The American Journal of Surgery 220 (2020) 55–61

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Review

Detecting delayed intracranial hemorrhage with repeat head imaging in trauma patients on antithrombotics with no hemorrhage on the initial image: A retrospective chart review and meta-analysis

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ARTICLE INFO

Article history:
Received 10 July 2019
Received in revised form
10 September 2019
Accepted 1 October 2019

Meeting Presentation: Information contained in this manuscript was presented at: 1) the Society of Critical Care Medicine 47th Critical Care Congress, February 25–28, 2018, San Antonio, Texas, USA; 2) Society of Critical Care Medicine 2017 Critical Care Congress, January 21–25, 2017, Hawaii Convention Center Honolulu, Hawaii, USA; 3) Mercy Health Youngstown, Resident Research Day, May 13, 2016, in Youngstown, Ohio, USA.

Keywords:
Delayed intracranial hemorrhage
Head computed tomography
Blunt trauma
Antithrombotic
Antiplatelet
Anticoagulant

ABSTRACT

Background: There is debate regarding routine repeat head computed tomography (CT) in blunt trauma patients on a pre-injury antithrombotic when the initial CT is negative for intracranial hemorrhage (ICH).
Data sources: Retrospective chart review and systematic literature review with meta-analysis.
Conclusions: In the chart review, 32.1% did not have a repeat head CT and 67.9% did. The delayed ICH incidence between those with and without a repeat head CT was similar (1.7% vs 0, $p = .3101$). The current study was combined with the identified 24 studies. Delayed ICH with or without routine repeat CT was similar between antiplatelet and anticoagulant categories (1.4% vs. 1.3%, $p = .5322$). Delayed ICH was lower for patients without routine repeat CT compared to those with routine repeat CT (0.8% vs 1.7%, $p = .0008$). For this patient population, repeat scans should be discretionary. Routine repeat CT may identify a larger proportion of minor delayed ICH.

Introduction

Antithrombotic agent use such as anticoagulants and antiplatelet agents, including but not limited to: warfarin, aspirin (ASA), clopidogrel, and direct acting oral anticoagulants (DOAC), are commonly accepted risk factors for traumatic intracranial bleeding.[1–27] Current clinical guidelines from the Eastern Association for the Surgery of Trauma (EAST) recommend performing brain computed tomography (CT) for patients with head trauma taking antithrombotic agents.[27] There is debate regarding the need for repeat neuroimaging in patients with blunt trauma to the head on a pre-injury antithrombotic, when initial neuroimaging is negative for intracranial hemorrhage (ICH).[1–26] This uncertainty in management is driven by the possibility of delayed ICH.[1–26] The EAST guidelines acknowledge that anticoagulated patients remain at risk for delayed ICH, and consider antiplatelet agents as systemic anticoagulants.[27]

Three systematic literature reviews attempt to address delayed ICH in this patient population.[24–26] These reviews focused on anticoagulants and did not address antiplatelet agents.[24–26] Miller et al.[26] reviewed warfarin patients and reported a delayed ICH incidence up to 72 per 1,000 patients. Chauny et al.[25] focused on vitamin K antagonists (VKA), and Verschoof et al.[24] examined anticoagulants (therapeutic heparin, DOAC, or VKA). Both report a

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https://doi.org/10.1016/j.amjsurg.2019.10.006
0002-9610/

delayed ICH proportion less than 1%.[24,25] There are no known published meta-analyses that address delayed ICH among antiplatelet agents, yet multiple institutional studies report delayed ICH in trauma patients taking pre-injury antiplatelet agents.[3–6,11,12,14,16,18,20,21]

The aim of the current study was to evaluate our institution's incidence of delayed traumatic ICH in patients with blunt trauma to the head taking pre-injury antithrombotic agents and perform a systematic review and a meta-analysis with the inclusion of our cohort. The authors hypothesized that routine repeat head imaging in blunt trauma patients taking a pre-injury antithrombotic would not be clinically necessary.

To the authors' knowledge, this is the first study to include all antithrombotic agents. Additionally, the authors compare patient characteristics and outcomes between patients with and without routine repeat head imaging.

Methods

Institutional chart review

This retrospective chart review was performed at a Level I Trauma Center in Northeast Ohio and was approved by the Institutional Review Board. The retrospective study is an evaluation of the institution's practice management guideline for trauma service patients who take antithrombotic agents and sustain blunt trauma to the head. The guideline recommended that trauma service patients taking an antithrombotic agent who presented with physical signs of blunt trauma to the head received stat CT head imaging, thromboelastography (TEG), and international normalized ratio (INR) lab analyses. If the initial head CT was negative, the patients were observed with neurologic assessments every hour, and a head CT was repeated within four to 6 h. Antithrombotic reversal is not routinely performed in patients with an initially negative head image.

Patients were identified through the monthly Trauma Census from the Trauma Registry. The institution's monthly Trauma Census includes a sub-section of patients for whom trauma services treated, but subsequently did not meet criteria for entry into the Trauma Registry. This sub-section of patients that were seen by trauma services but did not meet Registry criteria were purposefully reviewed for inclusion. Included patients were: 1) aged 18 or older, 2) sustained blunt head trauma, 3) taking any antithrombotic agent, 4) admitted from July 1, 2014 through December 31, 2015, and 4) had an initially negative head CT. Excluded patients were: 1) younger than 18 years, 2) had an initially positive head CT, or 3) were not taking an antithrombotic agent.

For the purposes of this analysis, an antithrombotic agent was defined as any pre-injury anticoagulant or antiplatelet medication, including but not limited to: ASA, clopidogrel, warfarin, and all DOACs. Blunt head trauma was defined as 1) a documented statement that the patient hit his/her head, 2) any craniofacial soft tissue injury, cephalohematoma, craniofacial fracture, or cognitive alteration. A head CT was considered positive if there was intracranial blood present. Skull fractures without intracranial blood were considered a negative head CT. A Lightspeed™ VCT 64-slice scanner (GE Healthcare, Waukesha, WI, USA) was used for all head CTs at the institution.

Data was collected from the Trauma Registry and the electronic medical record. Variables included age, sex, mechanism of injury, Trauma Service role (team, alert, consult, or none), admission vital signs, Glasgow Coma Scale (GCS), base excess, hemoglobin, platelets, INR, TEG reaction time and maximum amplitude, antithrombotic therapy type, initial and repeat head CT results, admission disposition (operating room, intensive care unit (ICU), non-ICU, and home), mechanical ventilation requirement, blood product administration, hospital and ICU length of stay, ISS, the highest head/neck/face Abbreviated Injury Score (AIS), discharge disposition, mortality, and 30-day readmissions. Trauma service patients were compared to injured, non-trauma service admissions. For patients with a delayed ICH, the authors collected day two GCS, head CT characteristics per the Brain CT Score,[28] and measured brain atrophy.[29] The authors did not collect data on guideline noncompliance or antithrombotic reversal procedures.

Meta-analysis literature search process

The meta-analysis objective was to define the delayed ICH proportion in patients with blunt trauma to the head who had received a pre-injury antithrombotic agent and had an initial head CT without ICH. Manuscripts of any study design were included if adult patients sustained blunt trauma, had received a pre-injury antithrombotic agent, had a documented absence of ICH on the initial head CT, and had a follow-up process to identify the presence of a delayed ICH. Articles reporting on pediatric populations and case reports were excluded, as well as commentaries, and letters to the editor. The authors followed methods for the synthesis of studies without control groups.[30] The following processes were used to identify manuscripts to be included in the current meta-analysis.

Two authors (CMD, EAC) independently performed literature searches in PubMed, Cochrane Library, and Cumulative Index to Nursing and Allied Health (CINAHL) databases. In PubMed and CINAHL, the text search including the following criteria: 1) English language and years 2005–2019; AND 2) "blunt trauma" or "trauma"; AND 3) "delayed intracranial hemorrhage". Using these criteria, six separate searches were then sequentially performed using the additional following text entries: 1) "anticoagulation", 2) "antiplatelet", 3) "warfarin", 4) "clopidogrel", 5) "antithrombotic", and 6) "aspirin". The same process was repeated by replacing "delayed intracranial hemorrhage" with "repeat head CT." In the Cochrane Library a keyword search was performed with the following criteria: 1) English language and years 2005–2019; AND 2) "trauma"; AND 3) "delayed intracranial hemorrhage". The same process was repeated by replacing "delayed intracranial hemorrhage" with "repeat head CT".

The authors retrieved and reviewed the bibliographies of all relevant full-text articles and systematic literature reviews to identify additional relevant articles. All authors reviewed and agreed upon the selected articles and extracted data points. Two authors (GH, CMD) independently assessed the reliability of the relevant studies using the Newcastle-Ottawa Scale.[31] A maximum score of 8 was possible because non-exposed cohorts were not included. One point was subtracted 1) if repeat head CT was not routinely done or 2) cohort GCS was missing or less than 13 or cohort age was missing or less than 65 years. A point was subtracted for GCS and age because those articles are relatively distinct from the others, and slightly reduce their reliability.

Statistical analysis

All data were entered into Microsoft Excel 2016 (Microsoft Corp., Redwood, WA, USA) and imported into SAS System for Windows, release 9.2 (SAS Institute Inc., Cary, NC, USA). For the current study, the mean and standard deviation were used for continuous data. The Fisher's exact test was used to assess intergroup comparisons for categorical data. The two sample *t*-test was used to assess intergroup comparisons for parametric continuous data and the Wilcoxon Rank Sum test was used for ordinal rank data. Significance was established with a $p < .05$ for all comparisons.

The principal use of the meta-analysis technique was to compute a combined study proportion estimate for delayed ICH. A total estimate was computed for all patients included in the review, whether receiving an anticoagulant and/or anti-platelet agent. Sub-analyses were included for ASA, clopidogrel, oral anticoagulants, combination antithrombotic agents (≥2 anti-platelet and/or anti-coagulant drugs without drug sub-categorization and its delayed ICH proportion), and aggregated antithrombotic agents (a group of patients receiving an anti-platelet and/or anticoagulant drug without drug sub-categorization and its delayed ICH proportion). Where possible, additional sub-analyses included a comparison of delayed ICH meta-analysis proportions by routine or discretionary repeat CT. MedCalc Statistical Software version 19 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019) was used to compute the combined studies proportion for delayed ICH. When the inter-study test for heterogeneity was <0.05, the random effects model estimates were used. Otherwise, the fixed effects model estimates were used.

Results

Institutional chart review

The current study included 349 patients who met all criteria. Of the 349 patients, 112 (32.1%) did not have a repeat head CT and 237 (67.9%) had a repeat head CT within 4–6 h. TEG was obtained in 51.9% (181/349), base excess in 52.1% (182/349), and INR in 93.4% (326/349) of the sample. The patients with and without a repeat head CT had similar admission traits (Table 1). Of the 349 patients, only 12 (3.4%) had an ISS of zero. A substantially larger percent of patients without a repeat head CT had no contact with the trauma service. The percent of patients with an admission GCS of 3–12 were <5%.

The ventilator days, ICU stay, hospital stay, death rate, discharge disposition, and 30-day readmission outcomes were similar for the patients with and without a repeat head CT (Table 2). The highest head, neck, or face AIS was greater for the group undergoing a repeat head CT (median 1, Interquartile range (IQR) 2 vs median 0, IQR 1). Of those undergoing a repeat head CT, an ICH was detected on the follow-up scan in 4 of the 237 patients (1.7% [95% confidence interval (CI) = 0.5–4.3%]). There was no significant difference for ICH between those with and without a repeat head CT (Table 2). The ICH CI was 0–3.2% for the group without repeat head CT (0/112) and 0.3–2.9% for the entire group (4/349).

Admission traits and trauma center outcomes for the 4 patients with ICH are described in Table 3. The admission GCS was 15 and remained 15 on hospital-day 2. Repeat CT demonstrated that patient 3 and 4 had no midline shift and the other 2 had a mild shift (4 mm and 5 mm). No repeat CT showed lateral ventricular or cistern compression. The brain CT showed that all 4 patients had central and cortical atrophy. No patient required tracheal intubation and patient 3 was the only one needing admission to the intensive care unit. That patient also sustained a burst fracture of the fifth lumbar vertebra, had a mechanical heart valve, and had a short run of ventricular tachycardia in the ICU. There was no significant hematoma associated with the lumbar fracture despite an increased INR. All patients were discharged to subacute rehabilitation or home.

The delayed ICH rates by antithrombotic categorization are displayed in Supplemental File 1. The mortality by antithrombotic category in patients with and without a repeat head CT are as follows: ASA only, 3.2% (5/158); clopidogrel only, none; warfarin only, 3.5% (3/85); other 3.6% (1/28); combination, none. There were no differences in mortality rates among the various antithrombotic regimens (p = .6099).

Meta-analysis for delayed ICH

The literature search process identified 24 relevant publications

Table 1
Trauma patient admission traits.

Variable	No Repeat CT	Routine Repeat CT	p-value
Number	112 (32.1%)	237 (67.9%)	
Age (years)	72.9 ± 13.2	75.6 ± 13.9	.0887
Male	52 (46.4%)	107 (45.2%)	.8231
Mechanism:			
Fall	84 (75.0%)	180 (76.0%)	.8476
Vehicular	25 (22.3%)	47 (19.8%)	.5927
Other	3 (2.7%)	10 (4.2%)	.4794
Injury Severity Score	7.5 ± 4.9	7.3 ± 5.8	.8210
Admission GCS	14.7 ± .7	14.4 ± 1.4	.0133
Admission GCS:			
3–8	0 (0%)	3 (1.3%)	
9–12	2 (1.8%)	6 (2.5%)	
13–15	110 (98.2%)	228 (96.2%)	.7523
Antithrombotic:			
Aspirin	59 (52.7%)	99 (41.8%)	
Clopidogrel	7 (6.3%)	20 (8.4%)	
Warfarin	23 (20.5%)	62 (26.2%)	
Other	10 (8.9%)	18 (7.6%)	
Combination	13 (11.6%)	38 (16.0%)	.3415
Hemoglobin (g/dL)	12.8 ± 1.8	12.4 ± 1.9	.0625
Platelet Count (E9/L)	218.9 ± 68.3	227.7 ± 76.3	.2993
INR	1.6 ± 1.4	1.8 ± 1.3	.2907
TEG Reaction Time (minutes)	5.4 ± 3.2	4.8 ± 1.8	.1859
TEG Maximum Amplitude (mm)	65.6 ± 5.0	64.9. ± 7.8	.6348
Heart Rate (bpm)	82.2 ± 16.9	82.4 ± 16.7	.9199
Systolic Blood Pressure (mmHg)	151.3 ± 29.8	153.0 ± 29.9	.6301
Base Excess (mmol/L)	−2.5 ± 5.3	−1.4 ± 3.8	.1155
Trauma Service Role:			
Team	5 (4.5%)	20 (8.4%)	.1799
Alert	35 (31.3%)	96 (40.5)	.0960
Consult	36 (32.1%)	98 (41.4%)	.0993
None	36 (32.1%)	23 (9.7%)	<.0001

CT, computed tomography; GCS, Glasgow Coma Scale score; INR, international normalized ratio; TEG, thromboelastography.

Table 2
Trauma patient outcomes.

Variable	No Repeat CT	Routine Repeat CT	p-value
Number	112 (32.1%)	237 (67.9%)	
Admission Disposition:			
Home	10 (8.9%)	25 (10.6%)	
Non-ICU	87 (77.7%)	181 (76.4%)	
ICU	10 (8.9%)	26 (11.0%)	
Operating Room	5 (4.5%)	5 (2.1%)	.5872
Highest HNF AIS	.5 ± .8	.9 ± 1.1	.0002
Highest HNF AIS ≥2	20 (17.9%)	71 (30.0%)	.0186
Delayed ICH	0 (0%)	4 (1.7%)	.3101
Intubation	5 (4.5%)	15 (6.3%)	.6244
Ventilator Days	.3 ± 2.7	.4 ± 2.4	.8486
ICU days	.6 ± 2.9	.9 ± 2.6	.3032
Hospital days	4.8 ± 3.9	5.0 ± 4.8	.6394
Blood products (total units)	.6 ± 1.8	.5 ± 1.3	.4256
Received Any Blood Product	23 (20.5%)	41 (17.3%)	.4628
Discharge Disposition:			
Home	53 (47.3%)	122 (51.5%)	
Acute Rehabilitation	13 (11.6%)	17 (7.2%)	
Subacute Rehabilitation	43 (38.4%)	81 (34.2%)	
Hospice or Death	1 (.9%)	8 (3.4%)	
Long Term Acute Care	2 (1.8%)	7 (3.0%)	
Other	0 (0%)	2 (.8%)	.4222
30 Day Readmission	9 (8.0%)	30 (12.7%)	.2744

CT, computed tomography; ICU, intensive care unit; HNF, head, neck and face; AIS, Abbreviated Injury Scale score; ICH, intracranial hemorrhage.

Table 3
Patients with delayed intracranial hemorrhage on repeat head computed tomography.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Mechanism	Fall	Fall	Vehicular	Fall
Antithrombotic	Clopidogrel only	Clopidogrel only	Warfarin only	Clopidogrel only
Clopidogrel Dose	75 mg daily	75 mg daily	–	75 mg daily
ISS	21	5	26	17
Brain Atrophy:				
LV Width (>30 mm)	34	37	38	39
≥2 Sulci (≥2.5 mm)	3.8 & 4.1	3.6 & 5.7	3.4 & 3.7	3.7 & 4.0
Intubation	No	No	No	No
ICU Days	0	0	9	0
Hospital Days	8	3	16	5
Discharge Disposition	Subacute Rehab	Home	Subacute Rehab	Home
Age (years)	92	90	79	81
Heart Rate (bpm)	100	66	100	82
Systolic BP (mmHg)	118	122	140	182
Base Excess (mmol/L)	2.8	−1.6	−1.3	-.7
TEG R (minutes)	3.4	3.8	6.2	2.8
TEG MA (mm)	72.5	59.8	68.2	73.4
Hemoglobin (g/dL)	11.6	11.5	12.7	13.0
Platelet Count (E9/L)	237	187	185	223
INR	1.0	1.2	3.5	1.0
Blood Products	1	0	4	1

ISS, Injury Severity Score; LV, lateral ventricular; ICU, intensive care unit; BP, blood pressure; TEG, thromboelastography; R, reaction time; MA, maximum amplitude; INR, international normalized ratio.

for inclusion in the meta-analysis (Supplemental File 2). Data characteristics and reliability assessments from the 24 published studies and the current study are shown in Table 4. The reliability scores were fair (score = 6) in 3 studies and good (score = 7 or 8) in 22 studies. Three studies[12,14,21] reported information on the model of CT scanner used, and 21 studies did not report the slices or model of the CT scanner.[1–11,13,15–20,22–24]

The meta-analysis delayed ICH proportions are displayed in Table 5. Comparing the data with and without a routine repeat head CT, the delayed ICH meta-analysis proportions were similar for 1) clopidogrel group; 2) DOAC group; and 3) antiplatelet (ASA and clopidogrel) groups (1.6% [CI = 0.4–3.5%] vs 0.9% [CI = 0.1–4.9%] respectively, p = .4375).The overall delayed ICH proportions were similar between the antiplatelet (ASA or clopidogrel) group (1.4% [15/1093] CI = 0.4–2.9%) and the anticoagulant (VKA or DOAC) group (1.3% [44/3,408] CI = 0.6–2.2%; p = .5322). Using the data with a routine repeat CT, the delayed ICH proportion was similar between the single agent (ASA, clopidogrel, VKA, or DOAC) group (1.7%) and the combination (dual or triple agent) group (2.8%; p = .3687).

The delayed ICH proportion was significantly lower for cohorts with non-routine repeat CT, when compared to those with routine CT, for the groups receiving 1) any antithrombotic; 2) a VKA; 3) any anticoagulant (0.9% [CI = 0.2–2.0%] vs 1.9% [CI = 1.1–3.0%] respectively, p = .0185); and 4) single agent therapy (ASA, clopidogrel, VKA, or a DOAC).

Discussion

Institutional chart review

The overall delayed ICH proportion was 1.7% at the study institution. There were no delayed ICHs diagnosed in patients taking ASA, but three delayed bleeds occurred in the clopidogrel group. One delayed ICH occurred in the warfarin group. All four delayed ICHs were neurologically intact and did not display clinical neurological changes. None required intubation, or surgical intervention. Three of the four patients with delayed ICH received blood products for coagulopathy reversal as a prophylactic intervention to prevent further ICH. For patients 1 and 4, the coagulopathy reversal was prompted by the repeat head CT results. For patient 3, reversal was prompted by supratherapeutic INR and lumbar burst fracture. The three clopidogrel cases did not require ICU admission and all had TEG-MA greater than 55 mm, which suggests the platelets were effective at clot formation. The one patient on warfarin required ICU admission but had high trauma burden with ISS of 26, INR of 3.5, lumbar burst fracture with hematoma, and a mechanical heart valve. Despite this patient's delayed ICH in the setting of polytrauma, he did not deteriorate neurologically.

Besides lower GCS and higher head/neck/face AIS in the routine repeat CT group, the overall patient population was similar. This low delayed ICH proportion (1.7%) suggests that other factors may contribute to delayed ICH. All four of the bleeds had brain atrophy which is commonly seen in the geriatric population and is a risk factor for head bleeding.[29] Our institution's results are in line with the established literature, closely aligned with the delayed ICH proportions of Battle et al.[3] and Peck et al.[16] Patients with and without routine repeat CT had similar traits with the majority sustaining mild traumatic brain injury (GCS 13–15) on admission. These patients had mild injuries collectively with over 75% due to fall mechanism. Over half the patients in each group were on antiplatelet agents followed by warfarin.

The development of delayed ICH on antithrombotics was rare. Statistically, there was no difference in the rate of delayed ICH between those with and without a repeat head CT. The CIs were wide reflecting the small sample size of the institutional study data when individual antithrombotic categories were assessed. However, the CI for the total group is relatively narrow. There were no differences in clinical outcomes despite higher head, neck, and face AIS in the routine repeat head CT group. The delayed ICHs in this cohort were not large, did not require neurosurgical intervention, did not lead to neurologic deterioration or intubation and did not appear to influence mortality. A common theme that emerges in the literature is that delayed ICHs do not usually lead to neurosurgical intervention, and very rarely affect the course of care after diagnosis.[1–8,10,12,16,17]

The study institution's practice management guideline has changed. Routine repeat head CTs in patients with initially negative head CTs are no longer recommended, and now left to physician discretion. Patients are observed for 4–6 h with neurologic checks

Table 4
Delayed intracranial hemorrhage study proportions included in the meta-analysis.

Study	No.	ICH	Antithrombotic	GCS	Age	Routine Repeat CT	Reliability
Afaneh, 2018[1]	273	6	Warfarin	15	74	yes	8
Barmparas, 2018[2]	249	2	DOAC	15	81	no	7
Battle, 2018[3]	110	2	Aggregated	–	–	yes	7
Bauman, 2017[4]	1180	7	Aggregated	15	80	yes	8
Chenoweth, 2018[5]	343	1	Aggregated	–	79	no	6
Hill, 2018[6]	103	3	Aspirin only	15	69	yes	8
Hill, 2018[6]	77	0	Warfarin	15	69	yes	
Hill, 2018[6]	46	0	Clopidogrel	15	69	yes	
Hill, 2018[6]	112	5	Combination	15	69	yes	
Huang, 2019[7]	204	3	Warfarin	15	71	yes	8
Ivascu, 2005[8]	63	0	Warfarin	15	77	no	7
Kaen, 2010[9]	135	0	Aggregated	15	76	yes	8
Mann, 2018[10]	72	0	Warfarin	14	82	yes	8
Mann, 2018[10]	30	1	DOAC	14	82	yes	
Mann, 2018[10]	118	0	Aspirin	14	82	yes	
Mann, 2018[10]	36	0	Clopidogrel	14	82	yes	
Marcia, 2018[11]	55	2	Aggregated	15	80	yes	8
McCammack, 2015[12]	134	1	Aggregated	15	74	yes	8
Menditto, 2012[13]	87	5	Warfarin	15	82	yes	8
Muakkassa, 2012[14]	72	7	Aggregated	12	51	yes	6
Nishijima, 2012[15]	243	0	Clopidogrel	14	75	no	7
Nishijima, 2012[15]	687	4	Warfarin	14	75	no	
Peck, 2011[16]	362	4	Aggregated	15	75	yes	8
Reddy, 2015[17]	194	1	Warfarin	15	83	no	7
Scantling, 2017[18]	228	2	Aggregated	15	81	yes	8
Schoonman, 2014[19]	211	5	VKA	14	77	no	7
Swap, 2016[20]	254	6	Clopidogrel	–	77	no	6
Swap, 2016[20]	178	5	Warfarin	–	77	no	
Tauber, 2009[21]	100	4	Aspirin	15	81	yes	8
Taylor, 2012[22]	49	0	Aspirin only	–	79	yes	7
Taylor, 2012[22]	25	0	Clopidogrel	–	79	yes	
Taylor, 2012[22]	53	1	Warfarin only	–	79	yes	
Taylor, 2012[22]	31	0	Combination	–	79	yes	
Uccella, 2016[23]	69	0	VKA	15	–	yes	7
Verschoof, 2018[24]	899	0	VKA	14	82	no	7
Current study, 2019	99	0	Aspirin	15	72	yes	8
Current study, 2019	20	3	Clopidogrel	15	81	yes	
Current study, 2019	62	1	Warfarin	14	80	yes	
Current study, 2019	18	0	Other	14	73	yes	
Current study, 2019	38	0	Combination	14	76	yes	

Aggregated category, any patient that received any antiplatelet and/or anticoagulant; Combination category, received ≥2 antiplatelet and/or anticoagulant agents; ICH, intracranial hemorrhage; GCS, Glasgow Coma Scale score; CT, computed tomography; DOAC, direct acting oral anticoagulant; –, not reported; VKA, vitamin K antagonist.

every hour. Patients are then re-evaluated by the treating physician and the decision to repeat the head CT is based upon neurological changes such as deterioration or failure to improve. This process could be easily adaptable in other level I trauma centers.

Literature review and meta-analysis

The search identified 24 studies including 35 cohorts for inclusion in the meta-analysis. When the current study was combined with the identified cohorts, over 7,000 patients were assessed. Using the Newcastle-Ottawa Scale,[31] virtually all studies were assessed as good for reliability.

Only 3 of the 24 studies reported the slices or model of CT scanner used. McCammack's group and Muakkassa's group both report using a 64-slice CT scanner.[12–14] Tauber's group reported using a 16-slice scanner.[21] This may help explain why they experienced the highest delayed ICH proportion of the 5 ASA cohorts. The type of CT scanner used in the other studies is not reported. Despite the lack of this information, the delayed ICH proportions among all included studies were relatively similar.

Five of the 24 studies did not report GCS and/or age.[3,5,20,22,23] Eight of the 24 studies used discretionary repeat head CT.[2,5,8,15,17,19,20,24] Muakkassa's study[14] had one of the highest incidences of delayed intracranial bleeds. This could be attributed to several differences. First, they report the lowest age (51 years) and GCS (12) of all included cohorts,[14] Second, their average time to repeat CT was 3 days.[14] Last, the age and GCS differences might be related to the high proportion of patients (79%) involved in a motor vehicle crash, a high-velocity injury, whereas the other 23 studies were mostly related to low-velocity falls. Overall, the study groups were homogenous populations with mainly geriatric patients (age 69 or greater) and mild brain injury (GCS 14–15) making these cohorts appropriate for meta-analysis.

Delayed intracranial hemorrhage meta-analysis proportions

The synthesized overall delayed ICH rate was 1.4% (CI = 0.9%–1.9%) for any antithrombotic. The overall delayed ICH proportions were similar between antiplatelet and anticoagulants. Delayed ICH rates were also similar between single and combination therapy. The narrow CI indicates the 25 studies had similar delayed bleed rates suggesting the overall data is a credible point-estimate. The proportion of delayed bleeds is statistically the same whether a discretionary or routine repeat head CT is ordered for 1) clopidogrel group; 2) DOAC group; and 3) antiplatelet group. This delayed ICH pooled proportion for antiplatelets (ASA and clopidogrel group) is unique because other published meta-analyses assess delayed ICH on anticoagulants.[24–26] The subgroup of DOAC patients is less than

Table 5
Delayed intracranial hemorrhage meta-analysis proportions.

	All Patients	Routine Repeat CT	Non-Routine Repeat CT	p-value
Any Antithrombotic:				
studies	25	17	8	
total	7,319	3,998	3,321	
Delayed ICH % (CI)	1.4 (.9–1.9)	1.7 (1.1–2.4)	.8 (.3–1.6)	
		68/3998	27/3321	.0008
Aspirin:				
studies	–	5	–	
total	–	469	–	
Delayed ICH % (CI)	–	1.3 (.2–3.5)	–	–
Clopidogrel:				
studies	6	4	2	
total	624	127	497	
Delayed ICH % (CI)	1.5 (.1–4.4)	2.4 (.01–8.7)	.9 (.09–4.9)	
		3/127	4/497	.1530
VKA:				
studies	14	8	6	
total	3,129	897	2,232	
Delayed ICH % (CI)	1.3 (.6–2.3)	1.8 (1.1–2.9)	.9 (.2–2.2)	
		16/897	20/2232	.0416
DOAC:				
studies	2	1	1	
total	279	30	249	
Delayed ICH % (CI)	1.3 (.2–3.4)	3.3 (.1–17.2)	.8 (.1–2.9)	
		1/30	2/249	.2901
Combination:				
studies	–	3	–	
total	–	181	–	
Delayed ICH % (CI)	–	2.8 (1.0–6.4%)	–	–
Single agent:				
studies	16	9	7	
total	4,501	1,523	2,978	
Delayed ICH % (CI)	1.3 (.8–2.1)	1.7 (.9–2.7)	.9 (.3–1.9)	
		26/1523	27/2978	.0274

CI, 95% confidence interval; Combination category, received $\geq$ 2 antiplatelet and/or anticoagulant agents; CT, computed tomography; DOAC, direct acting oral anticoagulant; ICH, intracranial hemorrhage; Single agent, aspirin, clopidogrel, VKA, or DOAC (excludes combinations); VKA, vitamin K antagonist.

5% of the total sample. The reported proportion of delayed ICH in DOAC patients may be under-represented. However, the 95% CI for the DOAC group is relatively narrow (0.2–3.4%). The overall delayed ICH proportion is low regardless of antithrombotic type.

The finding of similar delayed ICH proportions among all types of antithrombotics suggests that patients who take these medications do not need a routine repeat head CT. Patients with blunt trauma to the head on these agents can have a discretionary repeat head CT based upon neurologic assessments, since the delayed ICH diagnosis rarely changes the course of clinical care. The results also show that when ASA or clopidogrel use is compared to someone taking a VKA or DOAC, the choice of antithrombotic, or combination does not affect delayed ICH rate. This finding suggests that in practice, patients who take any type of antithrombotic can be clinically treated similarly. Coagulopathy reversal is usually indicated when there is a large ICH that creates cognitive dysfunction. However, coagulopathy reversal may be indicated based upon the patients overall clinical state and injury burden, and this complex clinical decision should be performed according to local trauma service guidelines. The results indicate that other etiologies such as age and brain atrophy[29] may have a greater role in delayed ICH rather than the choice of antithrombotic.

The delayed ICH proportion was significantly lower for patients without a routine repeat head CT, when compared to those with routine CT for any antithrombotics, VKA, anticoagulants in general, and single agent therapy. Numerically, the proportion of delayed ICH in those with routine repeat CT are double the proportion of delayed ICH in those who do not routinely repeat CTs. This finding suggests that institutions who adopt routine repeat head CT protocols will detect more clinically insignificant delayed ICHs compared to institutions who order repeat head CT based on neurologic exam and clinical discretion. The differences in delayed ICH proportions between those with and without routine repeat CT suggest that most delayed ICHs in the routine repeat head CT group are very minor and would not have been diagnosed if discretionary repeat head CT was obtained. While the diagnosis of minor delayed ICH seems to be nonconsequential, it affects hospital resources, in turn, affecting hospital efficiency and cost.

Conclusion

The current retrospective chart review and systematic review is fully inclusive of all antithrombotic types, and study designs currently available in the literature. Moreover, the retrospective chart review compares characteristics and outcomes in patients with and without routine repeat head CT. For patients with blunt trauma to the head receiving an antithrombotic without ICH on initial CT, repeat scans should be discretionary based on neurologic assessments. Routine repeat CT may identify a larger proportion of minor delayed ICH.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjsurg.2019.10.006.

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