The Effects Of Pre-Injury Oral Anticoagulant Use On Outcome In Older Patients With Traumatic Brain Injury: A Systematic Review

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Citation

R Reuvers, J Schimmer, G Giannakopoulos, W Zuidema. *The Effects Of Pre-Injury Oral Anticoagulant Use On Outcome In Older Patients With Traumatic Brain Injury: A Systematic Review*. The Internet Journal of Emergency Medicine. 2014 Volume 9 Number 1.

Abstract

Background: The elderly population in Europe is growing rapidly. With increasing age the risk of falling increases and since elderly are the main users of anticoagulation, this leads to a larger group at risk for suffering traumatic brain injury (TBI).

Objectives: In this review we look at the possible effects of pre-injury OAC usage on TBI and the mechanisms behind them.

Discussion: The search results show mixed results regarding the relationship between the OAC usage and increased risk of mortality, morbidity and length of hospital stay. The mechanisms remain unclear. The different study designs make comparison of the results difficult.

Conclusions: Most studies show a trend towards a negative correlation between the use of OAC and outcome after TBI in elderly patients. To clarify the effects and exact mechanisms more unified prospective studies are needed.

INTRODUCTION

The average age of the West-European population is increasing and will continue to do so in the coming years. In the geriatric population the use of anticoagulants is higher than in the non-geriatric population. Elderly have a higher risk of falling and it is assumed that this is caused by decreasing mobility and polypharmacy. Consequently, those who have a higher risk of falls, also have a higher risk of antithrombotic related injuries, such as traumatic cranial brain injury (TBI). In this particular group of patients OAC may have negative side effects such as increased mortality, morbidity, increased use of post-traumatic blood transfusions, and prolonged hospitalstay [1-6].

Besides the possible effects anticoagulants have on outcome after TBI we also searched for explanatory mechanism about the risk of pre-injury OAC usage on TBI, by evaluating different kinds of anticoagulants and their specific outcome.

In summary our review focused on two questions: (i) what are the effects of pre-injury OAC usage on TBI outcome and (ii) are there differences in outcome on TBI with the use of different anticoagulants?

MATERIAL AND METHODS

Available studies were found in the databases of Pubmed, Embase, Up to Date, Psych-info, Cochrane by the search-term ‘trauma AND brain AND hemorrhage AND (coagulation OR anticoagulation)’. The articles were included if they met the following criteria: studies with a human population, studies dating from 1 January 2007 to 1 April 2012. This time period is consistent with the commonly used OAC at the present. Article language was either Dutch, English or German. Use of OAC pre-injury was registered and the injury had to be caused by trauma. Case-reports were excluded.

In the databases Pubmed, Up to Date and Embase 294, 150, and 799 articles were found, respectively. Other databases showed no eligible studies. After applying the inclusion criteria, Pubmed revealed 4 and Embase 12 studies. Cross-referencing added another three studies, bringing the total number of included studies to 19.

Items scored were average age of patients, the presence of bleeding and other injuries, specific OAC type, length of hospital stay, mortality, morbidity, INR values, neurotrauma

score, and whether or not a second CT-scan was performed during hospital stay.

RESULTS

Incidence of TBI is not know for all European countries. An estimation can be made by TBI incidence numbers in surrounding country's. A study from Germany points out that there is an incidence of 300-400 per 100.000[7]. However a study in the U.K. shows an incidence of 2300 per 100.000 [8]. These are incidence numbers for the general population.

The anticoagulants will be discussed in three groups according to their working mechanism and effect in case of TBI.

Coumarin derivatives

The literature mostly originates from the USA. In the USA warfarin is used on large scale. In the Netherlands, warfarin is only used in exceptional cases. Instead, other coumarin derivatives, such as acenocoumarol and fenprocoumon are used frequently. The working mechanism of all coumarin derivates is the same, for they all lead to an artificial vitamin K deficiency. The different coumarines differ only concerning the duration of the effect.

Franko et al. showed that advanced age and warfarin usage were risk-factors for a higher mortality rate after TBI. Patients were divided into four groups based on age and OAC usage. The first group was 70 years or older. The second group was between 55 and 70 years of age. In these two groups the patient were divided into users and non-users. The outcome showed that mortality rate was statistically higher in the first group, both in the group of warfarin users (25.6% vs 16.4%, $p < 0.001$) as well as in the non-user group (8.2% vs. 3.2 % $p < 0.001$). Furthermore, a correlation was found between INR-value and mortality rate ($p < 0.001$).

The total population warfarin users, independently of their age, had higher chances of intracranial bleeding (ICB) after trauma (60.4% vs 40.2%, $p < 0.001$). Anticoagulated patients had a higher risk of mortality than the control group (23.9 vs 4.9%, $p < 0.001$). In addition, they had higher chances of mortality after TBI (37.5% vs 11.4%, $p < 0.001$) [1].

A higher risk of mortality with an increasing INR was also found by Pieracci et al. [6]. In this study, the group with a therapeutical INR-value had a higher risk of GCS ≤13 when presented to the emergency room (ER) and a higher mortality, compared to a non-therapeutical group and a group of non-users [6].

This is backed up by White et al. They were looking for effects of oral anticoagulation on progression of ICB after TBI on CT-scan. The patients with the largest progression had a statistically higher INR compared to the group with a less progressive ICB (1.4 vs 1.2, $p < 0.05$) [9].

A progressive ICB was correlated with an increased mortality by Ivascu et al. The mortality rate was higher in patients with progressive ICB compared with patients without progression of their ICB (60% vs 6%, $p = 0.004$) [10]. In another study of Ivascu et al.[11] they concluded that Warfarin usage led to an increased risk of ICB. In addition, patients using warfarin who developed a posttraumatic ICB had a five times higher risk of mortality compared to similarly injured non-anticoagulated patients. The implementation of a new protocol, which was based on early detection of an ICB with a CT-scan and normalizing the INR with Fresh Frozen Plasma, led to a decrease of the mortality rate from 48 to 10 percent ($p<0.001$), compared with the control group which consisted of historic data [11]. Vogel et al. also recommended performing a CT-scan repeatedly after ICB in order to detect early progression of ICB[12].

Washington et al. studied a population of patients with mild TBI and ICB and the need for a routine repeat imaging. They found the following to be predictors of progression of the ICB on CT-scan: ICB with a volume >10 ml, subfrontal/temporal contusion, age ≥ 65 years, antiplatelet or coumarin therapy [13].

Cohen et al. compared characteristics and recovery of a group of patients with severe TBI with a group with minor TBI. They found in the group with severe TBI an average Glasgow Coma Scale (GCS) of 4.7, INR of 6.5 and a mortality rate of 87.7%. Half the patients had an INR higher than 5.0. The survivors recovered to a vegetative state or with a severely disability. Patients with a minor TBI had an average INR of 4.4. In 47% the INR was higher than 3.0. Mortality rate in this group was 80,6%. Out of 77 patients twelve made it to good recovery [14].

The most dismal outcome after a lower GCS is supported by the study of Parmar et al. This study included patients admitted to hospital because of head injury and who were at the time of accident taking warfarin. Although they included

only 13 patients, those who died had a significant lower GCS on admission compared with those who survived[15].

Additionally, Fortuna et al. showed a correlation between GCS at presentation on the ER, recovery and age. Patients were divided into four groups based on age (over 70 or between 50 and 70 years) and use of OAC (yes or no). Patients over 70 without OAC showed a statistically significant increased mortality rate compared with the non anticoagulated younger subgroup ($p = 0.001$). Recovery was worse as well in the older group. After treatment 30% had an acceptable recovery, against 65% in the younger group. Warfarin users had the highest mortality rate.

Surprisingly, in the group older than 70 years of age mortality rate was lower in OAC-users. This effect is explained by the protective effect of warfarin against microembolisms, which can cause an ischemic brain injury after TBI [16].

The study of Dosset et al. showed a multicentre study with 1,230,422 patients included in the study. They described a two-fold increase of mortality rate in patients using warfarin compared with nonusers (9.3% vs. 4.8%, $p < 0.001$). When stratified for age and injury this association became less strong but is still significant [2].

Siracuse et al. examined Trauma Registry databases in two time periods, T1=1999-2000 and T2=2007-2008 and looked for patients admitted with post-traumatic ICB and TBI. Between T1 and T2 the total amount of patients with TBI doubled (6.2% vs 12.3%, $p =<0.01$). Only in T1 they found a higher mortality rate in warfarin users compared with nonusers. The length of stay in the hospital for warfarin users with an INR ≥2 decreased between the two time periods from 22 to 19 days($p <0.05$). The found effect of a lower mortality in T2 is explained by a increased attention to post-traumatic ICB in warfarin users. Despite the decreased mortality rate in warfarin users the total mortality rate between T1 and T2 did not change. This was explained by the possibility that in the group non warfarin users the amount of clopidogrel users increased in T2 compared to T1. They claimed that the patients who use clopidogrel have a higher mortality rate for post-traumatic ICB because it is harder to reverse [3].

Aspirin

Ivascu et al. described that aspirin or clopidogrel users are more likely to present after TBI with more severe IBC and a higher mortality rate than similarly injured patients not using OAC.

The cause of death in most patients was exacerbation of other clinical conditions or the severity of intracranial hemorrhage at the time of presentation, not progression to a worse grade of hemorrhage. They described that therapeutic efforts in patients taking anticoagulants after admission are less efficacious than in pre-injury warfarin users, therefore more aggressive preventive measures are even more important.

An important characteristic of non survivors of ICB was their significantly older age compared with survivors (80 vs. 75 years, $p = 0.046$) [4].

In contradiction to the previous study Gangavati et al. found an increased risk of ICB when patients did not use aspirin ($p = 0.04$), also when the aspirin was used in combination with clopidogrel people they were less likely to sustain a ICB ($p=0.01$). The protective effect can be explained by the patient education aspirin users got. Therefore they went to the ER faster after small trauma, and as mentioned earlier, aspirin might prevent ischemic brain damage by reducing micro embolisms [17].

In the study of Bond et al., the population existed of in-hospital patients. There were 462 TBI's described, and only one case of ICB was seen despite 50% was using some form of anticoagulation. They suggested this is possible because there was a preference for more fit patients to undergo anticoagulation therapy, besides that, they were in the hospital during their trauma (mostly patients falling out of bed). This can help in faster diagnostics and intervention [18].

Clopidogrel

The study of Jones et al. found a significant difference in the amount of rebleeds in the patients on clopidogrel therapy (five of nine patients) against the control group (one out of ten patients) ($p = 0.05$). However, the population was very small and thus difficult to interpret [5].

Pieracci et al. included over 47.000 patients admissions related to falls. They made no differentiation in their results for different anticoagulants.

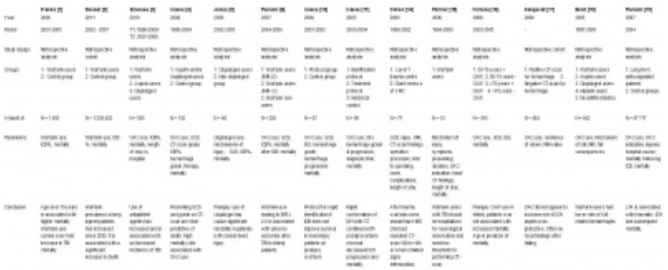
They showed that pre-injury anticoagulated patients had a chance of 8.0% on ICB after TBI against 5.2% in the control group ($p <0.001$). Also an increased mortality rate was

found, 21.9% vs. 15.2%, for OAC users vs. control group following ICB (p = 0.04).

In their study they also performed a subgroup analysis of patients with atrial fibrillation to search for a possible confounding effect. They found no statistically different results between the two groups. This supports their hypothesis that OAC therapy itself and not the physical condition of the patient is explanatory for the effects found compared with the control group [19].

Table 1

Overview of all articles. OAC = oral anticoagulant, GSC = Glasgow Come Scale, ICB = intracranial bleeding, INR = international normalized ratio, ISS = International Severity Scale, CAW = Clopidogrel, Aspirin, Warfarin.



DISCUSSION

This review evaluates the recent articles on the relation between pre-injury OAC therapy and the effect on TBI and ICB.

Six of the mentioned studies support the hypothesis that pre-injury OAC therapy, leading to therapeutically INR-values, influences outcome by the anticoagulant effect of OAC.This includes higher mortality rate, morbidity, higher risk on ICB and worsening of the bleeding. Three studies show a protective effect of using OAC on mortality and morbidity. Five studies are inconclusive but see an association between OAC usage and a worse outcome. The last five studies don't say anything about OAC effect on TBI but describe diagnostic procedures around CT-scan.

So different studies show that age is a predictor for a higher mortality after TBI or leads to a higher risk of worsening of their initial ICB [13, 14].

The question whether there is a different effect between the different anticoagulants is difficult to answer. Different and contradictional effects of different anticoagulants are found. To clarify the effect of different anticoagulants it is important that in future studies the different anticoagulants are compared in a single study and they are also compared to a non-OAC group.

Despite the statistically significant effect of anticoagulants on TBI and ICB it does not become clear that this effect is caused by the OAC or by another characteristic of the OAC using population. To distinguish between different factors it is important in future studies to describe the height of the INR at admission. This may be an explanation for worse outcome in the higher INR group and can lead to a differentiated way to treat patients when they are using different anticoagulants. In this way we can learn if patients with certain combinations of OAC and ICB should be treated more aggressively than other combinations.

CONCLUSION

Most studies show a negative correlation between the use of OAC and outcome after TBI in elderly patients, the different study designs make it difficult to compare the studies. Besides this, almost all studies are retrospective. More prospective studies are needed.

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