

Oral Anticoagulants can Improve Functional Outcomes for Survivors of Spontaneous Intracerebral Hemorrhage

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BACKGROUND: Intracerebral hemorrhage (ICH) accounts for 10-15% of strokes worldwide. Anticoagulation has been believed to induce ICH for a long time; however, oral anticoagulants can have some beneficial impact, especially on the patient's outcome.

OBJECT: This study demonstrates how the history of oral anticoagulant administration can affect the outcome of patients surviving spontaneous intracerebral hemorrhage.

METHODS: A retrospective analysis of prospectively collected data of 93 patients were included in the study.

All patients underwent thorough neurological examination and the size of the hematoma was calculated in cm³. Patients' outcome was estimated using Extended Glasgow Outcome Score (EGOS) one day after surgery, and 4 months later. Statistical analysis was performed using the Wilcoxon signed ranks test for numeric data, and the Chi-squared test for categorical data, a Cox regression model was used to calculate the degree of correlation.

RESULTS: Among the 93 cases, 37 were females and 56 were males, age ranged from 18-90 years (mean= 58,26 ± 9.62),. Fifty-one patients received anti-coagulation, while 42 did not receive anti-coagulation prior to the onset of the condition. The average size of the hematomas was 42.94 ml (± 8.63), and while larger sizes, being recorded with the use of anticoagulation (Mean = 43.75 ± 7.99) than without anti-coagulation (mean= 41.98 ± 9.36) (p value < 0.001 95% conf interval [1.499966 6.000077] . Analysis showed that there was positive correlation between the intake of the anti-coagulation prior to the onset of the symptoms and the overall outcome improvement at the end of the follow-up period. (p value< 0.0001).

CONCLUSION: Outcome of survivors of hematoma evacuation in patients who were on oral anticoagulants was better. Further studies are required to improve the clinical practice.

KEYWORDS: Anticoagulants, functional outcome, intracerebral hemorrhage.

INTRODUCTION

Intracerebral hemorrhage accounts for 10-15% of strokes worldwide, and 2 million ICH are registered annually¹. ICH achieves its disastrous impact not only by exerting a mass effect, but also by generating pathophysiological changes in brain tissue by destroying blood brain barriers, edema, and damage to glial and neuronal tissues.² Anticoagulation has been believed to induce ICH for a long time, and the incidence in individuals receiving oral anticoagulant is as double as in those who do not,^{3,4} however, oral anticoagulants can have some beneficial impact, especially on the patient's outcome.⁵

This study demonstrates how the history of oral anticoagulant administration can affect the outcome of patients who survive spontaneous intracerebral hemorrhage.

METHODS

Between 2016 and 2020, cases of ICH underwent surgery in our university's neurosurgery department, were reported. History was meticulously taken, and a complete preoperative neurological examination was performed. Cases with a history of previous anticoagulation therapy were identified, and all patients receiving oral antiplatelet therapy were excluded to avoid statistical and clinical confrontation. A total of 93 patients were finally included in the study. (Table 1).

All patients were reversed using vitamin K injection (10 mg), and transfusion of Fresh Frozen Plasma (FFP) (20 ml/ Kg Body weight).

All cases underwent a thorough neurological examination before and after surgery, a brain CT without contrast was performed preoperatively, immediately after, 24 hours and 3 days after surgery. Size of the hematoma was calculated in cm³ in all images using the ellipsoid equation (Fig. 1), and the decision of surgery was based on the ICH score of patient⁶ (Table 2), and the patient's outcome was

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estimated using the Extended Glasgow Outcome Scale (EGOS) one day after surgery, and 4 months later, and the collected data were compared to the preoperative data.

All cases resumed anticoagulation therapy 5 days post operatively.

Statistical analysis was performed using R[®],⁷ degrees of significance were calculated using the Wilcoxon signed ranks test for numeric data, and the Chi squared test for categorical data, a Cox regression model was used to calculate the degree of correlation.

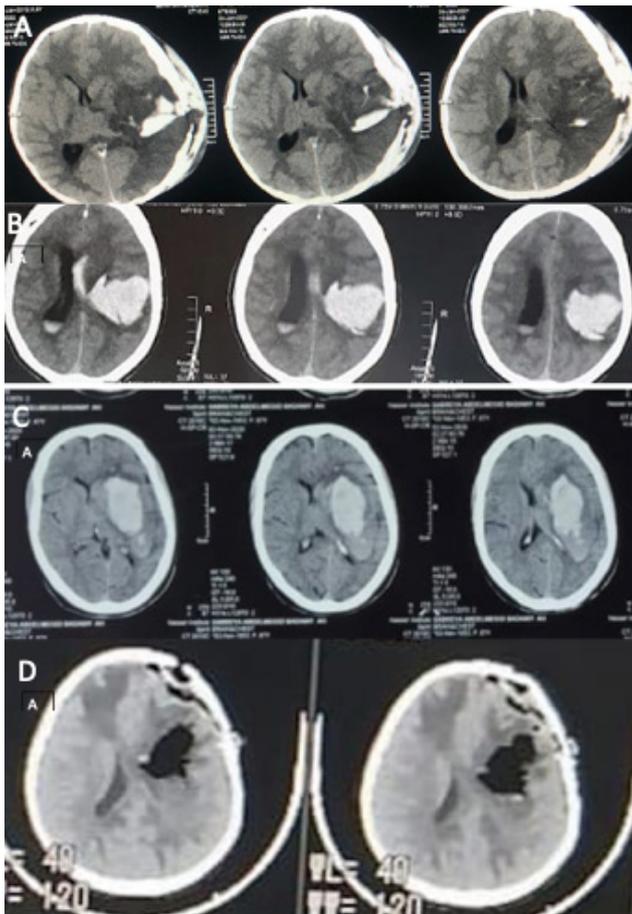


Fig 1: A postoperative (A) and preoperative (B) non-contrast CT brain of a 43-year-old female who did not receive anticoagulation and a preoperative (C) and postoperative (D) non-contrast CT brain of a 55-year-old male who received anticoagulation.

RESULTS

Among the 93 cases included, 37 were females and 56 were males, age ranged from 18-90 years (Mean = 58,26 ± 9.62), males were generally older (Mean= 58.98 ± 7.94) than females (Mean= 57.16 ± 11.75) (p <0.001),. Fifty-one

patients received anti-coagulation, while 42 did not receive anti-coagulation prior to the onset of the condition,. The average size of the hematomas was 42.94 ml (± 8.63), with slightly more sizes being demonstrated at older ages (correlation coefficient, Cor= 0.15 (95% conf. int. [-0.057 - 0.340]) (**Fig. 2**), having larger sizes, being recorded with the use of anticoagulation (Mean = 43.75 ±7.99) than without anti-coagulation (Mean= 41.98 ± 9.36) (p <0.001 95% confidence interval [1.499966 - 6.000077]) (**Fig. 3**). The outcome was scored one day after surgery and 4 months later using the Extended Glasgow Outcome Score (EGOS). Most of the patients showed minimal improvement on the day after surgery (**Fig. 4**), and much more improvement on the 4 months follow-up period, with statistically significant improvement in the EGOS (p < 0.0001, 95% conf interval = [2.4999-6.9999]). Analysis showed that there was positive correlation between the intake of the anti-coagulation prior to the onset of the symptoms and the overall outcome improvement at the end of the follow-up period. (p value< 0.0001) (**Fig. 4**). There was no statistically significant relation between ICH score measured at time of admission and the functional outcome as measured by the EGOS after four months of surgery (p value = 0.303, 95% confidence interval = [-0.000033 - 0.999949]). There were also increased risk of developing intraventricular hemorrhage in the anticoagulant group (41.2%, odds= 0.700) than the group which did not receive anti-coagulation (33.3%, odds= 0.500), with markedly increased relative risk of 1.24 (95% confidence interval= [0.72, 2.12], Odds Ratio OR=1.4). The risk of redo surgery was higher in anticoagulation group (7 patients (13.72%)) than those who did not receive anticoagulation (3 patients (7.14%)) (p-value is 0.307827 which was non significant).

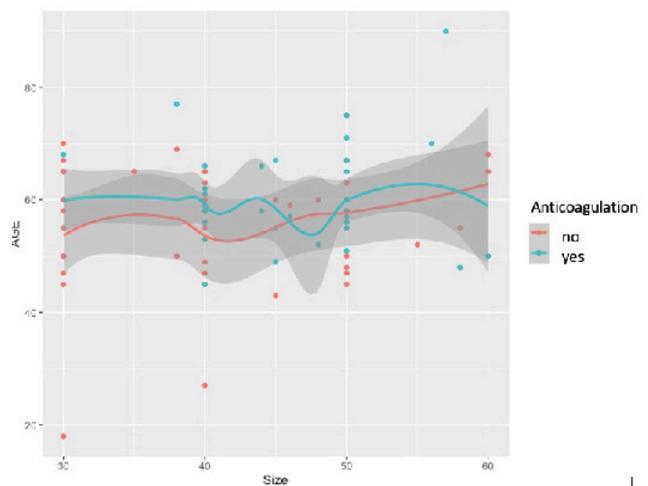


Fig 2: A scatterplot with spline lines plotting the size of the ICH as measured in ml, and the age in years, showing the distribution of cases administering oral anticoagulation (in green) and those who did not (in orange).

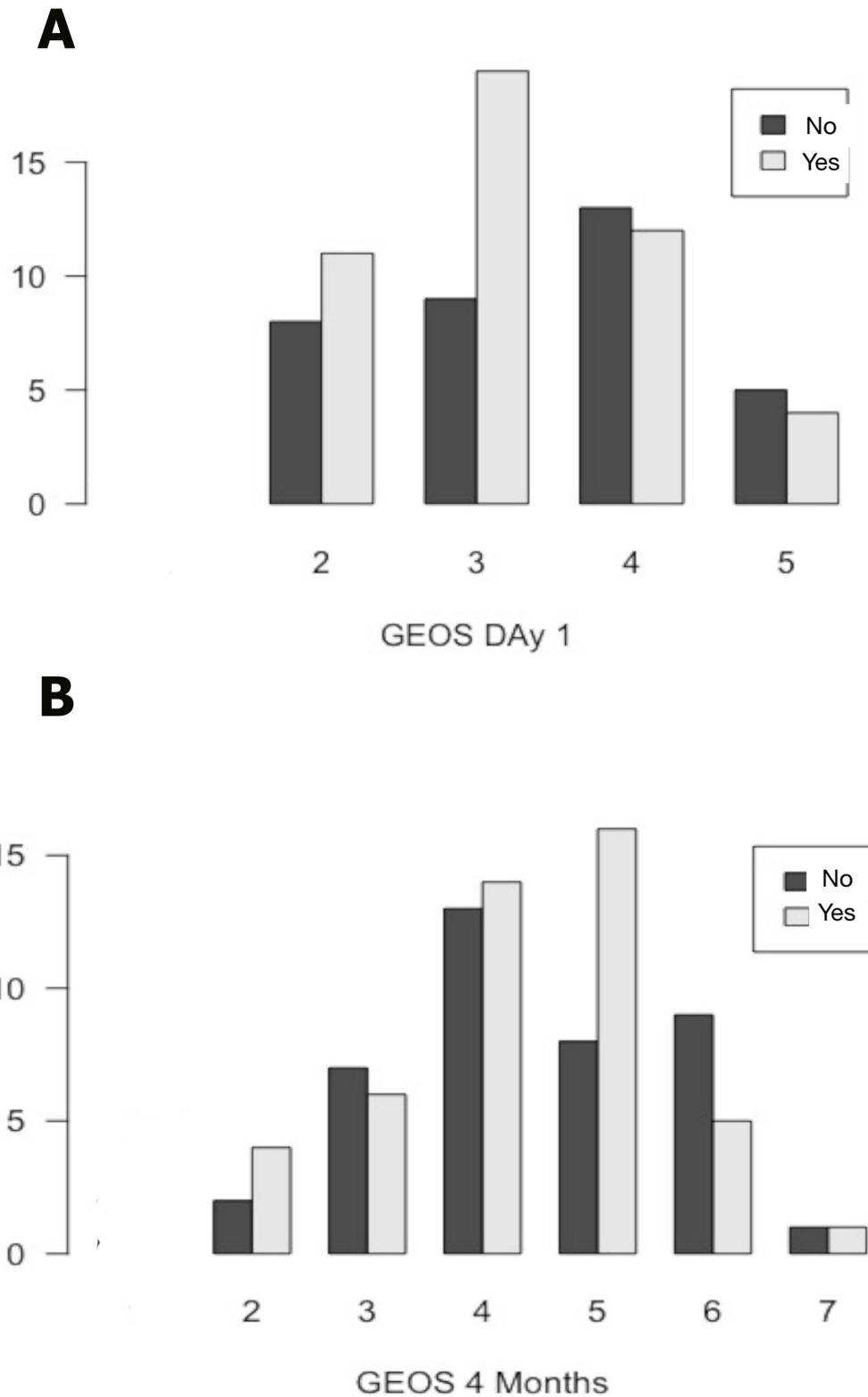


Fig 3: Bar plot visualizing the Extended Glasgow Outcome Score on day 1 post-operative (A) with (Light grey), and without (Dark grey) administration of oral anticoagulants. Bar plot visualizing the Extended Glasgow Outcome Score 4 months post-operative (B), with (Light grey), and without (Dark grey) administration of oral anticoagulants.

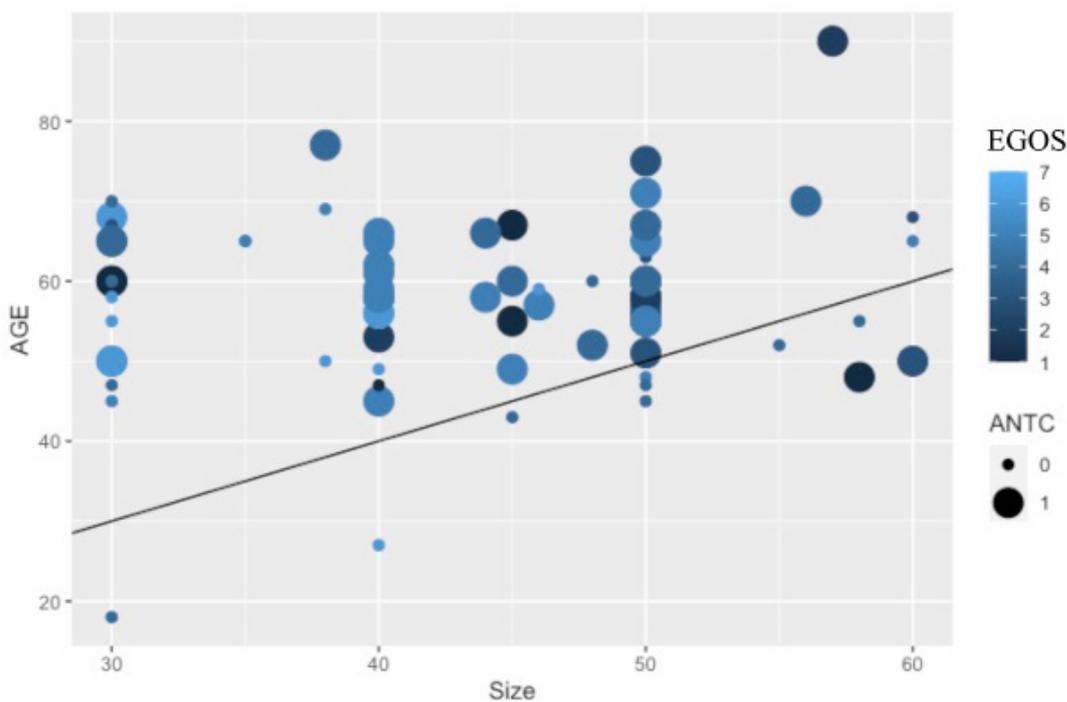


Fig 4: A scatterplot plotting the size of the ICH as measured in ml, and the age in years, showing the distribution of cases administering oral anticoagulation (Large dots) and those who did not (Small dots), and the Extended Glasgow Outcome Score at 4 months after surgery (EGOS II) in grades of blue.

Table 1: Demographic properties of the sample studied

N= 93	Males	Females
Sex	56 (60.2%)	37 (39.8%)
Age	18-90 years (mean= 58,26 ± 9.62)	
	58.98 (±7.94)	57.16 (±11.75)
Anticoagulation	Yes	No
IVH	51 (54.8%)	42 (45.2%)
Hypertension	35 (37.6%)	58 (62.4%)
Smoking	73 (78.5%)	20 (21.5%)
	42 (45.2%)	51 (54.8%)

Table 2: The ICH score adapted from Hemphill et al.⁶

Feature	Finding	Points
GCS (Glasgow coma scale score)	3-4	2
	5-12	1
	13-15	0
ICH volume	≥ 30 cc	1
	< 30 cc	0
Age	≥ 80 years	1
	< 80	0
Location	infratentorial	1
	supratentorial	0
Intraventricular blood	yes	1
	no	0
ICH Score = Total Points.		0-6

DISCUSSION

Most of the authors described unfavorable outcomes with the use of anti-coagulations, widespread administration of oral anticoagulants has been a leading cause to increased incidence of spontaneous intracerebral hemorrhage (ICH).^{3,8} Although this is evidently correct, the assumption of a better outcome in survivors who had received oral anticoagulation than those who did not was a matter of debate that we tried to resolve.

Wide range of oral anticoagulants were introduced into medical practice, each of which has a specific mode of action and pharmacokinetics. We believe that discussing these different types of medications help understand the pathophysiology and functional outcome of Oral Anticoagulant therapy- Intracerebral cerebral heamatoma, (OAT-ICH).

Vitamin K antagonists

Oral anticoagulants interfere with the cyclic interconversion of vitamin K and its 2,3 epoxides to generate their effect. Vitamin K is a required component in N-terminal sections of vitamin K based proteins for post-translational carboxylation of glutamate residues to γ -carboxylglutamates. γ Carboxylation allows coagulation proteins to go through a conformational shift that is required for both calcium-dependent complexing of vitamin K-dependent proteins to their cofactors on phospholipid surfaces and biologic action.⁹

There is a dose-response connection between bleeding events and supratherapeutic international normalized ratio (INR) values, with INR levels greater than 4 having a significant increase in occurrence.¹⁰

Direct oral anticoagulants

Non- Vitamin K antagonists (Non VKA) anticoagulants currently on the market include three factor Xa inhibitors and the direct thrombin inhibitor dabigatran.¹⁰

These Direct oral anticoagulants (DOACs) have distinctive pharmacokinetic characteristics to VKA, such as a short elimination half-life ranging from 6 to 17 hours in individuals who have normal kidney function.¹¹

Novel oral anticoagulants (NOACs), unlike VKA or heparins, can inhibit a specific factor in the coagulation cascade in a direct and reversible manner. Thrombin is the target of dabigatran, while factor Xa is the target of xaban. The anticoagulant effect is predicted to start within 2 hours after the initial dosage.¹⁰

In this retrospective study we reviewed the data of intracerebral hemorrhage survivors to find if there is any difference in the functional outcome regarding anti-coagulation therapy.

Biffi et al. conducted a meta-analysis of anti-coagulation-related-ICH from 3 studies in Europe and USA to find the difference in functional outcome,⁵ they found a significant

correlation between better outcome and anti-coagulation resumption.

Despite the obvious connection between the increased size of the hematoma and the administration of oral anticoagulants, we found that the long-term outcome was better in those on oral anticoagulation, this may be presumably due to different factors:

First, the oral anti-coagulation decreases the risk of cognitive dysfunction, especially in Atrial Fibrillation (AF) patients.¹²

Second, since most elderly patients had associated cardiovascular conditions that can be implemented in the development of brain ischemic insults, compared to those who received anticoagulant that can ameliorate these effects.

Many authors have linked the administration of anti-coagulation to delayed cognitive disabilities and stroke evolution in many populations,¹³ others recommended lowering the targeted therapeutic levels to lower the rate of complications.¹⁴ We recommend combining both low dose anticoagulants and frequent control of blood pressure and other risk factors to lower the risk of bleeding.

Mongkhon et al. described the effect of oral anti coagulants on decreasing the cognitive dysfunction in patients with AF, the related this beneficial effect to the reduction of micro emboli formation.¹⁵

We assumed that the same mechanism may be related to the better functional outcome we have concluded; patients with oral anticoagulants have a better brain functional capacity than those with no oral anticoagulation when both survive ICH, and this explains our findings.

The functional outcome has been gaining more attention in recent literature, the Glasgow outcome scale (GOS) has been used as a measure of functional outcome in cases of ICH. The extended GOS (EGOS) has shown even better sensitivity and specificity in detecting changes in functional outcome,¹⁶ we have found that functional outcome is being reportedly different between different types of oral anticoagulants.¹⁷ As part of our study, we revised the documented ICH score and its relation to functional outcome. An obvious relationship was reported, but when it comes to the different types of anticoagulants, we found nearly no difference. This is mostly related to the fact that only cheap old-style anticoagulants are more widely used among the studied population, rather than the new-generation oral anticoagulants that were correlated with even better outcome after incidental ICH.¹⁸

To predict the short-term mortality of patients with intracerebral hemorrhages in general, logistic regression models have previously been reported.¹⁹ The present research was limited to incomplete data in several patients, but we still assume that our model may be clinically applicable and warrant validation in an independent patient sample, e.g., for clinical decision-making or patient advice.

Another important application is that potential oral anti-coagulant-induced intracerebral hemorrhage experimental trials, can now be monitored for the variables found in our research.

After thorough statistical analysis, we found that despite other factors as size of the ICH, age, and Glasgow Coma Score (GCS) at the onset, the administration of oral anti-coagulation was strongly related to better intermediate term functional outcome. This does not neglect the fact that oral anti-coagulation in general increases the risk of developing spontaneous intracerebral hemorrhage. With more extensive research, a well-compensated approach could be reached avoiding the unfavorable complications, and providing the expected cognitive and functional rewards.

Finally, our evidence also reinforces the value of early clinical evaluation and radiological confirmation of reported oral anticoagulation-induced intracerebral hemorrhage.

CONCLUSION

Outcome of survivors of hematoma evacuation in patients who were on oral anticoagulants was better. Further studies are required to understand more & improve the clinical practice.

List of abbreviations

AF: Atrial fibrillation.
 Conf. Int: Confidence interval.
 COR: Correlation coefficient.
 DOAC: Direct oral anti-coagulants.
 EGOS: Extended Glasgow outcome scale.
 FFP: Fresh frozen plasma.
 GCS: Glasgow coma scale.
 GOS: Glasgow outcome Scale.
 ICH: Intracerebral hemorrhage.
 INR: International normalized ratio.
 NOAC: Novel oral anticoagulants.
 OAT: Oral anticoagulation therapy.
 OR: Odds ratio.
 VKA: Vitamin K antagonists.

Disclosure

The authors report no conflict of interest in the materials or methods used in this study or the findings specified in this paper.

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