American Journal of Emergency Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking different oral anticoagulants☆

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ARTICLE INFO

Article history:
Received 16 July 2018
Received in revised form 29 November 2018
Accepted 3 December 2018
Available online xxxx

Keywords:
Minor head injury
DOACs
NOACs
Anticoagulants

ABSTRACT

The correlation between direct oral anticoagulants (DOACs) or Vitamin K Antagonist (VKAs) intake and the incidence of intracranial complications after minor head injury (MHI) is still object of debate: preliminary observation seems to demonstrate lower incidence in intracranial bleeding complications (ICH) in patients taking DOACs than VKA. METHODS. This prospective and observational study was performed to clarify the incidence of ICH in patients in DOACs compared to VKAs. Between January 2016 and April 2018 we have recorded in our ED patients with MHI taking oral anticoagulants. Their hemorragic risk score was calculated and recorded for each patient (Has Bled, Atria and Orbit). RESULTS A total of 402 patients with MHI taking anticoagulant were collected: 226 were receiving one of the four DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) while 176 patients were in therapy with VKA. The rate of intracranial complications was significantly lower in patients receiving DOACs than in patients treated with VKA ($p < 0.01$). In the VKA group two patients died because of intracranial bleeding. No deaths were recorded in the DOACs group. DISCUSSION patients with MHI who take DOACs have a significant lower incidence of intracranial bleeding complications than those treated with vitamin k antagonists. This statement is supported by the observation that the hemorrhagic risk, measured according to the chosen scores, was similar between the two groups.

1. Introduction

The introduction of Direct Oral Anticoagulants (DOACS) for prevention of thromboembolism atrial fibrillation had a great impact and they have partially replaced vitamin K antagonists (VKAs) because of their favorable characteristics [1]. Spontaneous intracranial hemorrhages are reported less frequently in patients treated with DOACs than in patients receiving VKA, but the correlation between chronic intake of DOACs and the incidence of intracranial complications after a minor head injury is not yet well defined. [2–6] Further, DOACs are linked to a reduction in all major bleeding and clinical relevant bleeding as compared to VKAs [7] and a preliminary paper shows minor intracranial bleeding complications (ICH) in patients taking DOACs than compared to patients taking VKA [1]: in our experience, in the first phase after their introduction, DOACs were prescribed in younger patients, with lower hemorrhagic risk than patients maintained in VKAs treatment, and this could lead to a potential bias in results [1]. We decided to perform this study collecting cases of patients affected by MHI and receiving the two different kind of oral anticoagulants with the aim of evaluating their bleeding risk assessed at the time of observation, according to some of the most commonly used scores. These data, supplemented by some demographic characteristics of the patients, allow a more reliable comparison between the two populations studied.

2. Methods

We perform an observational study in our Emergency Department (Ospedale San Paolo, Savona). The collection of the case series of patients with minor head trauma and taking oral anticoagulant therapies observed in our emergency department was started in January 2016 and continued until April 2018. As in our preliminary study [1] patients with mechanical heart valve replacement and those taking antiplatelet therapies together anticoagulants were not included in the study and MHI was defined according to Italian Guidelines on Head Trauma [1] as a GCS 14–15 score after a head injury, with no neurological defects during the emergency physician evaluation and without signs of skull fractures. Patients taking DOACs were divided from those treated with VKA. On the basis of their history and laboratory data the hemorrhagic risk score was calculated and recorded for each patient.

☆ This study was authorized by the medical direction of our hospital and patients were informed and signed their consent to their data collection.

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https://doi.org/10.1016/j.ajem.2018.12.003
0735-6757/

HEMORRHAGIC RISK SCORE: We have decided to use 3 different hemorrhagic risk scores, chosen from the most used and cited in the literature. They are the Has Bled score and the Atria bleeding risk score which are usually considered in the evaluation of the bleeding risk of patients affected by atrial fibrillation receiving anticoagulant therapy [7,8]. The third is the most recent Orbit bleeding score that according to some authors, has better ability to predict major bleeding in AF patient when compared with the previous two [9]: we calculated retrospectively the ORBIT score for 35 patients, because they were recorded prior before we decided to evaluate this score. We also recorded the clinical and demographic characteristics of the two patient groups with particular regard to the reason for the use of the anticoagulant therapy, the number of intracranial complications highlighted by the CT scan and the outcome of patients up to a month after the trauma using telephone calls and a computer search of any additional hospital admissions. Further details of patient management are reported in our previous study [1]. This study was authorized by the medical direction of our hospital and patients were informed and signed their consent to their data collection.

2.1. Statistical analysis

The Chi-Square test (χ^2) was used to analyze the categorical data. p values <0.01 were considered statistically significant.

3. Results

A total of 402 patients with MHI taking anticoagulant therapy were recorded from January 2016 to the end of April 2018. Two hundred and twenty-six patients were receiving one of the four DOACs (dabigatran, rivaroxaban, apixaban or edoxaban) while 176 patients were in therapy with VKA. Table 1 shows some demographic and clinical characteristics of the two groups of patients. Most of them were affected by atrial fibrillation. The finding of intracranial bleeding involved 18 patients in the VKA group (10.2%) and 6 patients receiving DOACs (2.6%). The rate of intracranial complications was significantly lower in patients receiving DOACs than in patients treated with VKA ($p < 0.01$). 5 of the 18 patients had a value of INR > 3 at the admission, while only 2 of the 6 of the DOAC group took the full dose of anticoagulant. Indeed, it is important to note that approximately 40% of patients in the second group took anticoagulants at the lowest effective doses (dabigatran 110 mg twice daily, apixaban 2.5 mg twice daily, rivaroxaban 15 mg daily and edoxaban 30 mg daily). In the VKA group two patients died because of intracranial bleeding. Their INR value was in the therapeutic range at the admission. Another patient was successfully submitted to neurosurgical intervention. The bleeding complications in the VKA group were treated with vitamin K and prothrombin complex according to conventional protocols while only 1 patient in therapy with dabigatran received the infusion of the antidote (idarucizumab).

Table 2
Bleeding risk of the two groups of patients.

Bleeding risk score	VKA	DOACs	P value
	176 pts	226 pts	
Has Bled High (≥3)	49 (28%)	60 (26.2%)	P = 0.82 (χ^2 0.08)
Atria			
High (score > 4)	45 (25.7%)	55 (24.4%)	P = 0.82 (χ^2 0.05)
Medium (4)	5 (2.8%)	14 (6.2%)	P = 0.16 (χ^2 2.46)
Low (<4)	126 (71.4%)	157 (69.3%)	P = 0.66 (χ^2 0.08)
Orbit			
High (score ≥ 4)	15 (8.6%)	20 (8.8%)	P = 1 (χ^2 0.01)
Medium (3)	45 (25.7%)	54 (24%)	P = 0.73 (χ^2 0.15)
Low (0–2)	116 (65.7%)	152 (67.1%)	P = 0.83 (χ^2 0.00036)

The analysis of the hemorrhagic risk of the two groups of anticoagulated patients is shown in Table 2. We found no statistically significant differences in the measurement of hemorrhagic risk levels predicted by the scores used.

4. Discussion

Our data show that patients with MHI who take DOACs have a significant lower incidence of intracranial bleeding complications than those treated with vitamin K antagonists: the current study collects a series about twice in size than the previous one and confirms our preliminary results. As the number of cases increases, this difference seems more and more marked. On the contrary, the age differences between the two groups are less evident than in previous report. This reflects the fact that the prescription of DOACs is increasing and these drugs are progressively replacing vitamin K antagonists in many cases. In fact, we are recording more patients with MHI in therapy with DOACs than in previous years and in our case series their number has exceeded patients in therapy with warfarin or other vitamin K antagonists. Certainly many patients taking vit K antagonists have now been switched to DOAC therapy, and this explains in part the smaller age difference between the two groups. This supports the superior safety of DOACs and a response to a limit of our previous study.

Also the hemorrhagic risk, measured according to the chosen scores, was similar between the two groups. Despite the fact that there are different opinions in the literature on the reliability of these scores, especially when DOACs are used [10], we decided to measure at least three of them to increase the level of certainty of our observation. One limitation of this study is contained in the scores themselves, mainly because the risk stratification schemes have developed in patients taking VKAs and one can only hypothesize they could be applied to DOACs. Moreover, ORBIT and HASBLED provide scores for the concomitant presence of antiplatelet therapy, but we have excluded those patients from the study. We probably excluded a small number of patients with a higher risk of bleeding, however this did not determine differences between the two groups. Another point concerns the HASBLED score, which foresees the liability of the INR value among the bleeding risk factors. This

Table 1
Demographic and clinical characteristic of patients.

	VKA	DOACs	P values
Number of patients	176	226	
Males	80 (mean age 81.7)	111 (mean age 80.3)	
	Range 53–95	Range 56–91	
Females	95 (mean age 84.4)	114 (mean age 82.7)	
	Range 64–97	Range 65–96	
Atrial fibrillation	167	216	
Thromboembolism	9	10	
Intracranial complications (ICH)	18 (8 Male 10 Female)	6 (5Male 1 Female)	P < 0.01 (χ^2 10.10)
Neurosurgery	1	0	P = 0.44 (χ^2 1.28)
Death	2	0	P = 0.19 (χ^2 1.28)
Admission after 1 month for ICH	0	0	

Please cite this article as: M.B. Spinola, A. Riccardi, P. Minuto, et al., Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking diff..., American Journal of Emergency Medicine, https://doi.org/10.1016/j.ajem.2018.12.003

aspect of the score is applicable only to patients treated with vit K antagonists and this may explain the slight difference between the two groups recorded by measuring the HAS Bled. Despite these limitations we believe that the fact of not having detected significant differences in bleeding risk between the two groups represents strong data to support the greater safety profile of DOACs.

In the group of patients taking DOACs there is a high percentage taking the drug at a reduced dose due to impaired kidney function and very old age. They were about the 40% of the total number. In these patients the prevention of thromboembolic events is not affected by the reduced dose [11-16] but probably it contributes to a lower incidence of intracranial bleeding although four cases of the six with intracranial complications were taking dabigatran, rivaroxaban or apixaban at reduced dose. The observation of greater safety of DOACs in relation to the incidence of both spontaneous [17,18] and post-traumatic brain hemorrhagic complications is very important because cerebral hemorrhage must be considered a major bleeding [19,20] even in non-anticoagulated patients. The intracranial hemorrhage in anticoagulated patients has usually a more devastating impact than other events, up to 50% mortality rate (i.e., the overall mortality rate for extracranial hemorrhages is 5.1%) [10]. Thus, the lower incidence of intracranial complications in the DOACs group can improve patients' safety and reduce mortality correlated to anticoagulation therapy.

The risk of severe disability or death due to hemorrhagic complications of anticoagulants is always possible especially when these drugs are prescribed to such elderly populations as in our case series. In the elderly population with atrial fibrillation, the benefits of oral anticoagulants of vitamin K antagonists (VKA), in terms of protection from thromboembolic events, are definitely superior to the bleeding risk associated with the same therapy. However VKA therapy is largely underutilized in elderly patients due to the increased perception of bleeding risk. In particular, the reported percentages of non-use of anticoagulant therapy in elderly patients with atrial fibrillation are high, ranging from 25% to 65% [21]. The most frequent reasons for this under-utilization include the risk of falling, a poor prognosis, a history of bleeding, refusal of the patient or family members, the presence of frailty, multiple pathologies or dementia, poor compliance with therapy or difficulty in managing INR. The most relevant aspect of our study is perhaps the observation that the group of patients with MHI treated with DOACs had an incidence of intracranial complications comparable to that found in a similar not-anticoagulated and at low-risk patient population analyzed in an our previous report [22].

The prognosis of post traumatic intracranial hemorrhages is still controversials [23,24]. Our paper observes a reduction on number of post traumatic intracranial hemorrhages but their number is too little to give a definitive information about outcome.

Therefore our results can be of support in the therapeutic choices of the physicians who treat these frail patients allowing a greater percentage of patients to be treated with anticoagulant therapy.

Declaration of interest

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work.

Submission declaration

All authors declare that our paper is not published or under consideration for publishing elsewhere.

Journal policies

All authors reviewed in details the journal policies.

References

[1] Riccardi A, Spinola B, Minuto P, Ghinatti M, Guiddo G, Malerba M, et al. Intracranial complications after minor head injury (MHI) in patients taking vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs). Am J Emerg Med 2017;35(9):1317–9. https://doi.org/10.1016/j.ajem.2017.03.072.

[2] Connoly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigratan versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

[3] Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in non valvular atrial fibrillation. N Engl J Med 2011;365:883–91.

[4] Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

[5] Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

[6] Sterne JA, Bodalia PN, Bryden PA, Davies PA, López-López JA, Okoli GN, et al. Oral anticoagulants for primary prevention, treatment and secondary prevention of venous thromboembolic disease, and for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis and cost-effectiveness analysis. Health Technol Assess 2017;21(9):1–386. https://doi.org/10.3310/hta21090.

[7] Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly, drugs/alcohol concomitantly) score. J Am Coll Cardiol 2011;57(2):173–80. https://doi.org/10.1016/j.jacc.2010.09.024.

[8] Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N. Singer DE. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) study. J Am Coll Cardiol 2011;58(4):395–401. https://doi.org/10.1016/j.jacc.2011.03.031.

[9] O'Brien EC, Simon DN, Thomas LE, Hylek EM, Gersh BJ, Ansell JE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. Eur Heart J 2015;36(46):3258–64. https://doi.org/10.1093/eurheartj/ehv476 [Epub 2015 Sep 29].

[10] Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. J Thromb Thrombolysis 2013;35(3):312–9. https://doi.org/10.1007/s11239-013-0899-7.

[11] Avezum A, Lopes RD, Schulte PJ, Lanas F, Gersh BJ, Hanna M, et al. Apixaban in comparison with warfarin in patients with atrial fibrillation and Valvular heart disease: findings from the Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial. Circulation 2015 Aug 25;132(8):624–32. https://doi.org/10.1161/CIRCULATIONAHA.114.014807.

[12] Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the effective aNticoaGulation with factor xA next GEneration in atrial fibrillation-thrombolysis in myocardial infarction study 48 (ENGAGE AF-TIMI 48). Am Heart J 2010;160:635–41.

[13] Ezekowitz MD, Nagarakanti R, Noack H, Brueckmann M, Litherland C, Jacobs M, et al. Comparison of dabigatran and warfarin in patients with atrial fibrillation and Valvular heart disease: the RE-LY trial (randomized evaluation of long-term anticoagulant therapy). Circulation 2016;134(8):589–98. https://doi.org/10.1161/CIRCULATIONAHA.115.020950.

[14] Bansilal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR, et al. Steering Committee and Investigators. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the rivaroxaban once-daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation (ROCKET AF trial). Am Heart J 2015;170(4):675–682.e8. https://doi.org/10.1016/j.ahj.2015.07.006.

[15] Li XS, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost 2017;117(6):1072–82. https://doi.org/10.1160/TH17-01-0068.

[16] Umei M, Kishi M, Sato T, Shindo A, Toyoda M, Yokoyama M, et al. Indications for suboptimal low-dose direct oral anticoagulants for non-valvular atrial fibrillation patients. J Arrhythm 2017;33(5):475–82. https://doi.org/10.1016/j.joa.2017.05.008.

[17] Inohara T, Xian Y, Liang L, Matsouaka RA, Saver JL, Smith EE, et al. Association of Intracerebral Hemorrhage among Patients Taking non-Vitamin K Antagonist vs vitamin K antagonist Oral anticoagulants with in-hospital mortality. JAMA 2018;319(5):463–73. https://doi.org/10.1001/jama.2017.21917.

[18] Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, et al. Effectiveness and safety of non-vitamin K antagonist Oral anticoagulants for atrial fibrillation and venous thromboembolism: a systematic review and meta-analyses. Clin Ther 2017;39(7):1456–1478.e36. https://doi.org/10.1016/j.clinthera.2017.05.358.

[19] Schulman S, Kearon C. Subcommittee on control of anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3(4):692–4.

[20] Schulman S, Beyth RJ, Kearon C, Levine MN. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133(6 Suppl):257S–98S. https://doi.org/10.1378/chest.08-0674.

[21] Xian Y, O'Brien EC, Liang L, Xu H, Schwamm LH, Fonarow GC, et al. Association of preceding antithrombotic treatment with acute ischemic stroke severity and in-

Please cite this article as: M.B. Spinola, A. Riccardi, P. Minuto, et al., Hemorrhagic risk and intracranial complications in patients with minor head injury (MHI) taking diff..., American Journal of Emergency Medicine, https://doi.org/10.1016/j.ajem.2018.12.003

hospital outcomes among patients with atrial fibrillation. JAMA 2017 Mar 14;317 (10):1057–67. https://doi.org/10.1001/jama.2017.1371.
[22] Riccardi A, Frumento F, Guiddo G, Spinola MB, Corti L, Minuto P, et al. Minor head injury in the elderly at very low risk: a retrospective study of 6 years in an emergency department (ED). Am J Emerg Med 2013;31(1):37–41. https://doi.org/10.1016/j.ajem.2012.05.023.
[23] M1 Zeeshan, Jehan F, O'Keeffe T, Khan M, Zakaria ER, Hamidi M, et al. The novel oral anticoagulants (NOACs) have worse outcomes compared to warfarin in patients with intracranial hemorrhage after TBI. J Trauma Acute Care Surg 2018. https://doi.org/10.1097/TA.0000000000001995.
[24] Prexl O, Bruckbauer M, Voelckel W, Grottke O, Ponschab M, Maegele M, et al. The impact of direct oral anticoagulants in traumatic brain injury patients greater than 60-years-old. Scand J Trauma Resusc Emerg Med 2018;26(1):20. https://doi.org/10.1186/s13049-018-0487-0.

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