RESEARCH ARTICLE

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Do We Need to Repeat the Initially Normal Head Computerized Tomography for Patients with Mild Head Trauma Using Anticoagulant and/or Antiplatelet Therapy?

ABSTRACT

Objective: Patients using anticoagulant and/or antiplatelet (AC/AP) medications are at an increased risk of intracranial hemorrhage (ICH) subsequent to head trauma and current guidelines recommend a head computed tomography (CT) scan for these patients. There is a lack of consensus about management recommendations for mild head trauma patients on AC/AP treatment who had an initially normal head CT. The aim of this study was to determine the rate of delayed ICH after a 24-hour observation in patients with mild head trauma using AC/AP who had an initially normal head CT.

Method: Patients aged 18 and older, using AC/AP drugs with mild head trauma were included prospectively. Patients underwent head CT for suspected bleeding. A repeat CT scan was performed after a 24-hours observation period for the patients who had an initially normal head CT for detecting delayed intracranial hemorrhage.

Results: A total of 101 patients were included and, 57.4% (n=58) of the patients were female. Delayed ICH was detected in 2.9% (n=3) of the patients after a 24-hour observation. None of the patients with delayed ICH needed surgical treatment or further intervention. Delayed ICH was found in patients who used acetylsalicylic acid (n=1), dabigatran (n=1), and apixaban (n=1).

Conclusion: In patients with mild head trauma using AC/AP, delayed intracranial hemorrhage is rare and may be clinically insignificant. A repeat CT scanning after 24-hour observation may not be necessary for patients with mild head trauma using AC/AP therapy who had initially normal head CT.

Keywords: Anticoagulant Drugs, Antiplatelet Drugs, Head Trauma, Intracranial Hemorrhage.

Antikoagülan ve/veya Antiplatelet Tedavi Kullanan Hafif Kafa Travmalı Hastalarda Başlangıçta Normal olan Bilgisayarlı Kafa Tomografisini Tekrarlamamız Gerekir mi?

ÖZET

Amaç: Antikoagülan ve/veya antiplatelet (AC/AP) ilaç kullanan hastalarda kafa travması sonrası intrakraniyal kanama (İKK) riski yüksektir ve güncel kılavuzlar bu hastalar için bilgisayarlı kafa tomografisi (BT) görüntülemesini önermektedir. Başlangıçta normal kafa BT'si olan ve AC/AP ilaçları kullanan hafif kafa travmalı hastalar için yönetim önerileri konusunda fikir birliği yoktur. Bu çalışmanın amacı, başlangıçta normal kafa BT'si olan ve AC/AP kullanan hafif kafa travmalı hastalarda 24 saatlik bir gözlem sonrasında gecikmiş İKK oranını belirlemektir.

Gereç ve Yöntem: AC/AP ilaç kullanan, 18 yaş ve üzeri hafif kafa travmalı hastalar prospektif olarak çalışmaya alındı. Hastalara kanama şüphesi nedeniyle kafa BT'si çekildi. Çekilen ilk kafa BT'si normal olan hastalara gecikmiş intrakraniyal kanamayı saptamak için 24 saatlik gözlem süresi sonrasında tekrar kafa BT görüntülemesi yapıldı.

Bulgular: Toplam 101 hasta çalışmaya dahil edildi ve hastaların %57,4'ü (n=58) kadındı. 24 saatlik gözlem sonrasında hastaların %2,9'unda (n=3) gecikmiş İKK saptandı. Gecikmiş İKK'li hastaların hiçbirinde cerrahi tedavi veya başka girişim gerekmedi. Gecikmiş İKK, asetilsalisilik asit (n=1), dabigatran (n=1) ve apiksaban (n=1) kullanan hastalarda saptandı.

Sonuç: AC/AP kullanan hafif kafa travmalı hastalarda gecikmiş İKK nadirdir ve klinik olarak önemli olmayabilir. Başlangıçta kafa BT'si normal olan, AC/AP ilaç kullanan hafif kafa travması olan hastalarda 24 saatlik gözlemden sonra kafa BT görüntülemesinin tekrarı gerekli olmayabilir.

Anahtar Kelimeler: Antikoagülan İlaçlar, Antiplatelet İlaçlar, Kafa Travması, İntrakraniyal Kanama.

INTRODUCTION

Head trauma is one of the common reasons for emergency department (ED) admissions. In the United States of America, over 2.5 million head trauma patients present to EDs annually (1). Over the years, the number of patients admitted to the ED with head trauma has increased in all age groups, though the largest increase is in patients over 60 years old (2). Anticoagulant and antiplatelet (AC/AP) drugs are of critical importance in the treatment protocols of diseases such as coronary artery disease and cardiac arrhythmia and the incidence of use of these drugs increases with age (3).

One of the important risk factors for intracranial hemorrhage (ICH) in patients with head trauma is the use of AC/AP. Delayed ICH is defined as the finding of a normal brain computerized tomography (CT) after head trauma with a repeat CT demonstrating ICH without subsequent trauma. Delayed ICH may be seen in 0.6% to 6.2% of patients with head trauma (4-11).

Current guidelines recommend an initial CT in patients on AC/AP presenting with head trauma (12-14). However, there is no consensus on recommendations for the follow-up of patients with mild traumatic brain injury (TBI) in terms of the observation period and routine repeat CT for delayed ICH (6-8). Among studies, three recommendations have emerged for the management of patients with mild TBI; The first one is to observe these patients for 6 to 24 hours after the first CT presenting no ICH (4,6,9), the second one is to perform a repeated CT after the time of observation (7,11,15), and the third one suggests discharging patients without clinical observation or a repeat CT (10,16). The management of these patients group remaining unclear and causes confusion among physicians. The aim of this study was to determine the rate of delayed ICH after a 24-hour observation in patients with a mild head trauma using AC/AP who had an initially normal head CT.

MATERIAL AND METHODS

Study Design: This was a prospective observational cross-sectional descriptive study. Initially, a head CT scanning without contrast-enhanced was performed in patients with head trauma according to NEXUS Head CT Instrument. CT scans were interpreted by the neuroradiologist in charge at the time. Patients with a negative initial head CT were observed in the ED for 24 hours from the time of hospital admission. If neurological deterioration (decrease in GCS, new neurological deficits, seizure) developed during the observation period, a repeat CT scan and a neurosurgical consultation was planned. For patients without neurological deterioration or worsening symptoms during the 24-hour observation period, a repeat head CT was performed at the end of the observation period. Patients with delayed ICH on repeat head CT were consulted to the neurosurgery department. Patients with no further complications were discharged from ED with instructions. Follow-up was extended up to one month and patients were called on one week and 30 days later after trauma. One month after the head trauma, the patients were invited to ED for evaluation of trauma impact, and a detailed neurological examination was performed but the brain CT was not repeated. It was questioned whether there were any neurological symptoms related to head trauma and whether patients were re-admitted to the hospital one-month period after head trauma.

Setting: The study was conducted in the ED of a university hospital with an annual ED presentation of 55,000 patients. Patients with blunt head trauma using any AC/AP medication presented to the ED between February 1, 2019, and January 31, 2020, were included in the study. Ethical approval was received from the Clinical Research Ethics Committee of the Ankara University School of Medicine with the approval number 02-114-19 and date of 28.01.2019.

Participants: All patients with blunt head trauma using any AC/AP medication presented to the ED between study dates were assessed for eligibility. The inclusion criteria were; patients aged ≥18 years, had a Glasgow Coma Scale (GCS) score of 13-15, had taken AC/AP drugs in the last 24 hours, and was admitted to the ED within the first 2 hours after trauma (14). We excluded patients referred from another health institution, and pregnant patients. Patients with ICH or skull fracture on initial CT were excluded from the study. In case the patients had other trauma in addition to the head trauma, appropriate diagnostic imaging modalities were performed for the affected body structure. Patients who did not accept the observation in the ED or declined a repeat head CT after the observation were excluded from the study. Written informed consent was obtained from all patients included in the study.

Variables: Patients who met the study inclusion criteria were enrolled in the study and patient information was recorded on the study form prepared in advance. Demographic characteristics, GCS score, mechanism of trauma, type of AC/AP drugs were collected for each patient. Complete blood count, activated partial thrombin time (aPTT), and international normalized ratio (INR) tests were performed to evaluate the bleeding risk of the patients. During the observation period, patients were monitored, and re-evaluated every two hours, vital signs (fever, pulse, respiratory rate, blood pressure) and GCS scores were recorded.

The primary outcome was to assess the presence of delayed ICH in mild TBI patients using AC/AP on the repeat CT scan. The secondary outcomes were 30 day-mortality after head trauma

and determining risk factors associated with delayed ICH.

Sample Size: The prevalence of ICH was accepted %4 and estimated with a marginal error of %3.5, and with a type 1 error of %5, at least 119 patients with at least 5 ICH needed to be included in to study.

Statistical Methods: For descriptive statistical evaluations, mean ±standard deviation was used for continuous variables, frequencies and percentages were used for categorical variables. For comparison of variables between two independent groups; the t-test, the significance test of the difference between two percentages, and the Mann-Whitney U test was used. Chi-square Test and Fisher's Exact Test were used to examine the relationship between categorical variables. A p value <0.05 was considered significant. SPSS 23.0 package program was used for statistical analysis.

RESULTS

A total of 1276 patients with mild head trauma were admitted to the emergency department during the study period, 171 of these patients were using AC/AP drugs, and 1105 of these patients were not using any AC/AP drugs. Patients with mild head trauma using AC/AP drugs were evaluated for eligibility (n=171) and 70 of patients were excluded. A total of 101 patients who had a normal initial head CT, were observed 24 hours in the emergency department and had a repeat head CT after observation included for the analysis (Figure 1).

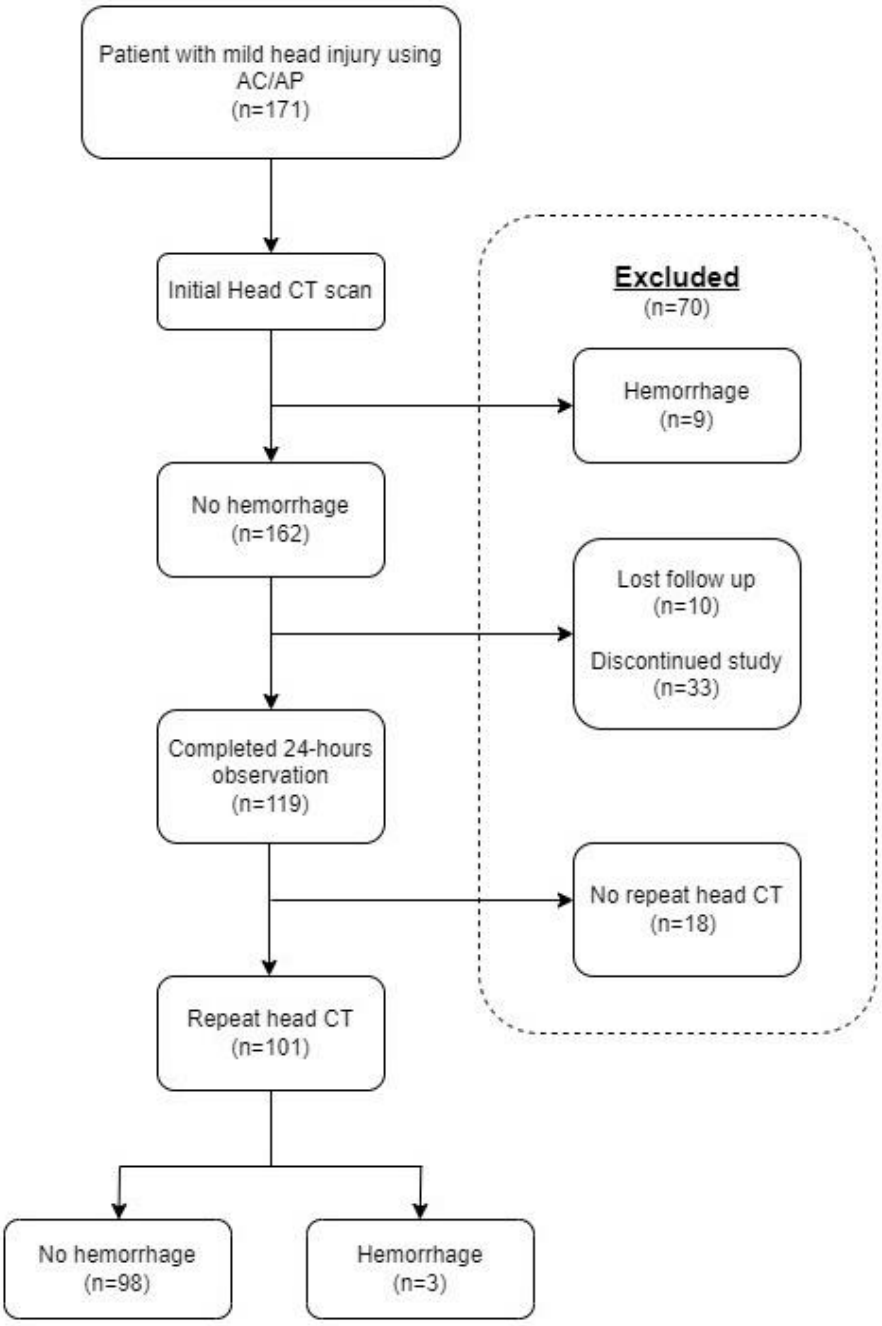

Figure 1. Flowchart of the patients and study protocol

The mean age was 75.52 ±10.01 years, and 57.4% (n=58) of these patients were women. The GCS score of 15 was found 99% of the patients (n=100). The most common trauma mechanism was ground-level fall (Table 1). Acetylsalicylic acid (ASA) (34.7%, n=35), clopidogrel (18.8%, n=19) and warfarin (9.9%, n=10) were found to be the most common AC/AP drugs. During the follow-up in the ED, no pathological changes in neurological examinations and no new symptoms were recorded in all patients. At the end of the 24-hour observation period, delayed ICH on repeat head CT was detected in 3 (2.9%, 95%CI: 0-6.3) of the patients. Factors reviewed for correlation to delayed ICH are shown in Table 2. The mean age of the three patients with delayed ICH was 78.66 ±8.5 years. None of them had new symptoms or neurologic deterioration in 24-hour observation. The clinical features of the patients with delayed ICH are shown in Table 3. Patients with delayed ICH were consulted to the neurosurgery clinic, none of them need further hospitalization, surgical intervention, or specific treatment, and they were all discharged with instructions. The follow-ups by telephone reported no complications.

Patients without delayed ICH on repeat CT (n=98) were discharged with instructions. Of the 94 patients who were reached by phone call did not have any complaints due to head trauma, and no mortality was reported at the end of the one-month period. Four of the patients could not be reached by phone call and the national health system was examined for these patients. It was observed that none of the patients was readmitted to the hospital within a one-month period and no mortality was noted.

Table 1. Demographic characteristics of the study population

Characteristics	**Number (%)**
Age, mean (±SD)	75.52±10.01
Gender	
Female	58 (57.4)
Mechanism of injury	
Ground-level fall	94 (93.1)
Traffic accident	6 (5.9)
Direct impact	1 (1)
GCS (on arrival)	
14	1 (1)
15	100 (99)
AC/AP	
Acetylsalicylic acid	35 (34.7)
Clopidogrel	19 (18.8)
Ticagrelor	5 (4.9)
Prasugrel	3 (3)
Warfarin	10 (9.9)
LMWH	8 (7.9)
Dabigatran	8 (7.9)
Rivaroxaban	9 (8.9)
Apixaban	9 (8.9)
Edoxaban	6 (5.9)
Combined use of AC/AP	11 (10.9)
Reason for AC/AP treatment	
Coronary artery disease	40 (39.6)
Atrial fibrillation	31 (30.6)
Stroke	13 (12.8)
Thromboembolic disease	8 (7.9)
Peripheral artery disease	6 (5.9)
Other	3 (2.9)
Total population	101(100)

GCS, Glasgow Coma Scale; LMWH, Low Molecular Weight Heparin; AC/AP, Anticoagulant and antiplatelet

Table 2. Factors affecting delayed ICH in repeat CT imaging

	No Delayed ICH (n=98)	**Delayed ICH (n=3)**
Age (years)	75.42 ± 10.08	78.66 ± 8.5
Gender*		
Female	58 (100%)	0 (0%)
Male	40 (93%)	3 (7%)
GCS score		
14	1 (100%)	0 (0%)
15	97 (97%)	3 (3%)
Mechanism of injury		
Ground-level fall	91 (96.8%)	3 (3.2%)
Traffic accident	6 (100%)	0 (0%)
Direct impact	1 (100%)	0 (0%)
Platelet count (10^9/L)*	231.5 ± 81.9	163 ± 92
aPTT (sec)*	28.5 ± 6.9	34.7 ± 8.08
INR*	1.2 ± 0.3	1.3 ± 0.1

ICH, Intracranial Hemorrhage; GCS, Glasgow Coma Scale; aPTT, Activated Partial Thrombin Time; INR, International Normalized Ratio. * $p<0.05$

Table 3. Characteristics of patients with delayed intracranial hemorrhage

Patients	Age	Sex	GCS score	Mechanism of injury	Type of AC/AP drug	Reason for AC/AP treatment	Platelet Count (10^9/L)	INR	Change in Neurological Status	Repeat CT pathologic finding	Neurosurgical Intervention	Outcome
No. 1	79	Male	15	Ground-level fall	Dabigatran	Atrial fibrillation	130	1.2	No	Intraparenchymal hemorrhage	No	Complete recovery
No. 2	70	Male	15	Ground-level fall	Acetylsalicylic acid	Stroke	92	1.4	No	Intraparenchymal hemorrhage	No	Complete recovery
No. 3	87	Male	15	Ground-level fall	Apixaban	Coronary artery disease	267	1.4	No	Intraparenchymal hemorrhage	No	Complete recovery

GCS, Glasgow Coma Scale; AC/AP, Anticoagulant and antiplatelet; INR, International Normalized Ratio.

DISCUSSION

Delayed onset of an intracranial hematoma is a major concern for patients with mild traumatic brain injuries. The use of AC/AP therapy is an independent and major risk factor for intracranial bleeding is. Patients taking AC/AP have been a challenging aspect of mild brain injury management and follow-up. The use of AC/AP drugs increases both early and delayed ICH (ranges from 0 to 6%) after head trauma (5,7,10,15,17,18). Many factors, such as the number and the demographic characteristics of patients included, severity, and mechanism of trauma may affect delayed ICH rates. Menditto et al (7) found a significantly high rate of delayed ICH with 6%. The authors explained that this might probably be due to an INR level greater than 3 in those patients. Additionally, we noticed that the age of the study population was relatively high with a median age of 82 (7).

Studies that aimed to detect delayed ICH, pointed out similar risk factors such as AC/AP drug type, patient age, and INR value. Studies in the past 10 years have mostly focused on patients receiving vitamin K antagonists (VKA), clopidogrel, and ASA (5,6,8,10,19), whereas studies published in the last few years examined mainly the use of direct oral anticoagulant (DOAC) group drugs which use has become more prevalent (20,21). There are a few studies that similarly to us have included a broad range of AC/AP drugs (22). DOACs are known to be safer with an appreciable reduction of spontaneous ICH rate than traditional oral anticoagulants (15,18). However, the outcome after TBI when using a DOAC remains uncertain (23). In our study, two of the 3 patients who revealed delayed ICH at the end of the observation period were using DOAC (respectively dabigatran and apixaban). In their study, Barmparas et al (21) showed that the incidence of delayed ICH was less than 1% in patients on trauma patients under DOACs with initial negative imaging.

Riccardi et al (15) reported a lower incidence of hemorrhage after mild head trauma in patients treated with DOACs compared to VKA. Conversely, a recent study showed a rate smaller than 1% (n=3) for delayed ICH in trauma patients, none of these patients were under DOACs (22). Tauber et al (11) observed that 4% of patients using ASA had a delayed ICH. Swap et al (24) found delayed ICH in 2.7% of the patients who used VKA and in 2.3% of the patients who used clopidogrel. Nishijima et al (8) detected delayed ICH in 0.6% (n=4) of patients using VKA, and none of them was taking clopidogrel. Considering all these results, it can be said that AC/AP drug use alone is not a risk factor for delayed ICH, and this entire drug group may cause delayed ICH.

In our study, the three patients with delayed ICH were over 65 years old. When we looked at the existing literature the majority of patients with delayed ICH were over 65 years old (8,9,16). Age-related cerebral atrophy and posttraumatic hemorrhages association has always been speculation. Likewise, Dunham et al (25) objectively documented that acute post-traumatic ICH and pre-injury cerebral atrophy are clearly correlated.

Many studies reported high INR levels as a risk factor for delayed ICH in patients with head trauma (7,26). In a study conducted by Schoonman et al (10), patients developing delayed ICH, were on VKA (n=5) and three of them had a supratherapeutic level of INR (>3). Patients with delayed ICH may have a normal INR level (defined as between 2-3) (27). Studies have shown that delayed bleeding may occur in patients with head trauma, whose INR value is in the therapeutic range (4,8). In our study, three patients with delayed ICH had a normal range of INR values. Using INR level for risk stratification of brain injury patients on VKA has been suggested however, resulting data should be interpreted rigorously considering the limited number of reported delayed ICH patients in these studies (26,27).

In our study, patients with delayed ICH had no complaints or neurological symptoms during the 24-hour follow-up. Similar to our study, Uccella et al (19) observed no neurological impairment during the observation period. A meta-analysis performed by Verschoof et al (16) showed a low frequency of 0.2% for neurological deterioration by cause of delayed ICH within 24 hours. Furthermore, the majority of patients with delayed ICH is asymptomatic and discharged without surgical treatment; routine observation appears unfounded when the initial head CT is absolutely normal. Hospitalization or follow-up may increase the financial cost of the health system, revealing uncertain benefits (16).

Due to the risk of delayed ICH in head trauma patients using AC/AP drugs, different recommendations have emerged for the management of this patient group. While some studies recommend clinical observation of patients for different periods (4-6,9,19), others affirm that observation will not be sufficient since the majority of patients with delayed bleeding is asymptomatic and a repeat CT before discharge from ED might be beneficial (7,11,28). In a systematic review, development of symptomatic ICH within 24 hours in patients with minor brain injury when the initial head CT was normal is rare, even for patients taking anticoagulants (16). Most of the patients (55% and n=5) with delayed ICH were diagnosed after 24 hours in this review (16). Schoonman et al (10) found that 80% (n=4) of the patients with delayed ICH had bleeding after 24 hours and findings do not support the observation recommendation for at least 24 hours from the European Federation of Neurological Societies. In the study of Afaneh et al (29), only two of 273

patients (0.7%) who underwent a repeat CT had clinically significant delayed ICH but none of the patients had a surgical intervention. Velmahos et al (30) do not recommend routine repeat head CT in patients with minor TBI, suggesting focusing on clinical examination clues to identify the few who will need intervention. Therefore, it can be said that monitoring these patients and undergoing a repeat CT scan may increase the cost burden in healthcare systems and exposure to radiation without providing any significant clinical benefits.

LIMITATIONS

Our study has some limitations for the generalizability of the results. First, our study was conducted in a single hospital and the majority of the patients were elderly and, the most trauma mechanism was ground-level fall so our study may not represent all patient populations. Second, the sample size in our study was relatively low and confidence intervals of the rate of delayed ICH were broad. Third, the number of patients who didn't complete the 24-hour observation and/or a repeat CT scan was high, and these patients may have asymptomatic delayed ICH. Finally, a repeat head CT after 24 hours of admission was not performed in patients who did not use AC/AP drugs therefore we cannot make interpretations on the rate of delayed ICH in this patient group.

CONCLUSION

The rate of delayed ICH after a 24-hour observation in patients with a mild head trauma using AC/AP who had an initially normal head CT is low and a repeat head CT scan may not be necessary. In the light of the literature reviewed, and based on our results, we consider that it would be more appropriate to discharge the mild head trauma patients taking AC/AP medications who had an initially normal head CT and remain clinically stable after a 24-hour observation.

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