed bleeding (positive subsequent scan) over the total number of patients undergoing repeat CT scans (our selected population) was used to conduct a single-arm meta-analysis. We used logit proportion transformation to estimate the pooled risk of presenting delayed bleeding. The pooled proportion was calculated as a back-transformation of the weighted mean of the transformed proportions (logit) using a random effect model (26). Possible heterogeneity was tested with χ^2 and I^2 tests. Descriptive statistics were generated with SPSS software, version 22.0 (released 2013, IBM Corp, Armonk, NY) and meta-analyses were performed with OpenMeta-Analyst software (http://www.cebm.brown.edu/open_meta). CIs were calculated with an α of 0.05.

RESULTS

Study Selection

The literature search was conducted in December 2014, with an update in September 2015 (Figure 2). This search yielded 892 unique citations, of which 89 full texts were

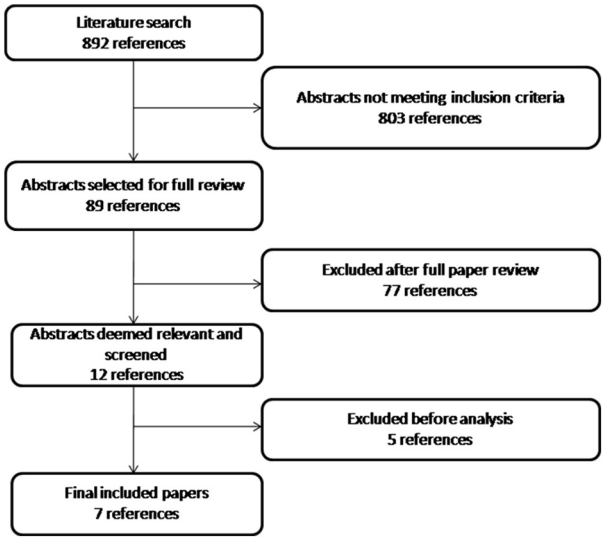

Figure 2. Flow diagram depicting the selection process for studies to be included into the systematic review.

reviewed by the authors, 12 studies were carefully considered, and 7 studies ended up meeting the final inclusion criteria, for a total of 1594 patients (27–38).

Exclusions

From the 12 studies identified, 5 had to be excluded from our meta-analysis. In the first study, only 4 of 346 patients were on warfarin before injury; the focus of this study was clearly not on warfarin-anticoagulated patients (34). Of note, none of the 4 patients had any significant findings on the second scan. Given the small sample size, we decided not to include these results in our analysis. In the second excluded study, the authors described a 1.19% (2 of 168) rate of delayed ICH (35). However, almost all patients had a positive initial scan (166 of 168 or 98.8%), while the 2 remaining patients were found to be positive on the subsequent CT scan. No data were available for patients with a normal initial scan, preventing the estimation of proportion of patients with delayed ICH. The third was a systematic review on delayed ICH in anticoagulated patients without any meta-analysis calculation (36). The last two studies were conference abstracts and were not retained for the following reasons: 2 of 130 patients had delayed ICH, however, no time frame was associated with the second CT scan (37); 1 patient on warfarin developed a delayed ICH, however, data on prior anticoagulant use were available for that patient only and not for the remainder of the cohort (38).

Selected Studies

The characteristics of included studies are reported in Table 1, while the details of the patient population are in Table 2. Four of the studies were retrospective and two involved more than one center (28–30,32,33). The sample size of the studies ranged from 58 to 687 patients, with a median of 137 patients. The mean age was 76.9 years, 55.6% of the patients were female, the Glasgow Coma Score was 15 for almost all patients, mean INR was 2.8, and the most common cause of injury was falls (79.2%). The overall incidence (number of new ICH cases during the first 24 h) of delayed ICH as reported in the included studies ranged from 0 to 6% (or up to 11% when considering CI). This wide disparity in results generated moderate statistical heterogeneity (I^2 = 42.8%). We chose to use the random effect model in our meta-analysis due to this apparent clinical heterogeneity in order to obtain a broader CI and err on the side of patients' safety.

Risk of Bias

The overall quality of the studies was moderate, mostly with respect to unclear or missing information, but none of the included studies contained biases that were deemed significant enough to justify exclusion. Two studies had a higher risk of bias. The main concern with these two papers was the short delay before the second CT scan, at 8.8 h and 6.0 h, respectively (28,32). For each study, the quality of the individual components is presented in Table 3.

Outcomes

Data on delayed intracranial bleeding were extracted from the 7 selected studies to generate the Forest plot for the overall risk of delayed ICH presented in Figure 3. Regarding the primary outcome (risk of delayed ICH), we reported signs of intracranial bleeding within 24 h in 14 of 1,594 patients. The nature and localization of the bleeding are reported in Table 3. Thus, the pooled estimated overall risk of delayed bleeding was 0.6% (95% CI 0–1.2%). In a sensitivity analysis including data from excluded studies, the risk of delayed bleeding did not change significantly (pooled estimate = 0.5%, 95% CI 0.1–0.9%) (34,35,37,38). The patients with delayed ICH were mostly male (10 of 14 or 71%), with a mean age of 79.1 ± 8.5 years, and an INR of 2.71 ± 0.92 at presentation (Table 4). Because we only had the INR for a limited number of patients and never for patients without delayed ICH, it was impossible to determine the impact of this variable. Falls were the most common mechanism of injury (6 of 13) within the group of affected patients.

Careful examination of the 13 patients with known outcomes revealed that only 1 required surgical intervention, while another died from his injuries (there was also

Table 1. Summary of Included Studies

First Author	Design	Study Setting	Patients Analyzed, n	Patients with Delayed ICH within 24 h, n (%)	Notes	Patients' Secondary Outcomes
Kaen (31)	Prospective	Madrid, Spain	137	2 (1.5)	Both patients on antiplatelet	Both discharged
Peck (28)	Retrospective	San Diego, CA	289	4 (1.4)	Second scan at 6 h	All 4 discharged, 1 suffering an unrelated death, without any ICH on autopsy
Menditto (27)	Prospective	Ancona, Italy	87	5 (6)	79% patients involved in high-velocity impact	4 discharged, 1 neurosurgery
Nishijima (29)	Prospective multicenter	Sacramento, CA	687	1 (0.15)	—	Discharged
Schoonman (30)	Retrospective	The Hague, Netherlands	211	1 (0.47)	—	Neurosurgery and died
Taylor (33)	Retrospective multicenter	Nambour, Australia	58	1 (1.7)	No mechanism of injury	No outcome
McCammack (32)	Retrospective	San Diego, CA	125	0	Second scan at 6 h	—

ICH = intracranial hemorrhage.

one case of unrelated death). All other patients were discharged without any further clinical interventions. The resulting risk of clinically relevant poor outcomes (secondary outcomes of neurosurgical intervention and death) was thus 0.13% (95% CI 0.02–0.45%) (2 of 1,594).

DISCUSSION

We have conducted a systematic review and meta-analysis of delayed ICH in patients with mild traumatic brain injury who were anticoagulated with vitamin K antagonists before injury. We report a combined 0.6% (95% CI 0–1.2%) incidence of delayed ICH and conclude that repeated CT scans 24 h after an initial normal imaging are not necessary in most situations.

The overall quality of the studies was moderate, mostly because of their observational design and missing or unclear data. However, the results were consistent throughout the seven studies, with one exception. It is possible that the higher prevalence of delayed ICH found in the study by the Menditto group was inflated by the inclusion of a very high proportion of patients involved in motor vehicle accidents (79%) compared to other study populations (4–11.8%) (27). This serious mechanism of injury may have led to a different and more severely injured patient cohort. It may be warranted to explore the different mechanisms of mild traumatic brain injury and their relative influence on the prevalence of delayed ICH.

For the majority of the 14 patients with the primary outcome, the extent of bleeding on the second scan was minor and no further clinical intervention was necessary (85% of patients with delayed bleeding). Bleeding signs not requiring further treatment are an outcome that is commonly recognized as clinically insignificant, and their clinical importance has to be questioned. The incidence of more important patient outcomes, such as neurosurgical intervention and death, should probably be considered instead (39). Interestingly, the risk of clinically significant outcomes causing death or requiring neurologic surgery was only 0.13% (2 of 1,594).

It is important to mention that there were a few additional patients presenting significant outcomes (neurosurgical intervention and death) who were not included in the analysis because their outcomes occurred after more than 24 h. In all, 9 patients presented themselves to the ED at a time point ranging from 2 to 28 days after the first 24 h of observation (2, 3, and 4 patients, respectively, in the studies by Menditto et al., Nishijima et al., and Schoonman et al.) and 2 of them had clinically significant adverse outcomes (27,29,30). Consequently, these delayed hemorrhages would probably not have been detected during a 24-h observation period and, despite

Table 2. Patient Population Characteristics from All Selected Papers*

First Author	Kaen (31)	Peck (28)	Menditto (27)	Nishijima (29)	Schoonman (30)	Taylor (33)	McCammack (32)
Year	2010	2011	2012	2012	2014	2012	2015
Design	Prospective	Retrospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective
Site (n)	Single	Single TC I	Single TC II	Multiple (6)	Single TC I	Multiple (2)	Single
n/N (included/total)	137	289/424	87/97	687/768	211	58	125/144
Age (y), mean (SD)	76 (9)	75 (13.6)	82 (9)	75.3 (13)	77 (11.7)	79	73.8
Female, n (%)	92 (67)	214 (50.5)	55 (63.2)	406 (52.9)	114 (54)	76 (48)	77 (53.5)
GCS, mean (SD)	14.9 (0.3)	14.8 (0.9)	15 (0)	—	—	—	14.9
GCS = 15	122 (89)	—	87 (100)	674 (87.8)	—	—	—
GCS = 14	15 (11)	—	0	73 (10)	—	—	—
GCS = 13	0	—	0	—	—	—	—
GCS < 13	—	—	—	21 (2.7)	—	—	—
Headache, n (%)	34 (25)	—	3 (3)	239 (31.1)	—	—	—
Vomiting, n (%)	27 (20)	—	3 (3)	34 (4.4)	—	—	—
LOC, n (%)	14 (10)	131 (35.7)	16 (18)	136 (17.7)	—	—	38 (26.5)
Amnesia, n (%)	6 (4.3)	—	4 (5)	—	—	—	—
Seizure, n (%)	2 (1.7)	—	—	—	—	—	—
Scalp wound, n (%)	38 (28)	—	—	448 (61.8)	—	—	—
Focal deficit, n (%)	—	17 (4.0)	0	—	—	—	—
Fall, n (%)	122 (89)	357 (84.2)	18 (21)	644 (83.9)	155 (73.5)	—	—
Traffic accident, n (%)	7 (5)	38 (9)	69 (79)	32 (4.2)	25 (11.8)	—	—
Assault, n (%)	4 (3)	—	—	—	—	—	—
Direct impact, n (%)	2 (1.7)	—	—	45 (5.9)	8 (3.8)	—	—
Pedestrian struck, n (%)	2 (1.7)	—	—	4 (0.5)	—	—	—
Associated injury, n (%)	29 (21)	—	30 (34)	—	—	—	—
INR, mean (SD)	3.8 (1.2)	2.5 (1.2)	2.34	2.5	3.37 (1.46)	—	2.4
Concomitant antiplatelet, n (%)	3 (2.2)	25 (5.9)	0	19 (2.5)	—	5 (8.6)	—
ISS, mean (SD)	—	4.9 (3.7)	—	—	—	—	—
Delay (h) before second CT, mean (SD)	19.8	8.8 (10.2)	—	Variable	—	17.1	6

CT = computed tomography; GCS = Glasgow Coma Scale; INR = international normalized ratio; ISS = Injury Severity Score; LOC = loss of consciousness; SD = standard deviation; TC = trauma center.

* n (%) extracted directly from publications.

Table 3. Quality Assessment of All Included Studies Using the Newcastle-Ottawa Scale for Selection, Comparability, and Outcome

First Author	Selection (Maximum ****)	Comparability (Maximum **)	Outcome (Maximum ***)
Kaen (31)	***	**	***
Peck (28)	***	**	**
Menditto (27)	***	—	**
Nishijima (29)	***	**	***
Schoonman (30)	***	**	**
Taylor (33)	**	**	***
McCammack (32)	**	*	*

their significance (a risk of significant outcomes at 0.13% [2 of 1,594], which is identical to the risk seen during the first 24 h of observation), these cases certainly do not justify keeping the patients after a normal first scan for such lengthy periods. Even when following the practice guidelines, these patients would have been discharged. Furthermore, the incidence of delayed hemorrhage described in our study does not warrant the risk of a prolonged hospital stay and supplemental scan. Patients and their family would benefit far more from being properly educated on the relative risk of delayed hemorrhage and being presented with a list of symptoms to monitor with the mention that they should come back to the ED for further investigations should any of the symptoms appear.

The recent review by Miller et al. also covers delayed ICH, but without taking into account the 24-h observation period currently proposed by the guidelines or the strict requirement of only including patients that had a normal initial CT scan in their cohort (36). These two key elements, plus the fact that they missed some papers while adding an irrelevant one, drastically changed the number of included patients. We also believe that by adding the meta-analysis calculations, we obtained a better interpretation of the overall data.

Although our current review of the literature does not support a routine hospital observation for 24 h or repeat cranial CT scans in all patients suffering from mild traumatic brain injury with a normal initial scan who were anticoagulated with vitamin K antagonist before injury, this course may still be warranted in specific patients presenting increased risk of delayed bleeding. These include patients with supratherapeutic INR levels (elevated INR > 3.0), with more serious mechanisms of injury (e.g., traffic accident), or with concomitant antiplatelet therapy (27,40). Also, patients living alone or with family members unable to monitor signs of neurologic deterioration, patients unable to return to the ED, or patients unable to understand the discharge advice could potentially be kept under observation for a supplemental period of time. In order to determine appropriate management, further studies are needed to identify and better describe the patients who are at higher risk of delayed bleeding. Even with the current evidence, it is important to remember that a generic approach may not be warranted, and that the physician's judgment should prevail if associated risk factors are encountered.

Limitations

This systematic review presents several limitations. The most important one is the small amount of available data, combined with the fact that retrospective or observational studies restrict the quality of evidence. Risk factors were also not accounted for in the different studies, reducing the perspective of secondary analyses. More thorough studies might be needed to determine with more certainty whether associated injuries had an effect on the incidence of ICH. Nonetheless, studies that were retained for the analysis were consistent and did not present a significant risk of bias.

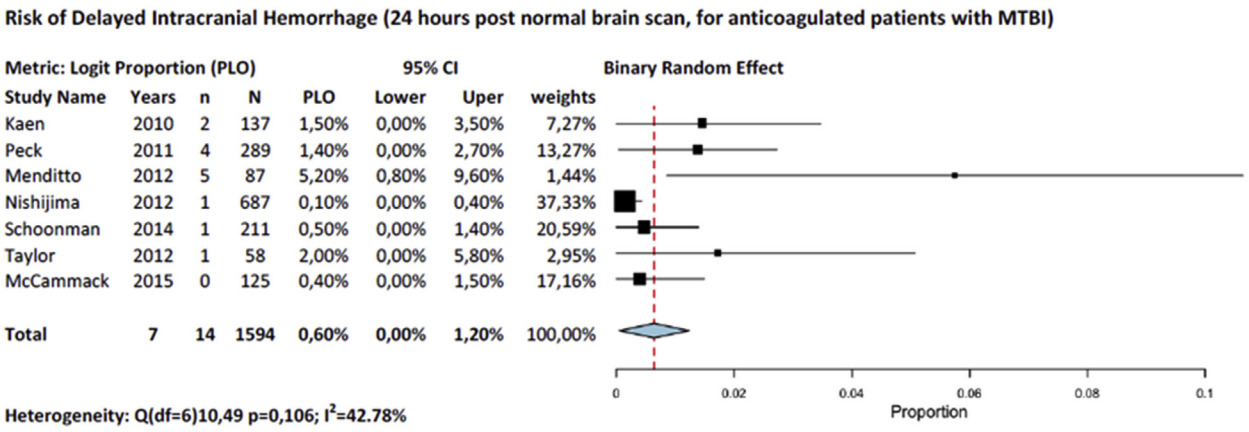

Figure 3. Forest plot of associated risk of delayed intracranial hemorrhage after mild brain traumatic injury (24 h post normal brain scan) in patients anticoagulated with vitamin K antagonist.

Table 4. Clinical Description of Patients with Delayed Intracranial Hemorrhage

First Author, Patients number	Co-Medication	Age (y)	Sex	INR	Mechanism	Time of First Scan	Outcome	Bleeding Description
Kaen (31), no. 1	ASA	67	M	3.10	Fall	2.5 h	Discharged	Minimal intraventricular hemorrhage
Kaen (31), no. 2	ASA	74	M	2.88	Fall	3.4 h	Discharged	Discrete subarachnoid hemorrhage over the convexity of the right hemisphere
Schoonman (30), no. 1	—	85	M	3.13	Fall	Within 12 h of trauma	Neurosurgery/ died	Subdural hematoma
Nishijima (29), no. 1	—	63	M	1.50	Fall	During initial ED evaluation	Discharged	Small intraparenchymal contusion and subarachnoid hemorrhage
Peck (28), no. 1	ASA	86	M	2.2	Vehicle accident	NR	Discharged	Small tentorial subdural hemorrhage
Peck (28), no. 2	—	86	F	2.2	Fall	NR	Discharged	Equivocal: possible intraparenchymal hemorrhage
Peck (28), no. 3	ASA	80	M	3.9	Fall	NR	Discharged	Minimal subarachnoid hemorrhage
Peck (28), no. 4	—	89	M	1.7	Fall	NR	Unrelated death	Small hematoma
Menditto (27), no. 1	—	68	F	3.8	Accident	*	Discharged	Minimal intracranial bleeding
Menditto (27), no. 2	—	78	M	2.4	Accident	*	Neurosurgery	Intracranial bleeding
Menditto (27), no. 3	—	88	M	1.4	Syncope	*	Discharged	Intracranial bleeding
Menditto (27), no. 4	—	78	M	2.1	Syncope	*	Discharged	Minimal intracranial bleeding
Menditto (27), no. 5	—	87	F	3.3	Accident	*	Discharged	Intracranial bleeding
Taylor (33), no. 1	—	78	F	4.3	NR	NR	NR	NR

ASA = acetylsalicylic acid; ED = emergency department; F = female; INR = international normalized ratio; M = male; NR = not reported.
* Median time between head injury and initial computed tomography scan for the study of 4.5 h.

The timing of the first and second scans is also a potential source of bias. In itself, the timing of the first scan in relation to the event was rarely reported in the selected studies. This could potentially affect our primary outcome because delaying the first scan increases its chance of being positive (at least after 6 h post-injury). Likewise, the second scan was conducted only 6 h post-intervention in two studies (28,32). This short delay with regards to the 24-h observation period stated in the research question may have artificially lowered the incidence of delayed bleeding, as determined by our analysis. However, it is important to note that these studies did not report cases of delayed bleeding during the follow-up period.

We are aware that newer anticoagulation agents are gaining widespread use, even supplanting warfarin in certain clinical settings. However, it was impossible for us to report on these direct-acting oral anticoagulants due to the absence of publications on this novel class of agents.

CONCLUSIONS

The aim of this meta-analysis was to assess the risk of delayed intracerebral bleeding in patients suffering a mild traumatic brain injury who have been anticoagulated with vitamin K antagonist before injury. We found that the incidence of delayed bleeding in patients with an initially normal head scan was very low at 0.6%. Furthermore, 85% of the patients with delayed hemorrhage did not require clinical intervention, reducing even further the risk of significant outcomes to 0.13%. This risk is sufficiently low to justify discharging the patients after the initial evaluation by a physician when the first scan is negative.

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ARTICLE SUMMARY

1. Why is this topic important?

Delayed intracranial hemorrhage is a potential complication of head trauma in anticoagulated patients after an initial normal head computed tomography (CT) scan. Current guidelines suggest a 24-h observation period ending with a control scan.

2. What does this review attempt to show?

The review attempts to determine the risk of delayed intracranial hemorrhage during the first 24 h after a head trauma in patients anticoagulated with vitamin K antagonist who had a normal initial brain CT scan.

3. What are the key findings?

The incidence of delayed bleeding was very low at 0.6% (95% confidence interval [CI] 0–1.2%), and the risk of clinically significant poor outcomes (neurosurgical intervention and death) was 0.13% (95% CI 0.02–0.45%).

4. How is patient care impacted?

The risk of delayed bleeding is sufficiently low in anticoagulated patients with mild head trauma and a negative first scan to justify discharging the patients with adequate instructions for follow-up.