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Incidence of intracranial bleeding in anticoagulated patients with minor head injury: a systematic review and meta-analysis of prospective studies.

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SUMMARY

Guidelines advise performing a CT head scan for all anticoagulated head injured patients, but the risk of intracranial haemorrhage (ICH) after a minor head injury is unclear. We conducted a systematic review and meta-analysis to determine the incidence of ICH in anticoagulated patients presenting with a minor head injury and a GCS score of 15. We followed Meta-Analyses and Systematic Reviews of Observational Studies guidelines. We included all prospective studies recruiting consecutive anticoagulated emergency patients presenting with a head injury. Anticoagulation included vitamin-K antagonists (warfarin, fluindione), direct oral anticoagulants (apixaban, rivaroxaban, dabigatran, and edoxaban) and low molecular weight heparin. A total of five studies (including 4,080 anticoagulated patients with a GCS score of 15) were included in the analysis. The majority of patients took vitamin K antagonists (98.3%). There was significant heterogeneity between studies with regards to mechanism of injury and methods. The random effects pooled incidence of ICH was 8.9% (95% CI 5.0-13.8%). In conclusion, around 9% of patients on vitamin K antagonists with a minor head injury develop ICH. There is little data on the risk of traumatic intracranial bleeding in patients who are GSC 15 post head injury and are prescribed a direct oral anticoagulant.

Key words: minor head injury, anticoagulation

INTRODUCTION

Head injury is one of the leading causes of emergency department (ED) visits(Mannix et al. 2013). A large number of head injuries are due to falls in the elderly population(Pickett *et al*., 2001). Hospital admissions following head injury are rising, particularly among the elderly(Fu *et al*., 2015). The rate of anticoagulant use in this population has been steadily increasing. In particular, direct oral anticoagulant (DOAC) prescriptions have increased among the elderly, mostly as a means of stroke prophylaxis in atrial fibrillation patients(Xu *et al*., 2013). While anticoagulants prevent ischemic stroke, paradoxically, they are associated with a small risk of haemorrhagic stroke. Therefore, anticoagulated patients with head trauma may be at a higher risk of intracranial haemorrhage (ICH) than others who are not prescribed an anticoagulant.

Head injured patients often undergo head computed tomography (CT) scanning(Ip *et al*., 2015). Guidelines for requesting a head CT were developed to determine which patients would benefit most from CT scan, to rationalize resources(Haydel *et al*., 2000). During derivation, decision rules for determining who requires head CT after head injury excluded anticoagulated patients, and these guidelines now recommend CT head scans for all anticoagulated patients with a head injury(Hoffman *et al*. 1998; Steill *et al*. 2001). This is most controversial for anticoagulated patients who have a Glasgow Coma Score (GCS) of 15 in the ED. The risk of ICH among anticoagulated patients with a minor head injury (GSC 15) remains unclear.

The objective of this study was to determine the incidence of ICH in anticoagulated patients presenting to the ED with minor head injury.

METHODS

The MOOSE (Meta-analysis of Observational Studies in Epidemiology) methodological approach was followed for the completion of this meta-analysis(Stroup *et al.* 2000). The protocol was registered with PROSPERO (CRD42015025448).

Search Strategy

Pubmed, EMBASE (via OVID 1974-2017), Cochrane, and Database of Abstracts of Reviews of Effects databases were searched for articles relevant to anticoagulated ED patients with head injuries, on 1st July 2015. An identical search was re-run and the results updated on March 1th, 2018. Individual bibliographies of full papers and reviews captured in the search were examined for additional relevant references that may have been missed in the electronic search. The Pubmed and EMBASE search strategies are shown in Appendix 1. An additional search was conducted on Google Scholar. Researchers in the field were contacted for information on any unpublished data. Conference abstracts from academic emergency medicine research conferences were hand searched.

The initial database search results were independently reviewed by MT and ME, while the updated search was independently reviewed by AW and HM. Potentially eligible papers were identified and the full texts reviewed by a minimum of three authors, (including KdW). These authors met to agree on inclusion or exclusion of each full text.

Inclusion and Exclusion

The authors followed strict inclusion and exclusion criteria. Included studies had to be prospective studies which identified consecutive ED head injured patients who were prescribed an anticoagulant in the community. Included studies had to report the incidence of diagnosed ICH among unselected anticoagulated head injured patients. Vitamin K antagonists, dabigatran, edoxaban, apixaban, rivaroxaban, fondaparinux and low molecular weight heparin were all considered anticoagulants. We included conference abstracts, unpublished and published studies. There were no language restrictions. Papers in a language other than English were forwarded to a colleague who was fluent in the language for translation.

Retrospective studies were excluded because of the difficulties of identifying all head injured patients (rather than those who sustained major trauma), of identifying patients who were anticoagulant users, and because of lack of standardized diagnostic assessment(Nagurney *et al*. 2005). To avoid inclusion of anomalous results, studies reporting on less than 20 anticoagulated head injured patients were excluded. Studies reporting only on a subset of anticoagulated ED patients (for example only those who were referred to the trauma service) were excluded, as these studies would not reflect the true incidence of ICH found among consecutive ED patients, the majority of whom are discharged directly home. We excluded cohort studies reporting only the incidence of delayed bleeding (not ICH on initial ED assessment). We excluded studies reporting on patients prescribed antiplatelet medication alone.

Where it was unclear from the manuscript, we contacted the authors to confirm whether the study met inclusion criteria. We used a systematic approach for contact by email. An email letter was sent to the corresponding author, followed two weeks later by a letter to both the first and last authors. If there was still no response, then a third and final email was sent.

Data extraction

The four reviewers independently abstracted data from the eligible studies using a table created by all those involved. Any discrepancy was resolved by consensus review. If the data were unclear, the primary authors were contacted for clarification.

We contacted the authors of all included studies to obtain separate data for patients who presented to the ED with a GCS of 15 at ED triage. We excluded any patient with a GCS of 14 or less at ED triage. Data were extracted on total number of GCS 15, anticoagulated head injured ED patients, the number of these patients diagnosed with ICH on initial presentation to ED and number of patients diagnosed with ICH during follow up. Demographic data extracted included: year(s) of study, country, type of study, mechanism of injury, definition of the primary outcome and protocol for the diagnosis of ICH.

The primary outcome was the proportion of GCS 15, anticoagulated head injured ED patients who were diagnosed with ICH either at the initial presentation to the ED or during study follow up. We used each study's primary outcome definition of ICH.

Assessment of study quality

A risk of bias assessment was completed independently by AW, HM and KdW. Discrepancies were resolved by consensus. The "Tool to Assess Risk of Bias in Longitudinal Symptom Research Studies Aimed at the General Population", created by the Clarity group at McMaster was used (Clarity, *accessed* 2018). The tool reviews three domains; whether the source population is representative of the general population, if the assessment of the outcome is accurate both at baseline and follow-up, and if there is missing data.

Statistical Analysis

The data were reviewed for statistical heterogeneity with I^2 and clinical heterogeneity was assessed by consensus between authors on similarity of populations and diagnostic strategies. Meta-analysis was performed using the random effects model. We did not construct funnel plots to assess for publication bias as these have been shown to be inaccurate for studies addressing proportions, and may cross the 0% or 100% boundaries(Hunter *et al*., 2014).[12] A sensitivity analysis was performed by repeating the meta-analysis after exclusion of studies with a high risk of bias. Statistical analysis was performed using MedCalc Version 17.7.2., Belgium. MedCalc uses the Freeman-Tukey (arcsine square root) transformation.

RESULTS

The search strategy yielded 10,391 articles in Pubmed and EMBASE. After screening the abstracts, 101 articles were selected and their full-texts were assessed for eligibility. Amongst those articles, 96 were excluded. A detailed schematic of the reason for exclusion can be seen in the PRISMA diagram (Figure 1 and Appendix 2). In total, we contacted 21 sets of authors for clarification about study inclusion / exclusion criteria. All but three answered our emails.

A total of five studies (4,080 GCS 15, anticoagulated patients) were included in the final meta-analysis(Smits *et al*., 2007; Menditto *et al*., 2012; Nishijima *et al*., 2012.; Versmée *et al*., 2017; Mason *et al*., 2017) from the Netherlands, France, Italy, USA and UK (Table I). All authors supplied data for GCS 15 patients. All papers in the analysis were prospective studies evaluating unselected patients who presented to an ED with a head injury. All studies included patients who were taking vitamin-K antagonists, while one study included 60 patients taking a DOAC and 10 patients prescribed enoxaparin(Versmée *et al*., 2017).

The studies differed in their diagnostic protocols with three requiring every patient to have a CT(Smits *et al*., 2007; Menditto *et al*., 2012; Versmée *et al*., 2017) and two leaving this to the physicians' discretion(Nishijima *et al*., 2012.; Mason *et al*., 2017). The studies also differed in their patient follow up. One study did not perform further CT scans or observe the patients(Smits *et al*., 2007). Follow up in the other studies consisted of 24-hour observation with the offer of a repeat CT(Versmée *et al*., 2017), 14-day telephone call(Nishijima *et al*., 2012), repeat CT with 30-day chart review(Menditto *et al*., 2012) and 10-week institutional electronic medical record review(Mason *et al*., 2017). No studies reported on repeat head injury during the follow up period.

Studies differed in their primary outcome. All studies included ICH (epidural, subdural, subarachnoid, intracerebral, intraventricular bleeding or contusion) in their primary outcome. One study(Menditto *et al*., 2012) also included skull fracture in their primary outcome definition.

All the studies demonstrated a low risk of bias with respect to the first domain, with consecutive ED patients. Two studies did not perform head CTs in every patient(Nishijima *et al*., 2012.; Mason *et al*., 2017). One of these studies(Mason *et al*., 2017) did not perform personal follow up on those who did not have a CT, other than electronic medical record review. The risk of bias review can be seen in Table II.

In total, there were 209 patients among the 4,080 anticoagulated patients who were diagnosed with intracranial bleeding. One hundred and eighty-nine patients were diagnosed at presentation and twenty during follow up (see Table I). The meta-analysis demonstrated significant heterogeneity between studies (I^2= 93%). The Forest plot seen in Figure 2 demonstrates a random effects incidence of ICH of 8.9% (95% CI 5.0-13.8%) amongst GCS 15 anticoagulated patients with head injury. A sensitivity analysis excluding studies with a high risk of bias, the random effects incidence of ICH was 10.9% (95% CI 4.6-19.6%).

DISCUSSION

We set out to identify the incidence of ICH in anticoagulated patients with minor head injury who have a GCS of 15. The meta-analysis found the incidence to be 9%, with significant heterogeneity between studies.

This is the first meta-analysis to address this question. Two recent meta-analyses reported a very low rate of delayed ICH in anticoagulated head injured patients with a normal head CT scan (Chauny *et al.,* 2016; Verschoof *et al*., 2017). These meta-analyses did not report on the incidence of ICH at evaluation in the ED. Our analysis included both initial and delayed diagnosis of intracranial bleeding among patients with GCS of 15 at triage.

Two studies by Nishijima *et al.* and Mason *et al*. contributed 3545/4080 (87%) of the patients. Both studies reported a similar 4% incidence of ICH in anticoagulated GCS 15 head injured patients. The three smaller studies by Menditto *et al*., Versmée *et al*. and Smits *et al*. (accounting for 535/4080 [13%] patients), reported the incidence of ICH to be 22%, 9% and 13% respectively. There are several differences between the studies which could explain this difference. Neither of the larger studies performed CT scans on all patients with Mason *et al*. performing CT scans in only 58%. However, their follow up showed that only 4/2757 without a diagnosis of ICH at presentation (0.1%) were treated for ICH within the following 10 weeks. The three smaller studies performed CT scans on every patient, and Menditto *et al*. and Versmée *et al*. repeated the CT scan 24 hours later. It is likely that these studies diagnosed sub-clinical ICH. We do not know whether such bleeding would become a later threat to life. If similar bleeds were missed in the study by Mason *et al*. their chart review suggested that few patients required intervention within 10 weeks.

All studies included subdural, epidural, subarachnoid, intracerebral, and intraventricular bleeding in their primary outcome, as well as cerebral contusion. Menditto *et al*. was the only study to include skull fracture in the primary outcome, which may also have contributed to their high primary outcome incidence (22%). The mechanism of injury varied by study with 80% of Menditto's study having had a motor vehicle accident. In contrast, the most common mechanism of injury for Mason *et al*. and Nishijima *et al*. was falling on level ground.

Our study has several limitations. Only five studies were included in the analysis. More studies would allow a more robust understanding of the topic at hand and might improve the generalizability of our findings. Our findings may not be applicable to the current clinical setting, because almost all of the included patients in this review were prescribed vitamin K antagonists. This is at odds with contemporary anticoagulation prescribing(Weitz *et al*., 2015). We do not report the bleeding location, severity or resultant disability. It is, however, reasonable to consider all intracranial bleeding to be clinically relevant because current clinical practice is to hold anticoagulation, even with small bleeds, along with follow up CT. An individual patient meta-analysis would provide information on the associations with diagnosis of intracranial bleeding in these patients, however data collection varied between studies which limited the additional benefit of such an analysis.

We have identified an important evidence gap in the literature since a growing proportion of anticoagulated patients are prescribed DOACs(Weitz *et al*., 2015). There is compelling evidence that DOACs are associated with a lower risk of ICH compared to warfarin(Sardar *et al*., 2013; Miller *et al*., 2012), although there is sparse data focusing on traumatic intracranial bleeding.

The incidence of ICH reported in similar studies of the non-anticoagulated population is between 4%- 7%(Barnes *et al*., 2015; Albers *et al*., 2013). This review found overall a higher incidence among GCS 15 anticoagulated patients, although there were differences between our included studies. UK Nice guidance recommends CT scanning in all anticoagulated patients with minor head injury, regardless of symptoms, as does the Centers for Disease Control and Prevention and American College of Emergency Physicians. A UK economic analysis reported a £94,895 cost per additional quality adjusted life year (QALY) when CT scanning all patients, compared to contemporary practice(Kuczawski *et al*., 2016). This is more than three times the UK threshold of cost effectiveness which raises the question of whether a selective CT scan protocol is required.

Ours is the first systematic review on this topic which lends support to the concept that patients prescribed anticoagulation may have a higher risk of ICH. Our findings might support implementation of a selective CT scanning policy. As yet, there has been no study to assess such an approach and we lack data for DOAC use. Since the majority of anticoagulated patients are older, and there are a growing number of elderly presenting to the ED following a fall, future studies on this population should be a priority among both funders and researchers. Without robust data, we will be unable to align our diagnostic practice appropriately to identify both immediate and delayed traumatic anticoagulated ICH.

In summary, we found a 9% incidence of ICH in anticoagulated, GCS 15, head injured patients (almost exclusively prescribed vitamin K antagonists). We recommend that future studies collect prospective data on patients prescribed all forms of anticoagulation and evaluate the safety of a selective CT scanning approach.

Author contribution statement: KdW designed the study and supervised study conduct. HM, AW, ME, MT and ML performed the title and abstract review. HM, AW, ME, MT, ML and KdW reviewed the full texts and agreed on study inclusion/exclusion. HM, AW, ME, MT and KdW performed risk of bias assessment and contacted authors for missing data. SM, DN, GV reanalyzed their data for the purposes of this review. HM, AW, ME, MT, KdW, SM, DN and GV drafted the manuscript. All authors approved the final version of the manuscript. KdW takes responsibility for the paper as a whole.

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Authors disclosure statement

None to disclose.

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