Hyperglycemia and Clinical Outcome in Aneurysmal Subarachnoid Hemorrhage
A Meta-Analysis

Nyika D. Kruyt; Geert Jan Biessels; Rob J. de Haan; Marinus Vermeulen; Gabriel J.E. Rinkel; Bert Coert; Yvo B.W.E.M. Roos

Background and Purpose—Hyperglycemia may worsen outcome after aneurysmal subarachnoid hemorrhage. We performed a systematic review to investigate the relation between admission hyperglycemia and outcome after aneurysmal subarachnoid hemorrhage.

Methods—We included cohort studies or clinical trials of patients with aneurysmal subarachnoid hemorrhage admitted within 72 hours that documented admission glucose levels or the rate of hyperglycemia. Outcome had to be assessed prospectively after 3 or more months. The overall mean glucose level was calculated by weighting for the number of patients included in each study. To calculate the effect size, we pooled the ORs and 95% CIs of poor clinical outcome in patients with or without hyperglycemia.

Results—We searched MEDLINE, EMBASE, Science Citation Index, and the bibliographies of relevant studies. We included 17 studies totaling 4095 patients. The mean admission glucose level was 9.3 mmol/L (range, 7.4 to 10.9 mmol/L; 14 studies, 3373 patients) and the median proportion of patients with hyperglycemia was 69% (range, 29 to 100; 16 studies, 3995 patients; cutoff levels of hyperglycemia, 5.7 to 12.0 mmol/L). The pooled OR (8 studies, 2164 patients) for poor outcome associated with hyperglycemia was 3.1 (95% CI, 2.3 to 4.3). Cutoff points for defining hyperglycemia varied across studies (6.4 to 11.1 mmol/L), but this had no clear effect on the observed OR for poor outcome.

Conclusions—After aneurysmal subarachnoid hemorrhage, admission glucose levels are often high and hyperglycemia is associated with an increased risk of poor clinical outcome. A randomized clinical trial is warranted to study the potential benefit of glycemic control after aneurysmal subarachnoid hemorrhage. (Stroke. 2009;40:e424-e430.)

Key Words: clinical outcome • glucose • hyperglycemia • subarachnoid hemorrhage

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating disease with a high case fatality and morbidity.1–3 Clinical outcome depends on the severity of the initial hemorrhage, but complications such as recurrent bleeding, secondary ischemia, hydrocephalus or general medical complications also play an important role in clinical outcome.4–7 Analysis of risk factors for primary and secondary damage, especially if these can be modified, is important because this has the potential to improve treatment.

Hyperglycemia is a frequent finding in critically ill patients admitted to the intensive care unit and is associated with poor clinical outcome.8 Randomized clinical trials have shown that tight glycemic control improves outcome in these patients,9,10 and today, this treatment is implemented in many intensive care unit facilities. Also, in patients with neurological emergencies such as ischemic stroke or primary intracerebral hemorrhage, levels of glucose are often high and hyperglycemia is associated with an increased case fatality. There are as yet no randomized clinical trials that favor tight glycemic control after ischemic stroke,11,12 but further trials investigating this treatment are currently in progress.13 Meanwhile, guidelines for the management of ischemic stroke do recommend treatment of hyperglycemia.14,15

Aneurysmal SAH, hyperglycemia was reported as early as 192516 and has also been associated with poor clinical outcome.17–24 Despite this observation, this association was never systematically investigated. Importantly, as can be seen from recent reviews and current guidelines, this potentially modifiable factor is not widely considered as a risk factor for poor outcome after aneurysmal SAH.1,3,6,25 We therefore decided to perform a systematic review to investigate mean levels of admission glucose in patients with an
aneurysmal SAH and to assess the strength of the association between admission hyperglycemia and clinical outcome.

**Methods**

**Selection of Studies**

Two reviewers (N.D.K., Y.B.W.E.M.R.) performed an independent computerized MEDLINE and EMBASE search of published studies (MEDLINE: 1966 to April 2008; EMBASE: 1980 to April 2008) written in English, German, French, or Spanish. One researcher (N.D.K.) was supported by a clinical librarian experienced in literature searching. We searched by subject headings “blood glucose” and “subarachnoid hemorrhage” truncated text words “hyperglycemia,” “glucose,” “subarachnoid,” “SAH,” “hemorrhage,” and “bleeding.” Additionally, experts in the field were contacted to identify any further citations. Full-text versions were obtained from all studies that were considered to be potentially relevant by one or both reviewers. After a first selection, the bibliographies of all relevant studies were searched manually for additional studies and this method of crosschecking was continued until no further publications were found. Finally, we performed a computerized search of the Science Citation Index from 1988 to April 2008 to retrieve studies citing any of the included studies. Any disagreement between the reviewers on whether an article had to be included was resolved by consensus or arbitration by a third author (M.V.).

Cohort studies were reviewed with the aim of the STrengthening the Reporting of OBServational studies in Epidemiology (STROBE) statement and had to comply with the following inclusion criteria: (1) original data report on an inception cohort or a clinical trial; (2) the diagnosis of SAH had to be made by the presence of extravasated blood in the basal cisterns on a CT scan, or, if the CT scan was negative, by xanthochromic cerebrospinal fluid. Patients with perimesencephalic or other nonaneurysmal causes for SAH had to be excluded; (3) admission within 72 hours from ictus; and (4) data available on the mean level of admission glucose or the proportion of patients with hyperglycemia on admission. To be included in the analysis on the association between hyperglycemia and clinical outcome, outcome had to be assessed prospectively with a validated analysis on the association between hyperglycemia and clinical outcome had to be assessed prospectively with a validated scale such as the modified Rankin scale (mRS) or the Glasgow Outcome Scale (GOS). We defined poor clinical outcome as a mRS score ≥4 or a GOS score ≤3 (ie, severe disability) if possible; otherwise, we adopted the definition from each individual study unless poor outcome was defined as death. Outcome had to be assessed ≥3 months after the ictus and in at least 90% of the included patients.

Mean age and clinical condition on admission were extracted because these characteristics are known to be strong predictors of poor clinical outcome. We adapted the definition used by each individual study to distinguish “good” and “poor” clinical condition on admission.

If a article complied with the inclusion criteria but lacked information on parameters for analysis, or when outcomes were reported but not related to hyperglycemia, we approached the authors to obtain these data.

Because studies had to fulfill these strict inclusion criteria, no further formal quality assessment was undertaken.

**Statistical Analysis**

Patient characteristics, mean glucose values, and the rates of hyperglycemia on admission were summarized using descriptive statistics. The weighted mean admission glucose across the studies was calculated as follows. We summed the mean glucose from each separate study multiplied by the number of patients in that study. This sum was then divided by the total number of patients included across all studies.

For the assessment of the strength of the association between admission hyperglycemia and poor clinical outcome, unadjusted ORs were extracted from the individual studies and verified with the raw data if provided or the ORs were calculated directly from the raw data if this was not reported in the text. To generate a summary estimate of the unadjusted OR and the corresponding 95% CI for poor outcome in patients with hyperglycemia compared with patients without hyperglycemia, the unadjusted ORs were pooled using a random effects model (RevMan Version 4.2.10). In subanalysis, we explored if the strength of the association between hyperglycemia and outcome was affected by the cutoff value used to define hyperglycemia. To this end, studies were assigned to either of 2 subgroups, one for studies with cutoff values for hyperglycemia below the median cutoff value across all studies and one for studies with cutoff values above this median.

Publication bias was evaluated using Egger’s bias plot and Egger’s test. Heterogeneity among studies was assessed by the Cochrane’s Q test (significant probability value set at <0.10). The I² value was calculated, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I² values of 25%, 50%, and 75% correspond to cutoff points for low, moderate, and high degrees of heterogeneity.

Finally, a random effect metaregression was performed (STATA Version 10) to estimate the extent to which study characteristics in terms of patients’ mean age and the proportion of patients with a poor clinical condition on admission explain heterogeneity in the size of effect between the studies.

**Results**

**Article Search**

The MEDLINE search yielded 185 citations and the EMBASE search 132 citations. Two additional relevant studies were found by searching the bibliographies. Screening reference lists of major published trials on aneurysmal SAH and a search of the Science Citation Index did not yield any additional studies. After filtering out duplicates, 207 citations remained. After review of the identified studies, 17 studies were included for analyses (Figure 1). Sixteen studies were observational cohort studies and one study was a randomized trial. From the randomized trial, we could use data from both the treatment and control group because no association was found between treatment and outcome (nicardipine versus placebo).

**Baseline Characteristics of Studies, Glucose and Hyperglycemia**

Patients were included within 24 hours in 5, within 48 hours in 3, and within 72 hours in the remaining 9 studies. All studies defined admission glucose as the first random (nonfasting) glucose assessment on admission, and these assessments were used to determine whether a patient was hyperglycemic. One study reported admission glucose to be missing in 1% of the included patients. All other studies reported that there were no missing admission glucose values; in 6 of these studies, the absence of admission glucose was an exclusion criterion.

For calculating the overall mean glucose, 14 of the 17 studies totaling 3373 patients could be included because in 3 studies, overall mean glucose levels were not reported and the authors did not have this information available for us. The weighted mean admission glucose was 9.3 mmol/L (range, 7.4 to 10.9 mmol/L). The median proportion of patients with hyperglycemia was 69% (range, 29 to 100; 16 studies, 3995 patients). The cutoff values used to define hyperglycemia varied considerably from study to study (range, >5.7 to >12.0 mmol/L), but most studies used a cutoff value between >6.0 and >8.0 mol/L (Table). Three
Hyperglycemia and Clinical Outcome

For the analysis of the association between hyperglycemia and clinical outcome, 8 studies including 2164 patients were included. Outcome was assessed after 3 months in 6 and after 6 months in 2 studies. These outcomes were assessed with the GOS in 5 and with the mRS in 3 studies. The proportion of patients with a history of diabetes mellitus (DM) was not always stated (3 studies\textsuperscript{18,40,43}) or patients with DM were excluded (4 studies\textsuperscript{20,21,32,35}). One study reported that 1% had DM. Regarding patient selection, one study only included patients with poor-grade SAH,\textsuperscript{32} and one study included surgically treated patients only.\textsuperscript{40}

Figure 2 shows the (pooled) unadjusted ORs for poor outcome in patients with hyperglycemia compared with patients without hyperglycemia on admission (pooled OR 3.1; 95% CI, 2.3 to 4.3; Cochrane’s Q test: \(P=0.10; \hat{I}^2=41.4\%\)). For studies with a definition of hyperglycemia \(\leq 7.0\) mmol/L, the pooled OR was 3.0 (95% CI, 1.9 to 4.6; Cochrane’s Q test: \(P=0.12; \hat{I}^2=45.4\%\)), and for studies with a definition >7.0 mmol/L, the pooled OR was 3.3 (95% CI, 1.9 to 5.8; Cochrane’s Q test: \(P=0.17; \hat{I}^2=43.6\%\)). Egger’s plot (not presented) and Egger’s test \((P=0.43)\) did not indicate publication bias.

For metaregression analysis, we could extract the mean age in all except one study\textsuperscript{21} (weighted mean, 53.1 years; range, 50.4 to 54.9 years). The proportion of patients with a poor clinical condition on admission was available in all studies (weighted mean, 42%; range, 21% to 100%). The results did not demonstrate significant associations between these study characteristics and the effect of hyperglycemia on outcome \((P>0.60)\).

Discussion

Our meta-analysis shows that after aneurysmal SAH, high levels of blood glucose on admission are a frequent finding and that hyperglycemia on admission is associated with poor clinical outcome. The point estimate of the observed effect size of hyperglycemia on poor clinical outcome is similar to the point estimates of the effect size of hyperglycemia on case fatality in nondiabetic patients with myocardial infarction\textsuperscript{45} or ischemic stroke.\textsuperscript{36}

There are several potential explanations for the high admission glucose levels and the observed association between hyperglycemia on admission and poor outcome in patients with aneurysmal SAH. First, hyperglycemia could be a secondary phenomenon to a transient stress reaction inflicted by the insult. Indeed, previous studies showed that the release of catecholamines and levels of glucose relate to the clinical magnitude of the SAH.\textsuperscript{17–23} Second, hyperglycemia could be part of an acute (ie, not pre-existent) metabolic response arising after the SAH that persists beyond the acute phase. Such a persistent state has been described in other groups of critically ill patients\textsuperscript{47–50} and has been associated with cardiovascular complications and poor clinical outcome.\textsuperscript{50,51} For example, after ischemic stroke, persistent hyperglycemia was associated with infarct expansion and worse clinical outcome.\textsuperscript{52} Indeed, also after aneurysmal SAH, (fasting) glucose values remain high during the clinical course,\textsuperscript{18–20} and persistent abnormalities of glucose metabolism predict the occurrence of vasospasm, secondary ischemia, and poor clinical outcome.\textsuperscript{17,20,24,33}

Third, as is common in ischemic stroke,\textsuperscript{53,54} hyperglycemia could represent pre-existent but previously unrecognized DM or disturbances in glucose metabolism short of DM. As such,
not hyperglycemia in itself, but the underlying, pre-existent metabolic abnormality could lead to a poorer outcome. In contrast to ischemic stroke, however, there appears to be no association between DM and the occurrence of aneurysmal SAH.\textsuperscript{4,55,56} Likewise, the number of patients with unrecognized DM will be relatively low.

Irrespective of its origin, high levels of glucose also could be causally linked with poor clinical outcome. There are several observations in support of this hypothesis. The relation with poor clinical outcome persisted when studies with a high or low median cutoff to define hyperglycemia were combined. This indicates that glucose levels relate to poor clinical outcome independent of the cutoff used to define hyperglycemia. Moreover, although not consistent,\textsuperscript{18,20} multivariate analyses in previous studies have shown that the association between hyperglycemia and poor outcome is independent from other predictors of poor outcome such as age or the severity of the ictus.\textsuperscript{17,21,35,37} Unfortunately, we did not possess individual patient data to include such predictors in our meta-analysis.

Improvement of clinical outcome as reported in randomized controlled trials\textsuperscript{57} that investigated tight glycemic control in surgical patients admitted to an intensive care unit\textsuperscript{58} in medical patients admitted to an intensive care unit treated for more than 2 days,\textsuperscript{10} in patients undergoing coronary artery bypass grafting,\textsuperscript{59} and in patients with myocardial infarction\textsuperscript{60} provide supportive evidence for a causal role of hyperglycemia in poor outcome. However, other randomized controlled trials that investigated the role of tight glycemic control showed neutral results in patients undergoing coronary artery bypass grafting,\textsuperscript{61} in patients with acute myocardial infarction,\textsuperscript{62,63} and in patients with acute stroke (non-SAH).\textsuperscript{12} Therefore, caution is warranted in extrapolating the positive finding of, for instance, patients in the intensive care unit to patients with aneurysmal SAH. Extrapolation of trial results is even more difficult and dangerous because of the significant differences between the treatments used in the trials. With regard to the trial investigating tight glycemic control in patients with stroke (not SAH),\textsuperscript{12} for instance, it was hampered by short treatment duration (24 hours) and poor glycemic control in the treatment group with only a small absolute reduction in blood glucose (0.57 mmol/L).

Unfortunately, most studies included in this review did not provide detailed data on glycemic control; therefore, we could not investigate whether such treatment would alter the association between hyperglycemia and outcome after aneurysmal SAH. To date, one randomized trial has been performed in which was tested whether intensive insulin therapy improves neurological outcome after aneurysmal SAH in patients admitted to an intensive care facility.\textsuperscript{64} Although the results did not favor such treatment, the number of included

### Table. Study Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author</th>
<th>Publication Year</th>
<th>No. of Patients</th>
<th>Time to Inclusion, Hours</th>
<th>Mean Age, Years</th>
<th>Men, %</th>
<th>Mean Glucose, mmol/L</th>
<th>Definition HG, mmol/L</th>
<th>HG, %</th>
<th>Cutoff to Treat HG, mmol/L</th>
<th>Poor Admission Condition, %</th>
<th>Definition of Poor Outcome</th>
<th>Time to Outcome Assessment, Months</th>
<th>Poor Outcome, %</th>
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<tr>
<td>Lanzino\textsuperscript{17}</td>
<td>1993</td>
<td>593</td>
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<td>NR</td>
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<td>9.3</td>
<td>&gt;6.7</td>
<td>83</td>
<td>NR</td>
<td>21</td>
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<td>≥3</td>
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<tr>
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<td>1993</td>
<td>99</td>
<td>&lt;72</td>
<td>50.4</td>
<td>32</td>
<td>10.7</td>
<td>&gt;9.0</td>
<td>67</td>
<td>NR</td>
<td>100</td>
<td>GOS &lt;4</td>
<td>≥6</td>
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<tr>
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<td>103</td>
<td>&lt;72</td>
<td>55.0</td>
<td>37</td>
<td>10.8</td>
<td>&gt;11.1</td>
<td>66</td>
<td>NR</td>
<td>67</td>
<td>GOS &lt;4</td>
<td>≥3</td>
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<td>2006</td>
<td>46</td>
<td>&lt;72</td>
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<td>9.5</td>
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<td>77</td>
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<td>47.0</td>
<td>47</td>
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<td>NR</td>
<td>54</td>
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<td>202</td>
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<td>58.0</td>
<td>38</td>
<td>12.7</td>
<td>&gt;6.7</td>
<td>97</td>
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<td>Frontera\textsuperscript{16}§</td>
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<td>281</td>
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</tr>
</tbody>
</table>

\*For studies included in the analysis with outcome.
\†For all studies.
\‡Only patients with poor-grade SAH were included.
\§Additional data were provided by the authors.
HG indicates hyperglycemia; NR, not reported.
patients was too small (N=78) to reliably assess effects on clinical outcome.

Our study has some limitations that need to be addressed. First, although we used strict inclusion criteria, the quality of the studies can vary from study to study and research questions were retrospectively established in some studies. Extrapolation of these data should therefore be done with caution, although the presented results show that the relation between hyperglycemia and poor outcome after SAH is robust and consistent. Second, although not statistically significant, there was moderate between-study heterogeneity. Our metaregression, however, did not show evidence that this heterogeneity could be explained by study characteristics with regard to patients’ age and clinical condition at admission. However, this analysis on heterogeneity was based on a small number of studies and a limited available set of possible effect modifiers.

It should be emphasized that it remains unclear whether hyperglycemia on admission is causally related to poor clinical outcome after aneurysmal SAH. Although the current article only investigated the association between admission hyperglycemia and clinical outcome, in previous studies, we20 and others17,19,24,33 showed already that persistent hyperglycemia throughout the clinical course is an even stronger predictor of poor outcome after SAH. With this in mind, the presented results provide sufficient support to justify a large-scale randomized controlled trials to determine whether glucose-lowering during the acute and subacute phases is beneficial in patients with aneurysmal SAH.

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Disclosures

None.

References


Table 2. Pooled analyses on poor outcome associated with admission hyperglycemia in patients with aneurysmal SAH. Included studies were subdivided according to the cutoff value used in each individual study to define hyperglycemia into studies with a definition of hyperglycemia ≤7.0 mmol/L or >7.0 mmol/L.


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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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