Neurosurgical Review (2019) 42:531–537
https://doi.org/10.1007/s10143-018-1000-y

ORIGINAL ARTICLE

Pain medication at ictus of subarachnoid hemorrhage—the influence of one-time acetylsalicylic acid usage on bleeding pattern, treatment course, and outcome: a matched pair analysis

Markus Bruder[1] · Sepide Kashefiolasl[1] · Fee Keil[2] · Nina Brawanski[1] · Sae-Yeon Won[1] · Volker Seifert[1] · Juergen Konczalla[1]

Received: 24 March 2018 / Revised: 12 June 2018 / Accepted: 18 June 2018 / Published online: 22 June 2018

Abstract

Acetylsalicylic acid (ASA) is a well-known and widely used analgesic for acute pain. Patients with acute headache due to subarachnoid hemorrhage (SAH) are inclined to take ASA in this situation. Due to the antithrombotic effects, ASA intake is related to higher bleeding rates in case of hemorrhage or surgical treatment. Between January 2006 and December 2016, 941 patients without continuous antithrombotic or anticoagulant medication were treated due to SAH in our institution. Fourteen of them (1.5%) had taken ASA as a single dose because of headache within 24 h before hospital admission. A matched pair analysis was performed. Admission status was good in 93% of patients with one-time use of ASA (OTA), but only in 59% of all other patients ($p < 0.01$). Bleeding pattern did not differ, but half of the patients with OTA had no identifiable bleeding source; this rate was significantly lower in the rest of the patients ($p < 0.005$). Aneurysm treatment and related complications did not differ between both groups. Cerebral vasospasm was more often only mild and rates of cerebral infarctions were lower in the OTA group but not on a significant level. Eighty-six percent of the OTA group and 84% ($p = 0.8$) of the matched pair control group reached favorable outcome according to mRS 6 months after SAH. Patients with OTA in case of SAH are usually in good clinical condition and bleeding pattern does not differ. In half of the patients with OTA, no bleeding source was detectable. In the case of aneurysm treatment, related complications did not differ and most of the patients reached favorable outcome. In the case of aneurysm treatment procedure, OTA does not influence treatment course and should not influence treatment decisions.

Keywords SAH · Aneurysm · Acetylsalicylic acid · Aspirin

Introduction

Acetylsalicylic acid (ASA) or aspirin is a well-known and widely used effective analgesic for acute pain [8]. Therefore, it is not surprising that patients with acute headache due to subarachnoid hemorrhage (SAH) are inclined to take ASA in this situation. Due to the antithrombotic effects, ASA is related to higher bleeding rates in the case of hemorrhage or surgical treatment. ASA has surprised the medical community more than once and there are some promising results regarding ASA and prevention of aneurysm formation, rupture, or reduction of secondary brain injury [4, 6, 15, 26]. Nevertheless, current evidence suggests that short-term use of ASA is associated with increased risk of aneurysmal SAH [21], and it is unclear if one-time usage of ASA can enable positive effects or lead to higher rates of hemorrhagic complications in case of SAH.

We performed a matched pair analysis to analyze characteristics, treatment course, and outcome of patients with single use of ASA prior to hospitalization due to SAH.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10143-018-1000-y) contains supplementary material, which is available to authorized users.

✉ Markus Bruder
markus.bruder@kgu.de

[1] Department of Neurosurgery, Goethe University, Frankfurt am Main, Germany

[2] Department of Neuroradiology, Goethe University, Frankfurt am Main, Germany

Material and methods

Patients with non-traumatic SAH treated in our clinic were entered in a prospectively kept database. All patients admitted between January 2006 and December 2016 were screened. After excluding patients with continuous anticoagulant or antithrombotic treatment, 941 patients were analyzed in this survey.

One-time ASA usage (OTA) was defined as ASA usage within 24 h before hospitalization with SAH.

SAH was confirmed by cranial computed tomography (CT) or lumbar puncture. A cerebral digital subtraction angiography (DSA) was performed within 12 h after admission. If DSA revealed an intracranial aneurysm as bleeding source, treatment decision (endovascular or microsurgery) was based on an interdisciplinary approach in each individual case, as previously reported [1, 2, 19]. If no bleeding source was detected by first angiography, MRI of the spine was performed to rule out any bleeding sources in this region. If none was detectable either, angiography was repeated 2 weeks in case of Fisher 3-like bleeding pattern, at the latest 2–3 months after the ictus [18].

Information including patient characteristics, existing medication, treatment modality, and radiological findings were prospectively entered into a computerized database (IBM SPSS Statistics©, Version 22, Armonk, NY, USA).

Ethics approval was obtained from the Ethics Committee of the University Hospital Frankfurt. For retrospective analysis patients consent was not sought.

Course of treatment

All patients were carefully monitored on our intensive care or intermediate care unit. CT or MR imaging was performed 12 to 24 h after aneurysm treatment to detect any treatment-related hemorrhagic or ischemic events. Screening for cerebral vasospasm (CVS) was performed daily via neurological examinations and transcranial Doppler sonography (TCD). In cases in whom CVS was suspected, a CT or MRI scan was performed. On day 7 ± 2 after aneurysm rupture, the patients received a regular control by CT, MRI, or digital subtraction angiogram. CVS was classified as mild, moderate, or severe according to narrowing < 33%, 33–66%, or > 66% vessel constriction. In patients with CVS until reversal of CVS (detected by CT-A or MR-A), hypertension was induced aiming at a CPP of 90–110 mmHg [17, 22]. Patients received nimodipine 6 × 60 mg/day orally during the first 3 weeks. Corticosteroids and anticonvulsants were not given as a matter of routine [23]. All unconscious patients, patients which had CVS, and conscious patients with neurological deficits received control MRI or CT before discharge. Those were independently screened for ischemia by the following authors: M.B., N.B., S.K., and S.W. Detection of ischemia was defined as cerebral infarction. In the case of ischemic lesions in more than two brain territories or both hemispheres, the lesions were defined as multiple ischemic lesions [24].

Outcome and follow-up

Outcome was assessed 6 months after SAH. Functional outcome was evaluated by modified Rankin scale (mRS). Where a favorable outcome was defined as mRS 0–2 and an unfavorable outcome was defined as mRS 3–6.

Matched pair analysis

To exclude factors with a known or potential impact on treatment and outcome, we performed a matched pair analysis. Matching parameters were age, admission status (according to WFNS and H&H scale), Fisher score, and the presence of an additional intracerebral hemorrhage (ICH) larger than 50 ml (Table 1).

Patients with one-time ASA usage within 24 h before hospitalization with SAH were identified and a multivariate and propensity score matching with balance optimization was performed [25]. As matched pair control group, 112 out of 927 patients without any continuous anticoagulant or antiplatelet treatment were matched as control group with a ratio of 1:8.

Statistical methods

Statistical analyses were performed using the Student's *t* test, Chi-square test, or Fishers exact test as indicated. Results with a p value < 0.05 were considered statistically significant. Statistical analyses and calculations were made using standard commercial software (IBM SPSS Statistics, Version 22, Armonk, NY, USA). For the matched pair analysis, the statistical computing program R© (The R Foundation for Statistical Computing; version 3.0.3, Vienna, Austria) was used.

Results

In 14 of 941 patients (1.5%) with SAH, one-time ASA usage before hospitalization was reported. ASA was used within 24 h before admittance to the hospital due to headache in all of 14 cases. Patient characteristics, admission status, and treatment modalities are given in Table 1.

Age did not differ among patients with OTA and the remaining 927 patients without any known anticoagulant or antiplatelet treatment. The rate of female sex was slightly lower in the OTA group, as well as the rate of additional ICH and early hydrocephalus, but not on significant levels. The bleeding pattern according to Fisher [13] was not different.

Table 1 Comparison of patient characteristics, admission status, and treatment of patients with one-time ASA use at the time subarachnoid hemorrhage (SAH) vs. all patients without ASA and vs. matched pair control group (1:8) without ASA (*matching parameters; ASA, acetylsalicylic acid; SD, standard deviation; WFNS, Word Federation of Neurosurgical Societies; ICH, intracerebral hematoma; IVH, intraventricular hemorrhage; *n*, number of patients; OTA, one-time ASA use)

	Patients with one-time ASA use	Patients without one-time ASA use			
		Matched pair control group	*p* value vs. OTA	All patients	*p* value vs. OTA
Patient characteristics					
Number of patients (*n*)	14	112		927	
Age in years (±SD)*	52.8 (± 12.7)	59.5 (± 14.5)	0.1	53.67 (± 12.9)	0.8
Female sex	7 (50%)	74 (66.1%)	0.3	598 (64.5%)	0.3
Admission status					
WFNS score 1–3 (good)*	13 (92.9%)	103 (92.0%)	1	545 (58.8%)	0.007
WFNS score 4–5 (poor)*	1 (7.1%)	9 (8.0%)		382 (41.2%)	
Fisher 3*	8 (66.7%)	61 (54.5%)	0.8	611 (69.3%)	0.6
ICH < 50 ml	1 (7.1%)	3 (2.7%)	0.4	128 (14.5%)	0.7
ICH > 50 ml*	0 (0%)	0 (0%)		70 (7.9%)	0.6
Early hydrocephalus	6 (42.9%)	35 (31.3%)	0.4	525 (57.1%)	0.6
Aneurysm and treatment					
Non-aneurysmal SAH	7 (50%)	24 (21.4%)	0.04	127 (13.7)	0.002
Endovascular	4 (28.6%)	61 (54.5%)	0.4	466 (50.3%)	0.5
Microsurgical	3 (21.4%)	22 (19.4%)		249 (26.9%)	
No treatment	0 (0%)	5 (4.5%)	0.6	85 (9.2%)	0.6

Admission status based on WFNS score was considered as good (WFNS 1–3) in 13 patients (93%) with OTA, but only in 59% of all other patients ($p < 0.01$; OR 0.11; 95% CI 0.01–0.84). Half of the patients (50%) with OTA had no identifiable bleeding source in cerebral angiography, which is a significant higher rate compared to the rest of the patients with only 14% non-aneurysmal SAH ($p < 0.005$; OR 0.14; 95% CI 0.05–0.4). Even though, 50% of the reference group but only 29% of the OTA group were treated endovascular, there was no statistical difference between treatment modalities.

Matched pair analysis

According to matching parameters, there was no difference in patient age and admission status as well as bleeding pattern between OTA patients and the matched pair control group (Table 1). The rate of non-aneurysmal SAH was significantly higher in the OTA group compared to the matched pair control group (50 vs. 21.4%; $p < 0.05$; OR 0.3; 95% CI 0.09–0.9). The rates of microsurgical and endovascular treated patients are given in Table 1. There was no difference between both groups.

Of the treated patients, in the OTA group, 57% were treated endovascularly and 43% microsurgical and in the matched cohort 74% were treated endovascular and 26% were treated microsurgical ($p = 0.3$).

Rebleeding before treatment of the aneurysm occurred in 3 cases (2.9%) of the matched pair control group and in none of the OTA patients (0%). Intracerebral hemorrhage related to EVD placement in case of early hydrocephalus occurred in one of 6 patients of the OTA group (16.7%) and in 3 of 35 patients (8.6%) of the matched pair control group ($p = 0.5$; Table 2).

Treatment-related complications did not occur in OTA patients and rates were low in the matched pair control group (Table 2).

CVS, cerebral infarctions, and outcome

CVS occurred in 4 patients (35.7%) of the OTA group and in 44 patients (40%) of the matched pair control group ($p = 0.5$). CVS cases of the OTA group were classified as mild in 2 cases (14.3%) and moderate in 2 cases (14.3%) respectively. Severe CVS, with a narrowing of the vessel diameter of more than 66%, was detected in one patient (7.1%). However, CVS in the matched pair control group were classified as mild in only 7 cases (6.3%), whereas moderate CVS occurred in 14 cases (12.5%) and severe CVS occurred in 17 cases (15.2%) ($p = 0.3$).

The rate of CI was 7.1% in the OTA group and 31.2% in the matched pair control group. However, this difference was only numerical but not on a statistically significant level ($p = 0.06$).

Outcome according to modified Rankin scale is given in Table 2. There was no difference in outcome assessed by mRS comparing patients with one-time usage of ASA and the matched pair control group. Favorable outcome (mRS 0–2) was achieved by 12 patients (85.7%) of the OTA group and in 94 patients (83.9%) of the matched pair control group ($p = 0.8$; Table 2).

Table 2 Complications and outcome in patients with one-time ASA use compared to matched pair control group (ASA, acetylsalicylic acid; mRs, modified Rankin scale)

	With one-time ASA $n = 14$	Matched pair control group $n = 112$	p value
Rebleeding before aneurysm treatment	0 (0%)	3 (2.9%)	1
EVD-related hemorrhage	1/6 (16.7%)	3/35 (8.6%)	0.5
Microsurgical complications			
Intraoperative aneurysm rupture	0/3 (0%)	1/22 (4.5%)	
Postoperative rebleeding	0/3 (0%)	/22 (0%)	
Postoperative cerebral infarction	0/3 (0%)	2/22 (4.5%)	
No complication	3/3 (100%)	19/22 (91%)	1
Endovascular complications			
Intraprocedural aneurysm rupture	0/4 (0%)	2/61 (3.3%)	
Postinterventional rebleeding	0/4 (0%)	/61 (%)	
Thromboembolic complications	0/4 (0%)	2/61 (3.3%)	
Post interventional cerebral infarction	0/4 (0%)	4/61 (6.6%)	
No complication	4/4 (100%)	53/61 (86.8%)	1
Outcome according to modified Rankin scale			
Favorable outcome (mRS 0–2) Unfavorable outcome (mRS 3–6)	12 (85.7%) 2 (14.3%)	94 (83.9%) 18 (16.1%)1	0.8

Discussion

In the treatment of patients with subarachnoid hemorrhage, preexisting anticoagulant or antithrombotic medication is of particular interest. As intensified bleeding and hemorrhagic complications are related with antithrombotics [12, 16, 21], treatment decisions might be influenced by the use of acetylsalicylic acid. Patients with acute headache are inclined to take ASA, as it is a widely used pain medication [8]. In this study, we analyze the influence of one-time use of ASA due to headache within 24 h before admission of patients with SAH on admission status, treatment course, and outcome.

Whereas patients with continuous ASA treatment at the time of aneurysm rupture are usually older [3, 27], age and sex of patients of the OTA group was not different from the rest of the patients. This is not surprising, as ASA use against acute pain is not necessarily related to age or any age-dependent comorbidity. However, the first finding of this study attracts attention, because all but one patient of the OTA group (93%) had a good admission status, whereas only 59% ($p < 0.01$) of the control group with SAH during the same time period had good clinical condition on admittance. Accordingly, Juvela et al. [16] reported better clinical condition of patients who used NSAIDs only after the ictus of SAH. As admission status does not differ in patients with continuous ASA use [3], we strongly assume that the admission status itself is the reason for this difference when comparing patients with OTA and patients without. First, patients need to be conscious to use medication. Patients with sudden and major SAH deteriorate very quickly and are less likely to be in the condition to use any kind of medication themselves. Second and most important, assessing the one-time use of ASA necessitates a conscious patient, able to tell the admitting staff that single-dose ASA was used. Only in one patient, relatives could report the one-time usage of ASA at the beginning of symptoms, before his status worsened and he was admitted unconscious to the hospital. In the case of continuous ASA usage, medication is often documented and can easily be assessed even in unconscious patients by questioning the relatives or the general practitioner. For further investigation of the results, we have to realize that we do not know how many patients with unconscious condition may have taken a single-dose ASA at the beginning of symptoms. Even though the number of patients with undetected single use of ASA might be low and should not influence the general results of the reference group, this might implicate a strong bias. Furthermore, patient characteristics of the 14 OTA patients are atypical and comparing them with the other SAH patients is not expedient, as good admission status and non-aneurysmal SAH is predictive for favorable outcome in SAH patients. To counteract this bias, we performed a matched pair analysis for outcome analysis.

Comparing the bleeding pattern at the time of admission, we identified that single use of ASA neither influence the extent nor the severity of SAH. The number of Fisher 3-like bleeding pattern and additional ICH was the same comparing OTA group to the matched pair group or to all patients without ASA in our database (Table 1). This is concordant with reports in literature of patients suffering from SAH while under continuous ASA treatment [3, 5].

The overall rate of patients in this cohort in whom cerebral angiography, CT, and MRI was negative for aneurysms or other vascular malformations is 14%, comparable to literature [10, 14]. Surprisingly, 50% of patients of the OTA group and

only 14% of patients without OTA suffered SAH without a detectable bleeding source ($p < 0.005$). One might think that the general good admission status in the OTA group—as explained above—explains their high rate of non-aneurysmal SAH, as patients without detectable bleeding sources more often present in good clinical condition [14]. However, the rate of non-aneurysmal SAH in the matched pair group was only 21% and therefore significantly lower than in the OTA group as well ($p < 0.05$). The reason why half of the patients with single use of ASA had non-traumatic SAH without a detectable bleeding source cannot be answered by this survey. Although an increased rate of non-aneurysmal SAH was detected during the last decade and related to a simultaneous increase of antiplatelet medication [11, 18], SAH is still rather seldom. Since rates of non-aneurysmal SAH in patients with continuous ASA use are not higher [3], and since we do not know if OTA patients did take ASA before or after the hemorrhage occurred, the assumption that ASA itself does cause non-aneurysmal SAH is not justified and misleading. In our opinion, patients with non-aneurysmal SAH are more likely to be able to take pain medication due to headache as they mostly display only milder symptoms [11, 14].

Treatment modalities did not differ between OTA and matched pair control group. Endovascular treatment was performed somewhat more often than microsurgical procedures in both groups. Despite some tendency showing higher rebleeding rates of the aneurysm before treatment in case of continuous ASA treatment [3, 27], no patient of the OTA group had rebleeding before aneurysm repair or any hemorrhagic complications despite endovascular or microsurgical treatment. In accordance with the known beneficial effect of ASA in coronary artery bypass surgery, where preoperative ASA medication is favored in order to decrease thrombotic complications and perioperative myocardial infarction [9], thromboembolic events did not occur in the OTA group. However, the small number of patients with ruptured aneurysm of the OTA group might explain the lack of any procedural complications in this survey.

Even though rates of rebleeding before aneurysm treatment or intraoperative aneurysm rupture in patients with continuous ASA use are higher [3], it is unclear if one-time or continuous ASA usage does influence the strength of the platelet/fibrin plug which forms at the site of rupture. Timely aneurysm repair after rupture is recommended anyway. However, as treatment-related complications seem not to be significantly affected by ASA, the decision to treat the ruptured aneurysm endovascular or microsurgical should not be influenced by ASA usage, but based on an interdisciplinary approach.

Ventriculostomy-related hemorrhage in case of early hydrocephalus occurred more often in the OTA group, but not on a significant level. As recent reports have shown, intraprocedural antiplatelet treatment (e.g., in case of stent-assisted coiling) can influence the rate of ventriculostomy-related hemorrhage [2, 20], thus patients with ASA usage should be monitored carefully. As ASA associated, ventriculostomy-related hemorrhages are rarely significant or clinically relevant; the most often life-saving ventriculostomy should not be withheld in case of hydrocephalus despite ASA usage.

The overall rate of CVS was equal in the OTA and the matched pair control group, but CVS was more often only mild or moderate in the OTA group and more often severe in the matched pair control group. Juvela et al. [16] found lower CI rates in patients with positive urine test for salicylates at the time of admission. Concordant to other reports, CI rates tended to be lower in patients with ASA use in the present survey [7, 16]. However, the lower rates of severe CVS and CI did not reach significant levels in the present survey and—most important—there was no difference in outcome after 6 months. Although most analyses (without matching and balance optimization) in literature report ASA users to be more likely to have poor outcome after SAH [5, 18], more than 80% of both groups reached favorable outcome and were able to live independently. This might again underline the importance of the clinical condition at the time of admission as one of the strongest predictive parameters for outcome in case of SAH.

Limitations

This study has several limitations. The main limitation might be its retrospective and monocentric design, such as the lack of data not documented initially in the medical records. Furthermore, we did not perform platelet tests to confirm ASA effects. However, the structured and standardized monocentric treatment and diagnostic course as well as the prospective outcome analysis might counteract these disadvantages.

Conclusion

Patients with one-time use of ASA before admittance to the hospital in case of SAH are usually in good clinical condition and most of the patients reached favorable outcome. There was no difference in bleeding pattern or rates of additional intracerebral hemorrhages. In half of the patients with OTA, no bleeding source was detectable and the rate of aneurysmal SAH was significantly lower, even compared to the matched pair group. Neither ventriculostomy nor aneurysm treatment procedures or treatment-related complications were affected negatively by OTA, especially not between endovascular and microsurgical procedures. One-time ASA usage at the time of SAH does not influence treatment course and should not influence treatment decision.

Acknowledgements We thank Marina Heibel and Anne Sicking for their excellent technical support.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was performed with approval of the institutional ethic committee.

Informed consent For this type of study, formal consent is not required.

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