neurocritical care society Neurocrit Care (2016) 24:122–127
DOI 10.1007/s12028-015-0202-1

ORIGINAL ARTICLE

Preventive Antibiotics and Delayed Cerebral Ischaemia in Patients with Aneurysmal Subarachnoid Haemorrhage Admitted to the Intensive Care Unit

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Published online: 8 October 2015
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Abstract

Introduction Delayed cerebral ischemia (DCI) is an important contributor to poor outcome after aneurysmal subarachnoid haemorrhage (aSAH). Development of DCI is multifactorial, and inflammation, with or without infection, is one of the factors independently associated with development of DCI and poor outcome. We thus postulated that preventive antibiotics might be associated with a reduced risk of DCI and subsequent poor outcome in aSAH patients.

Methods We performed a retrospective cohort-study in intensive care units (ICU) of three university hospitals in The Netherlands. We included consecutive aSAH patients with minimal ICU stay of 72 h who received either preventive antibiotics (SDD: selective digestive tract decontamination including systemic cefotaxime or SOD: selective oropharyngeal decontamination) or no preventive antibiotics. DCI was defined as a new hypodensity on CT with no other explanation than DCI. Hazard ratio's (HR) for DCI and risk ratio's (RR) for 28-day case-fatality and poor outcome at 3 months were calculated, with adjustment (aHR/aRR) for clinical condition on admission, recurrent bleeding, aneurysm treatment modality and treatment site.

Results Of 459 included patients, 274 received preventive antibiotics (SOD or SDD) and 185 did not. With preventive antibiotics, the aHR for DCI was 1.0 (95 % CI 0.6–1.8), the aRR for 28-day case-fatality was 1.1 (95 % CI 0.7–1.9) and the aRR for poor functional outcome 1.2 (95 % CI 1.0–1.4).

Conclusions Preventive antibiotics were not associated with reduced risk of DCI or poor outcome in aSAH patients in the ICU.

Keywords Aneurysmal subarachnoid haemorrhage · Delayed cerebral ischaemia · Intensive care unit · Antibiotics · Case–control study

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Introduction

Delayed cerebral ischaemia (DCI) is a major complication after aneurysmal subarachnoid haemorrhage (aSAH) and an important contributor to poor outcome [1]. The cause of DCI is multifactorial [2] with one of the postulated underlying mechanisms being the presence of an inflammatory response [3, 4]. Infections are seen in up to 30–40 % of patients with aSAH during hospitalisation [5] and signs of systemic inflammation, with or without the

presence of an infection, are independent predictors of DCI and poor functional outcome after aSAH [6–10].

Selective digestive tract decontamination (SDD; consisting of 4 days of intravenous cefotaxime plus topical application of tobramycin, colistin and amphotericin-B in oropharynx and stomach) and selective oropharyngeal decontamination (SOD; consisting of oropharyngeal application only) have been proven to reduce respiratory tract colonisation with Gram-negative bacteria and to improve 28-day survival in a mixed population of patients admitted to the intensive care unit (ICU) [11]. We postulated that preventive antibiotics, through influencing infection or inflammation, are associated with a reduced risk of DCI and subsequently improved outcome in patients with aSAH admitted to the ICU.

Materials and Methods

We retrieved data on aSAH patients aged ≥18 years, admitted to the ICU within 72 h after aSAH from three large university hospitals in The Netherlands: the University Medical Center Utrecht (UMCU); the Academic Medical Center Amsterdam (AMC); and the University Medical Center Groningen (UMCG) from May 2003 until May 2011. After 2011, preventive antibiotics (SOD or SDD), were considered standard care in all three participating centres. Aneurysmal SAH was defined as subarachnoid blood with an associated aneurysm found on CT-angiogram or digital subtraction angiography (DSA). However, we also included patients in whom no aneurysm was found during admission but who had a definite aneurysmal bleeding pattern since these patients are also at risk of developing DCI. The inclusion criterion within 72 h after the aSAH was used to minimize the risk that DCI had already occurred before ICU admittance.

Of the included patients, 73 participated in one of two controlled, cluster-randomised crossover studies in which SOD, SDD and no antibiotics [11] or SOD and SDD [12] were compared. In these studies, the treatment regime would only be assigned if the anticipated stay in the ICU was more than 72 h and/or expected duration of intubation was more than 48 h. Therefore, in order to equalize our inclusion criteria, all included patients outside these study periods had to have an ICU length-of-stay of at least 72 h, irrespective of intubation status. Whether these patients were treated with SOD, SDD or no preventive antibiotics depended on the local protocol of the treatment centre at the time of admittance.

During admission, all patients were treated according to a standardised protocol that consisted of absolute bed rest until aneurysm treatment, oral doses of nimodipine, cessation of antihypertensive medication and intravenous administration of fluid with the aim of normovolaemia.

For all patients, we extracted the following variables: age, gender, clinical condition at admission according to the World Federation of Neurological Surgeons (WFNS) scale [13], aneurysm location, modality of aneurysm treatment, amount of extravasated blood on admission CT as assessed with the Hijdra score [14], presence of an intracerebral haematoma (ICH), occurrence of DCI, occurrence of a recurrent bleeding, preventive antibiotics regime (SOD, SDD or no antibiotics), 28-day survival (the primary endpoint of the SDD studies) and functional outcome assessed with the modified Rankin Scale (mRS) [15] 3 months after aSAH. The clinical condition at time of admission assessed with the WFNS scale was dichotomised into good clinical condition (WFNS 1–3) and poor clinical condition (WFNS 4–5). The amount of extravasated blood as assessed with the Hijdra score was dichotomised at their median for both cisternal (sum score range 0–30) and ventricular (sum score range 0–12) blood. The two scores were added to a total Hijdra sum score which was in turn dichotomised at the added median scores for cisternal and ventricular blood.

The primary outcome measure was the occurrence of DCI defined as a new hypodensity on CT scan with no other explanation (e.g. edema or ischaemia from coiling or clipping) than DCI [16]. Secondary outcome measures were 28-day case-fatality and poor outcome after 3 months defined as a mRS score of 4, 5 or death.

Ethics

The ethical review board of the AMC approved the study protocol (reference number W14_151#14.17.0188).

Sample Size Calculation and Statistical Analyses

We calculated that a sample of 584 patients (292 per group) would yield a power of 80 %, at a significance level of 0.05, to detect a 10 % absolute difference (from 30 to 20 %) in occurrence of DCI in the preventive antibiotics group versus the control group.

Cox univariable and multivariable regression analysis (for DCI) and Poisson univariable and multivariable regression analysis (for 28-day case -fatality and poor outcome at 3 months) were performed to calculate hazard ratios (HR) and risk ratios (RR) with corresponding 95 % confidence intervals (CI). We primarily investigated the effect of preventive antibiotics combined (SOD or SDD) versus no antibiotics, but also investigated the effects of SOD and SDD alone. To identify which co-variables should be added to the multivariable analyses as important confounders (defined as variables that changed the crude

HR or RR by more than 10 %), we performed bivariable analyses with previously chosen co-variables known to be associated with occurrence of DCI or poor outcome (age, gender, clinical condition on admission (WFNS score), recurrent bleeding prior to DCI, aneurysm treatment modality, intracerebral haemorrhage, amount of subarachnoid blood (Hijdra score) and—for 28-day case-fatality and poor outcome—presence of DCI). With this analysis, the variables clinical condition on admission (WFNS score), recurrent bleeding and aneurysm treatment modality were identified and included in the multivariable analyses.

Since patients were derived from three different sites, we investigated whether all patients could be analysed together by adding an interaction term between preventive antibiotics regime and treatment site to the uni- and multivariable analyses. Interaction terms appeared not to be statistically significant, and thus we concluded it was justified to analyse all patients together. To adjust for other possible between-centre differences, we did add the variable treatment site to the multivariable analyses.

We added two sensitivity analyses. First, 61 patients had died or had been discharged to another hospital within 10 days without having had follow-up imaging. In the primary analysis, these patients were scored as having no DCI, but we added a sensitivity analysis in which they were all scored as having DCI. Further, 28 patients were transferred to another hospital and were lost to follow-up for the outcome of 28-day case-fatality. In the primary analysis, we excluded these patients, but we added a sensitivity analysis in which we assumed that these patients were alive at 28 days after aSAH.

Results

Of the 459 aSAH patients who fulfilled the inclusion criteria, 274 received preventive antibiotics (61 SOD, 213 SDD) and 185 did not. Seventy-three patients (16 %) were derived from one of the two SDD studies; the remaining patients originated from cohorts of patients in between or after the two studies. The mean age of the patients was 57 years and 322 (70 %) were female. Four hundred and eleven patients (90 %) were admitted to the ICU within 24 h after the haemorrhage and DCI had not yet occurred in any of the patients before admittance to the ICU.

Demographics and baseline characteristics are shown in Table 1. Compared with the group of patients not receiving preventive antibiotics, those in the antibiotics group were more often coiled (56 vs. 44 %,), less often clipped (30 vs. 40 %), and more often had a WFNS score >3 at admission (71 vs. 53 %), or an intracerebral haematoma (35 vs. 25 %).

The results for DCI and functional outcome are shown in Table 2. The primary outcome of DCI occurred in 122 (26 %) patients. Survival at 28 days was missing for 28 patients (6 %) and functional outcome at 3 months was missing for 76 patients (17 %). For 16 of these 76 patients, functional outcome at 6 months was known and was extrapolated to the 3 months, outcome. One hundred fourteen patients (26 %) had died at 28 days and 237 patients (59 %) had a poor functional outcome at 3 months. There was no difference in occurrence of DCI, 28-day case-fatality or poor outcome at 3 months for the combined preventive antibiotics group (SOD and SDD) versus no preventive antibiotics (Table 2). The aHR for DCI was 0.8 (95 % CI 0.4–1.6) for SOD and 1.1 (95 % CI 0.6–2.0) for SDD. The aRR for 28-day case-fatality was 0.9 (95 % CI 0.5–1.6) for SOD and 1.3 (95 % CI 0.7–2.2) for SDD. The aRR for poor outcome at 3 months was 1.1 (95 % CI 0.8–1.6) for SOD and 1.4 (95 % CI 1.1–1.9) for SDD. When all 61 patients without follow-up imaging were scored as having DCI instead of not having DCI, the aHR for DCI in patients who received preventive antibiotics was essentially the same (0.9 [95 % CI 0.6–1.4]).When all patients lost to follow-up were considered alive, the aRR for 28 days case-fatality in patients who received preventive antibiotics was essentially unchanged (1.2 [95 % CI 0.7–1.9]).

Discussion

In this retrospective study, no association was found between the use of preventive antibiotics and the occurrence of DCI or poor clinical outcome in aSAH patients who were admitted to the ICU within 72 h after SAH.

Several inflammatory parameters and infection, especially pneumonia, have been shown to be associated with DCI and unfavourable outcome after aSAH, which provides a window of opportunity for preventing DCI or unfavourable outcome by means of prevention of infection [6, 7, 17]. No previous studies have investigated the role of preventive antibiotics after aSAH, however, our results concur with recent studies on preventive antibiotic treatment in adults with ischaemic stroke and intracerebral haemorrhage showing that preventive antibiotics are unlikely to reduce mortality or poor outcome in these patients [18, 19].

Although both SDD and SOD have been proven beneficial in reducing 28-day case-fatality in the ICU population as a whole, this effect was probably not attributed to the aSAH patients, based on the results from the current study. Several explanations for the negative result of our study should be addressed. First of all, neurogenic or central fever, as defined by fever in neurological

Table 1 Baseline characteristics

	Preventive antibiotics (SOD/SDD) $n = 274$	No preventive antibiotics $n = 185$
Number of patients per centre		
AMC (%)	158 (58)	25 (14)
UMCU (%)	102 (37)	27 (15)
UMCG (%)	14 (5)	133 (72)
Mean age, years (range)	57 (24–84)	57 (25–84)
Female (%)	186 (68)	136 (74)
WFNS score >3	194 (71)	98 (53)
Aneurysm treatment		
Coil (%)	154 (56)	82 (44)
Clip (%)	81 (30)	73 (40)
Stenting (%)	0	1 (1)
No treatment (%)	39 (14)	29 (16)
Recurrent bleeding (%)	67 (25)	38 (21)
Radiological parameters		
Aneurysm location		
Anterior circulation (%)	179 (65)	122 (66)
Posterior circulation (%)	83 (30)	58 (31)
Not found (%)	12 (4)	5 (3)
Hijdra scores[a]		
Sum score cisterns >median of 26 (%)	126 (46)	87 (47)
Sum score ventricles >median of 3 (%)	142 (52)	84 (45)
Total sum score >median of 29 (%)	137 (50)	89 (48)
ICH present[b]	95 (35)	46 (25)
Length of ICU stay in days, median (IQR)	7 (4–12)	7 (4–16)

SOD selective oropharyngeal decontamination, *SDD* selective digestive tract decontamination, *AMC* Academic Medical Center Amsterdam, *UMCU* University Medical Center Utrecht, *UMCG* University Medical Center Groningen, *WFNS* World Federation of Neurological Surgeons, *ICH* intracerebral haematoma, *IQR* interquartile range, *ICU* intensive care unit

[a] 10 missing

[b] 7 missing

patients without associated infection, is common in patients with aSAH in the ICU and is associated with DCI after aSAH [20, 21]. Both neurogenic fever and the presence of a systemic inflammatory response syndrome (SIRS) without associated infection may have attributed to DCI or poor outcome. Further, the development of DCI is associated with other factors besides inflammation, such as larger and smaller vessel vasospasm, cortical spreading depression and microvascular thrombosis for which starting preventive antibiotics is not the all-embracing approach for decreasing the risk of DCI [2].

Several sources of bias may explain our results. First, the decision to start SOD or SDD was based on the existing local protocol or ongoing study, and on the judgement of the treating physician who did not start SOD or SDD when the expected ICU stay was less than 72 h. This inevitably has led to confounding by indication, which might have influenced outcome. Second, we had no information on possible use of antibiotics before admission to the ICU, but considering the fact that 90 % of patients were admitted to the ICU within 24 h after the ictus this probably has not affected our results. We also had no exact information on the additional use of antibiotics besides SOD or SDD treatment during ICU admission and we did not prospectively assess the occurrence of infections. However, the lacking of this information seems less relevant, as differences in inflammatory parameters or presence of infections between the groups would not alter the absence of an association between preventive antibiotics and DCI or poor outcome.

The large, multicentre consecutive series of patients and the complete data on DCI, accurately assessed based on

Table 2 Outcome measures per treatment group

	Preventive antibiotics (SOD/SDD) $n = 274$	No preventive antibiotics $n = 185$
DCI		
Number (%)	72 (26)	50 (27)
Unadjusted HR (95% CI)	1.0 (0.7–1.4)	Ref
Adjusted HR (95% CI)[a]	1.0 (0.6–1.8)	Ref
	Preventive antibiotics (SOD/SDD) $n = 255$	No preventive antibiotics $n = 176$
28-day case-fatality		
Number (%)	80 (31)	34 (19)
Unadjusted RR (95% CI)	1.6 (1.1–2.3)	Ref
Adjusted RR (95% CI)[a]	1.1 (0.7–1.9)	Ref
	Preventive antibiotics (SOD/SDD) $n = 224$	No preventive antibiotics $n = 175$
Functional outcome; mRS (%)		
0	9 (4)	16 (9)
1	22 (10)	18 (10)
2	23 (10)	32 (18)
3	20 (9)	22 (13)
4	30 (13)	28 (16)
5	26 (12)	16 (9)
6	94 (42)	43 (25)
Poor functional outcome		
Number (%)	150 (67)	87 (50)
Unadjusted RR (95% CI)	1.3 (1.1–1.6)	Ref
Adjusted RR (95% CI)[a]	1.2 (1.0–1.4)	Ref

SOD selective oropharyngeal decontamination, *SDD* selective digestive tract decontamination, *DCI* delayed cerebral ischemia, *HR* hazard ratio, *RR* risk ratio, *CI* confidence interval, *ICU* intensive care unit, *mRS* modified Rankin Scale

[a] Adjustments were made for WFNS, recurrent bleeding, treatment centre and treatment modality

previously defined definitions [16], are strong points of our study.

In conclusion, our results do not support a role of preventive antibiotics in reducing the occurrence of DCI and subsequent poor outcome in patients with aSAH admitted to the ICU. Although a positive effect of antibiotics on DCI and poor outcome cannot be excluded definitively by our results, we consider the chance of a positive effect with a larger sample size to be small, also in the light of the recent negative trials in other subsets of stroke.

Compliance with Ethical Standards

Conflict of interest C.S. Gathier is supported by a grant from the Dutch Heart Foundation (Grant 2009B046) and the Brain Foundation Netherlands (Grant 2009(1)-72). M.J.M. Bonten is supported by The Netherlands Organization of Scientific Research (NWO-VICI 918.76.611). M.D.I. Vergouwen is financially supported by a personal grant from the Dutch Heart Foundation (Grant 2011T18). D. van de Beek is supported by Grants from the European Research Council (ERC Starting Grant [proposal/contract 281156]) and Netherlands Organization for Health Research and Development (ZonMw; NWO-Vidi Grant 2010 [proposal/contract 016.116.358]). S.M. Dorhout Mees, E.A. Oostdijk, W.P. Vandertop, D. Verbaan, G.J.E. Rinkel, W.M. van den Bergh, A.M. de Smet and A. Algra report no conflict of interest.

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