International Journal of Research in Medical Sciences
Potdar NV et al. Int J Res Med Sci. 2017 Jul;5(7):2947-2951
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20172538

Original Research Article

Effect of antiplatelet/anticoagulant agents in elderly patients of chronic subdural hematoma: a case control study from a tertiary care centre

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Received: 12 May 2017
Accepted: 23 May 2017

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ABSTRACT

Background: Bleedings are well known risks of both antiplatelet and anticoagulant therapy and both therapies have historically been considered as risk factors for CSDH. The aim of the study was to evaluate the association between exposure to anticoagulant/antiplatelet therapy and chronic subdural haematoma (CSDH).
Methods: Single institution case-control study was conducted in patients older than 60 years who visited our academic tertiary care Emergency Department from January 2012 to December 2016. Patients with CSDH were identified by review of case and controls were selected with a 1:3 ratio for gender, age (60 years), year of admission and recent trauma.
Results: There were 124 cases and 372 controls included in the study. Both anticoagulant and antiplatelet agents were associated with an increased risk of CSDH with an OR of 1.22 (CI 95% 0.66-1.54) and 1.12 (CI 95% 0.68-1.54), respectively. While OR was 1.11 (CI 95% 0.54-2.32), 1.21 (CI 95% 0.61-2.45), and 0.53 (CI 95% 0.33-0.78) for patients receiving oral anticoagulants, ADP-antagonists, and Cox-inhibitors, respectively. History of recent trauma was an effective modifier of the association between anticoagulants and CSDH. OR of 1.69 (CI 95% 0.99-2.96) was found for patients with history of trauma and OR of 4.27 (CI 95% 2.23-8.32) for patients without history of trauma.
Conclusions: Anticoagulant and antiplatelet therapy have a significant association with an increased risk of CSDH. This association appears even stronger in those patients under anticoagulant therapy, who develop a CSDH in the absence of a recent trauma.

Keywords: Anticoagulant, ADP-antagonists, Antiplatelet agents, Chronic subdural haematoma, Trauma

INTRODUCTION

Chronic subdural hematoma (CSDH) is one of the most frequent neurosurgical entities caused by head trauma. Since CSDH affects mainly elderly patients and the population continues to age, it has become a common neurosurgical disease seen by both general and specialized health-care practitioners. Incidence is about 5 per 100000 per year in the general population. Because the proportion of people aged 65 years and older is expected to double worldwide between 2000 and 2030, a large rise in incidence is expected. Despite the benign nature of CSDH reaccumulation of hematoma is still a matter of concern, and disease progression can be fatal without timely surgical intervention. Nevertheless, the early diagnosis and proper treatment result in complete recovery in most cases.[1-6]

In the last decade, there has been an increasing use of antiplatelet and anticoagulation therapy among adult patients, especially in the elderly.[3] Bleedings are well known risks of both antiplatelet and anticoagulant therapy and both therapies have historically been considered as risk factors for CSDH. However, there is a

lack of epidemiologic studies analysing the relationship between antiplatelet/anticoagulant therapy and the development of a CSDH. Therefore, the aim of this case-control study was to determine whether patients with antiplatelet/anticoagulant therapy were more likely to develop a CSDH than patients without antiplatelet/anticoagulant therapy.

METHODS

The hospital ethical Committee approved the present study. Written consent was given by the patients for their information to be stored in the hospital database and used for study.

A case control study was carried during a period between January 2012 and December 2016 among the patients older than 60 yrs who affected by CSDH. Medical records and imaging findings were reviewed and only patients with chronic subdural hematoma were included in the study. Controls were selected among patients older than 60 yrs of age who visited the Emergency Department during the same years with a 3:1 ratio with respect to cases. Case and controls were matched for gender, age (65 years), year of admission and history of previous recent trauma (i.e. up to two months before hospital admission). Patients with no imaging findings were excluded from the study. The study was approved by Institutional Ethics Committee. Written consent was taken from the patients for their information to be stored in the hospital database and used for study.

Statistical analysis

A descriptive statistical analysis was carried out by using SPSS software (v16, IBM, NY, USA), ± standard deviation (SD) were used for qualitative and quantitative variables respectively. A multivariable logistic model was built in order to evaluate the association between exposure to anticoagulant, antiplatelet and anticoagulant/antiplatelet therapy and CSDH; the analysis was adjusted by age, gender and previous trauma. Results have been reported as Odds Ratios (OR) and 95% Confidence Intervals (95% CI). In order to investigate the potential for effect modification, an interaction term was included in the model with respect to trauma and anticoagulant/antiplatelet therapy.

RESULTS

Total 124 cases of CSDH patients with anticoagulant/antiplatelet therapy and 374 CSDH controls without anticoagulant/antiplatelet therapy were included in the study. The mean age of the sample was 77 years (SD: 8.3) and the majority (427; 71. %) was represented by males. Among the 498 total patients, 271 (68%) were taking an antiplatelet therapy while 49 (12%) were under an anticoagulant one. Among the 271 patients assuming antiplatelet therapy, 210 (77%) were taking COX inhibitors, 42 (15%) ADP antagonists and 19 (8%) were under dual antiplatelet therapy, for 5 (1.6%) patients, the information was missing. Among the 49 patients taking anticoagulants, 41 (83.3%) were under oral anticoagulant therapy (OAT), 8 (16.7%) under heparin. Study population characteristics stratified by the status are shown in Table 1.

Table 1: Demographic data of subjects.

Demographic data		Cases (n=124)	controls (n= 375)
Age*		74.2	74.2
Gender	Female	37 (29%)	112 (29%)
	Male	87 (71%)	263 (71%)
Recent history of trauma	No	34 (27.4%)	103 (27%)
	Yes	90 (72.6%)	272 (73%)
Anticoagulant therapy	No	111 (88.7)	340 (90.6%)
	OAT	11 (8.8%)	30 (8.1%)
	Heparin	3 (2%)	5 (1.3%)
Antiplatelet therapy	No	56 (48%)	172 (45%)
	Cox inhibitor	51 (41%)	159 (43%)
	Adp antagonist	12 (9.6%)	30 (8%)

Mean(sd), OAT; oral anticoagulant.

After dichotomizing the variables antiplatelet therapy and anticoagulant therapy, the assumption of either anticoagulant or antiplatelet therapy was shown to be associated with an increased risk of CSDH (Tables 2 and 3).

Table 2: Result from regression model.

	Cases	Control	OR (95%)
Antiplatelet therapy			1.12 (0.6-1.54)
Yes	68	203	
No	56	172	
Anticoagulant therapy			1.22 (0.63-2.36)
Yes	14	35	
No	111	340	

Adjusted for age, gender and previous trauma.

Table 3: Result from regression model.

	Cases	Controls	OR (95%)
No therapy	54	745	1
Anti-platelet	68	203	0.87 (0.5-1.23)
Anti-coagulant	14	35	1.23 (0.64-2.34)
Anti-platelet/ anti-coagulant	5	11	1.42 (0.48-4.2)

Adjusted for age, gender and previous trauma.

Sixteen patients were taking both anticoagulant and antiplatelet therapy: their risk was shown higher excluding patients who were under unknown anticoagulant/antiplatelet therapy (n=5 controls), we observed that the risk for CSDH development was

significantly increased for patients receiving heparin (OR 1.83; 95% CI 0.43-7.79%) or ADP antagonists (OR 1.21; 95% CI 0.6-2.45) (Table 4). Patients receiving Cox inhibitors had an increased -but not significant- risk of developing a CSDH (OR 0.5; CI 95% 0.33-0.78). The risk for CSDH was shown to be slightly but not significantly increased also for patients under dual antiplatelet therapy in comparison to patients assuming only one drug (OR 1.42; 95% CI 0.49-4.2). Finally, history of recent trauma seemed to play a role as potential effect modifier of the association between anticoagulant therapy and subdural hematoma, results stratified by trauma are shown in Table 5.

Table 4: Effect of drug classes.

		Cases	Controls	OR (95%)
Anti-platelet therapy	No therapy	56	172	1
	Cox inhibitor	51	159	0.5 (0.33-0.78)
	ADP antagonist	12	30	1.21 (0.6-2.45)
	Dual antiplatelet	5	14	1.08 (0.38-3.07)
Anti-coagulant therapy	No therapy	112	340	1
	OAT	11	30	1.11 (0.51-2.3)
	Heparin	3	5	1.83 (0.43-7.79)

Adjusted for age, gender and previous trauma, OAT; oral anticoagulant.

Table 5: History of recent trauma.

	History of recent trauma	No history recent trauma
	OR (95%)	OR (95%)
Anti-platelet therapy	2.56 (1.63-4.01)	1.16 (0.59-2.2)
Anti-coagulant therapy	1.69 (0.99-2.96)	4.27 (2.23-8.32)
Anti-platelet/ anti-coagulant therapy	3.51 (0.66-16.47)	3.67 (0.58-26.65)

DISCUSSION

Antiplatelet and anticoagulant therapy have traditionally been cited among the risk factors for the development of CSDH.[7-10] However, this statement is mainly based on individual case-series. Among the 124 cases, 68 patients (54%) were taking antiplatelet drugs and 14 patients (11.2%) were under anticoagulant therapy. In the control population, the percentage of patients taking antiplatelet and anticoagulant therapy was 54% and 9%, respectively.

In both populations, COX inhibitors and Vitamin K antagonists (Oral Anticoagulant Therapy) were the most frequently used drugs. In a recent systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials, Mc Quaid and Laine provided evidence that low-dose aspirin was associated with an increased risk of intracranial haemorrhage (without specifying which type of intracranial haemorrhage) and major bleedings.[11] A well described case-control study, instead, showed that the incidence of anticoagulant associated intracerebral haemorrhage in the US population quintupled during the 90s and the majority of that change was explained by increasing warfarin use.[12]

Our results confirm that anticoagulant and antiplatelet/ anticoagulant therapy have a significant association with an increased risk of CSDH, with an OR of 1.23 (95% CI 0.68-2.34) and 1.42 (95% CI 0.48-4.2), respectively. The more significantly associated drug classes were heparin with an OR of 1.83(0.43-7.79), and ADP antagonists among anti-platelets, OR (95% CI) 1.21 (0.6-2.45). Dual antiplatelet therapy showed a slight but not significant increased risk of CSDH, OR (95% CI) 1.08 (0.40-3.23). These data can be explained by the relatively low number of patients under dual antiplatelet therapy.

A history of trauma (usually a mild trauma which occurred between 2 weeks and 2 months before the symptoms onset) was referred by 90 out of 124 patients (72.5%) with CSDH. Among these patients, 59 (65%) were on antiplatelet therapy and 11 (8%) were on anticoagulant therapy. Among the remaining 34 CSDH patients with no referred history of recent trauma, 68 (50.75%) were taking anti-platelets and 14 (9%) were on anticoagulant therapy. Stratifying the analysis by trauma, both therapies showed an association with CSDH in the two categories: trauma and no trauma patients (Table 4).

However, a history of previous trauma seemed to play a role as potential effect modifier of the association between anticoagulant therapy and subdural hematoma. Interestingly, the association seemed to be stronger for patients with no history of recent trauma.

Obviously, present study has a number of limitations. The control population was selected among patients visited for other pathologies at our Emergency Department, assuming that the diffusion of the use of the analysed drugs was representative of that of the general population of the same age. Notwithstanding confounding a constraint in explanatory observational studies, may be possible, it should be observed that few factors are known to increase the risk for a chronic subdural hematoma. Major risk factors for bleeding in chronic subdural hematoma, which is the study outcome, are represented by age and trauma, that have been taken into account in matching process. Among other risk factors, alcohol, epilepsy, coagulopathies and CSF shunts may be listed.[13] All these factors were very uncommon in our cases; indeed, they were not considered in the analysis.

Since the accuracy of a positive history of recent and often minor trauma depends from the patient's collaboration and cognitive state or from patient/relative's knowledge of the previous history, the event might have been underestimated. Another possible limitation could be that the use of the investigated drugs might have been omitted in the medical records of those patients who referred to A and E for other reasons.

However, the Emergency Department electronic records include a detailed description of home therapy: data about drugs intake, as well as family and medical history, were collected by a dedicated physician at the Emergency Department through a standardized form. For this reason, even though misclassification was present, it would be non-differential with respect to cases and controls. We did not take into account the length of the chronic medical treatment. Moreover, we did not compare the drug dosage nor the INR values at presentation in the case of anticoagulants.

However, drug dosage in the case of aspirin (within the recommended therapeutic range of 75-325 mg/daily) has been demonstrated not to influence the complication rate.[14] Moreover, INR values at presentation could not reflect the INR values in the weeks before the admission (when traumatic event was supposed to happen).

CONCLUSION

Significant association with an increased risk of CSDH found in this case-control study confirms that both anticoagulant and antiplatelet therapy have a significant association with an increased risk of CSDH. This association appears even stronger in those patients who develop a CSDH in the absence of a recent trauma. Since the exposure to antiplatelet and anticoagulant drugs increases the risk of developing a CSDH, as well as the risk of reoperation and of a lower quality of life after surgery, the indication to these therapies should strictly follow the current evidences in order to avoid a dangerous undue risk-benefit imbalance.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Ajith TA, Professor, Department of Biochemistry, Amala Institute of Medical Sciences, Thrissur, Kerala, India, during the preparation of this manuscript.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Potdar NV, Kumar SS, Kaplinghat B. Effect of antiplatelet/anticoagulant agents in elderly patients of chronic subdural hematoma: a case control study from a tertiary care centre. Int J Res Med Sci 2017;5:2947-51.