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ORIGINAL ARTICLE

Clinical response following hypertension induction for clinical delayed cerebral ischemia following subarachnoid hemorrhage: A retrospective, multicenter, cohort study

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Abstract

Background: Hypertension induction (HTI) is often used for treating delayed cerebral ischemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH); however, high-quality studies on its efficacy are lacking. We studied immediate and 3–/6-month clinical efficacy of HTI in aSAH patients with clinical DCI.

Methods: A retrospective, multicenter, comparative, observational cohort study in aSAH patients with clinical deterioration due to DCI, admitted to three tertiary referral hospitals in the Netherlands from 2015 to 2019. Two hospitals used a strategy of HTI (HTI group) and one hospital had no such strategy (control group). We calculated adjusted relative risks (aRR) using Poisson regression analyses for the two primary (clinical improvement of DCI symptoms at days 1 and 5 after DCI onset) and secondary outcomes (DCI-related cerebral infarction, in-hospital mortality, and poor clinical outcome [modified Rankin Scale 4–6] assessed at 3 or 6 months), using the intention-to-treat principle. We also performed as-treated and per-protocol analyses.

Results: The aRR for clinical improvement on day 1 after DCI in the HTI group was 1.63 (95% CI 1.17–2.27) and at day 5 after DCI 1.04 (95% CI 0.84–1.29). Secondary outcomes

were comparable between the groups. The as-treated and per-protocol analyses yielded similar results.

Conclusions: No clinical benefit of HTI is observed 5 days after DCI due to spontaneous reversal of DCI symptoms in patients treated without HTI. The 3–/6-month clinical outcome was similar for both groups. Therefore, these data suggest that one may consider to not apply HTI in aSAH patients with clinical DCI.

KEYWORDS
aneurysmal subarachnoid hemorrhage, delayed cerebral ischemia, hypertension induction, intracranial vasospasm

INTRODUCTION

In patients with aneurysmal subarachnoid hemorrhage (aSAH), delayed cerebral ischemia (DCI) is an important cause of disability and death [1–3]. Therapeutic treatment options for DCI are directed at restoration of cerebral perfusion to prevent irreversible brain damage. The most frequently applied treatment is hypertension induction (HTI) [4, 5], which is mainly based on findings from uncontrolled studies [6]. Clinical improvement following HTI ranges from 50% to 100%, where some studies anecdotally report fluctuations in neurological deficits closely related to changes in mean arterial blood pressure (MAP) [7, 8]. Some guidelines consider the available literature to be convincing proof of efficacy and recommend HTI [9, 10], whereas other guidelines refrain from this recommendation based on the absence of high-level evidence and the presence of reports on serious complications [11–13].

The HIMALAIA trial, the first and only randomized controlled trial (RCT) on the efficacy of HTI, showed no effect of HTI on 3-month clinical outcome. However, the HIMALAIA trial was underpowered for clinical outcome analysis, as it was stopped prematurely due to slow recruitment and lack of efficacy on cerebral blood flow [13]. Consequently, as the conduction of an RCT on this matter has now been proven to be difficult, research is likely limited to observational studies.

AIMS

The main objective of the present observational study was to evaluate whether a strategy of HTI is associated with clinical improvement in patients with clinical deterioration due to DCI (clinical DCI), assessed on days 1 and 5 after DCI onset and 3–/6-month clinical outcome, assessed by the modified Rankin Scale (mRS) score.

PATIENTS AND METHODS

Design

This retrospective, multicenter, comparative, observational, cohort study included consecutive aSAH patients admitted between 2015 and 2019 to the Amsterdam University Medical Center (Amsterdam UMC), University Medical Center Utrecht (UMCU), and Haaglanden Medical Center (HMC) who had clinical DCI. All three centers are large, tertiary SAH treatment centers that treat more than 100 SAH patients per year. The institutional review board of Amsterdam UMC reviewed the present study and granted a waiver of informed consent due to the retrospective nature of the study (W19_476 #19.550), with which the institutional review boards of UMCU and HMC agreed. The results of this study are reported according to the STROBE guidelines [14].

Patients

We used the institutional prospective SAH registries of Amsterdam UMC and UMCU to select aSAH patients with clinical DCI. For HMC, patients with DCI were identified retrospectively. Inclusion and exclusion criteria are listed in Table 1. In case of ambivalence, an expert opinion was made by another author (D.V., M.D.I.V., P.V.).

Intervention

Amsterdam UMC and HMC use a strategy of HTI as treatment of DCI (HTI group), whereas UMCU does not (control group).

At Amsterdam UMC and HMC, treatment of DCI includes maintaining normovolemia and vasopressor-induced (usually noradrenalin) augmentation of blood pressure in the intensive care unit (ICU). The initial target MAP is usually set at approximately 10–20 mmHg above the MAP measured at DCI onset, after which the target MAP is titrated to clinical response. The upper limit for the target MAP is generally set at 120 mmHg to avoid systemic complications. In case of clinical improvement, the target MAP is maintained for at least 24 h, after which the vasopressor is gradually tapered. In case of relapsing DCI symptoms during vasopressor tapering, the abovementioned process of HTI is repeated. In patients who reach maximum MAP values without clinical improvement, vasopressor is also gradually tapered. At UMCU, treatment of DCI includes immediate infusion of 500 mL isotonic crystalloids, followed by maintenance of normovolemia and preventing hypotension (MAP > 80 mmHg) by using isotonic infusion and, rarely, additional vasopressors.

TABLE 1 Study inclusion and exclusion criteria.

Inclusion criteria	
1	18 years or older
2	Computed tomography (CT)-confirmed subarachnoid hemorrhage (SAH) with evidence of a causative aneurysm on CT angiography or digital subtraction angiography
3	Clinical deterioration due to delayed cerebral ischemia (DCI), which was defined based on a previously published consensus statement as the occurrence of focal neurological impairment or a decrease in consciousness of at least two points on the Glasgow Coma Score (GCS) scale, which lasts for at least 1 hour and cannot be attributed to any other cause [15]
Exclusion criteria	
1	Clinical deterioration due to DCI before obliteration of the ruptured aneurysm
2	Signs of DCI on imaging without clinical symptoms of DCI (i.e., radiological DCI)
3	Clinical symptoms suggestive of DCI, though not meeting the aforementioned definition of DCI
4	Application of any other DCI treatment strategy than hypertension induction (HTI)

Note: Patients with second-tier DCI treatment in addition to HTI were not included in the main analyses but were used for the sensitivity analyses.

At HMC, second-tier treatments (e.g., intra-arterial nimodipine or vessel expansion by balloon angioplasty or stent retriever devices) may be applied in patients who do not improve clinically following HTI. Amsterdam UMC and UMCU do not apply second-tier DCI treatments.

Furthermore, all three centers treated aSAH patients according to the Dutch SAH guideline, including the enteral administration of nimodipine 60 mg six times daily for 21 days to prevent DCI (more detailed information on general SAH management in Data S1, page 2) [11].

Data collection

We used prospectively collected data from the SAH registries of Amsterdam UMC and UMCU, and retrospectively collected data from HMC. We collected baseline characteristics, common SAH-related complications (definitions in Data S1, page 1), DCI-specific and HTI-related data (listed in Data S1, page 2), length of stay, in-hospital mortality, and clinical outcome as assessed by the mRS score at 3 or 6 months after aSAH. Characterization of DCI symptoms and potential adverse events were based on the clinical entries of the neurological and neurosurgical physicians. In case of scarce reporting, clinical records of other specialties were searched for additional information. We used the prospectively, routinely, and blindly assessed mRS scores of the ULTRA trial, a multicenter RCT with clinical outcome at 6 months as primary outcome, in which all three centers participated [16]. Additionally, we used the mRS scores obtained from the SAH registries, which were assessed by trained physicians or nurses, using a structured interview at 3 (UMCU) or 6 months (Amsterdam UMC) after aSAH (3–/6-month clinical outcome) [17]. HMC did not obtain mRS scores via structured interviews.

Outcome measurements

The two primary outcomes of this study are the clinical response on days 1 and 5 after DCI. Two authors (B.A.C., F.W.A.H.), blinded for the patients' hospital and treatment given, independently assessed whether the neurological status of the patient on days 1 and 5 after DCI onset was clinically improved, stable, or further deteriorated, compared to neurological status at DCI onset, using the Glasgow Coma Score (GCS) scale and physician notes on neurological status. Discrepant assessments were independently scored by a third author (W.P.V.), unaware of the assessments of the previous two authors and also blinded for the patients' hospital. Discrepant assessments were considered solved if two of three authors scored in accordance; if all three scored differently, the collected neurological information was deemed insufficient for clinical response assessment and the response was recorded as 'unknown'. Finally, the clinical response was dichotomized into 'improvement' and 'no improvement' (stable condition and further deterioration combined).

Secondary outcomes included cerebral infarction due to DCI on available CT/MRI within 6 weeks of DCI onset (not routinely assessed), in-hospital mortality, and poor outcome (defined as mRS 4–6) at 6 months (ULTRA trial mRS scores). As research has shown that most SAH patients have reached a relatively stable clinical status after 3 months [18], we additionally used the pooled mRS scores obtained at 3 or 6 months from the UMCU and Amsterdam UMC SAH registries as an additional secondary outcome.

Statistical analysis

Data were primarily analysed according to the intention-to-treat principle in which patients admitted to a hospital using a strategy of HTI are considered the HTI group and patients admitted to a hospital without such a strategy are considered the control group, irrespective of actual application of HTI.

Data were reported as means with standard deviations (SD), medians with interquartile range (IQR), or percentages. Normality of data was explored by a normal Q-Q plot and tested by the Shapiro–Wilk test (threshold 0.9). Differences in baseline characteristics

between treatment groups were analyzed using the independent *t*-test, Fisher's exact test (2×2 table), chi-square test (*n*×2 table), or Mann–Whitney U test, depending on the distribution of the data. The mean hourly MAP values during the first 24 h after DCI onset were compared using a linear mixed-effect model with random intercept. To evaluate the timing of treatment effect (i.e., the time point after DCI onset with significantly different MAP values between treatment groups) we also compared the mean MAP values for each hour separately. For primary outcomes and secondary outcomes, we calculated relative risks (RR) with 95% confidence intervals (CI) using a Poisson regression model with robust error variance [19], including clinical response as dependent variable and HTI treatment as independent variable. Adjusted relative risks (aRR) were calculated for the two primary outcomes with adjustments for several predefined variables known to increase the probability of poor outcome: age, World Federation of Neurological Surgeons (WFNS) grade, and Fisher scale, and significantly differing baseline characteristics. To assess the overall efficacy of HTI treatment, we additionally compared the proportion of patients with clinical improvement on both days 1 and 5 between the treatment groups. As-treated and per-protocol analyses (definitions in Data S1, page 1) were performed for the primary and secondary outcomes. Since patients who are considered for second-tier DCI treatments often comprise patients without clinical improvement following HTI, the results of our main analyses may be misled by exclusion of these patients. Therefore, a sensitivity analysis was performed for the primary and secondary outcomes, including the initial cohort and patients who received second-tier DCI treatments.

Statistical analyses were performed using SPSS Statistics Software version 24 (IBM Corporation, New York, NY, USA). Significance was set at the $p<0.05$ level for all analyses. Missing data were handled using a pairwise deletion method.

RESULTS

From 1659 SAH patients, admitted to three hospitals between 2015 and 2019, we identified 206 (12%) aSAH patients who met the inclusion criteria (Figure 1). Ten patients were excluded because they received second-tier DCI treatment ($n=1$ balloon angioplasty, $n=4$ temporary stenting, $n=9$ intra-arterial nimodipine; some patients had more than one second-tier treatment) and were selected for the sensitivity analyses. Of the included patients, 104 patients participated in the ULTRA trial. The HTI group comprised 130 and the control group 76 DCI patients. The two groups did not differ in age, gender, WFNS grade, and Fisher grade (Table 2). The onset of DCI was at a mean of 7.3 days (SD 3.8) after aSAH ictus.

In the control group, one (1%) DCI patient was treated with noradrenalin following DCI onset in order to maintain normotension. In the HTI group, actual HTI was applied in 127 of 130 (99%) patients using noradrenalin in 121 (93%) patients (Figure 1). The mean MAP at DCI onset was 98 mmHg (SD 17) in the HTI group and 106 mmHg (SD 15) in the control group ($p=0.004$). The HTI group had a median target MAP of 120 mmHg (IQR 110–120, $n=126$), which was a mean 17 mmHg (SD 13, $n=121$) higher than the MAP at DCI onset. Noradrenalin was administered at a median of 5.8 (IQR 3.4–11.6) hours after DCI onset. The linear mixed-effect model showed a significant larger increase in MAP values during the first 24 h after DCI in the HTI group ($p=0.02$). Comparison of MAP values for each hour separately showed significantly higher MAP values at 8, 12, 16, 18, and 23 h after DCI in the HTI group (Figure 2). Noradrenalin was continued for a median of 4.3 days (IQR 2.4–7.0). HTI was discontinued in seven patients (5%) because of persistent electrocardiogram (ECG) changes indicative of cardiac ischemia ($n=4$), progressive heart failure ($n=1$), rebleeding ($n=1$), and excessive urine production ($n=1$).

Two independent assessors, blinded for patients' hospital and treatment, assessed 399 of 412 clinical response assessments in 206 patients ($n=13$ insufficient data available from clinical records). The assessors disagreed on clinical response in 65 of 399 (16%) assessments, after which the third independent and blinded assessor was consulted. Clinical response at day 1 following DCI onset was obtained in 197 of 206 (96%; $n=7$ insufficient available data from clinical records, $n=2$ scored differently by all three assessors) and at day 5 in 195 (95%; $n=6$ insufficient available data from clinical records, $n=5$ scored differently by all three assessors). At day 1 after DCI, 103 of 197 (52%) patients had clinical improvement of DCI symptoms. In the HTI group, 75 of 126 (60%) patients improved clinically, whereas in the control group 28 of 71 (39%) patients improved clinically (RR 1.51, 95% CI 1.09–2.08; Figure 3a). After adjustment for age, WFNS grade, Fisher grade, and aneurysm treatment modality, the aRR was 1.63 (95% CI 1.17–2.27) ($n=196$). At day 5 after DCI, 130 of 195 (67%) patients had clinical improvement of DCI symptoms. In the HTI group, 85 of 126 (67%) patients had clinical improvement, and in the control group 45 of 69 (65%; RR 1.03, 95% CI 0.84–1.28; Figure 3b). After adjustment for age, WFNS grade, Fisher grade, and aneurysm treatment modality, the aRR was 1.04 (95% CI 0.84–1.29) ($n=194$). Clinical improvement on both days occurred in 71 of 134 (53%) patients in the HTI group compared to 27 of 65 (42%) in the control group (RR 1.28, 95% CI 0.92–1.77; aRR 1.36, 95% CI 0.97–1.91). Proportions of cerebral infarction due to DCI, in-hospital mortality, and poor outcome at follow-up were comparable for both groups (Table 3). The as-treated and per-protocol analyses yielded similar results for the primary outcomes (as-treated analyses aRR day 1 after DCI: 1.71, 95% CI 1.27–2.28, day 5: 1.10, 95% CI 0.89–1.37; per-protocol analyses aRR day 1 after DCI: 1.64, 95% CI 1.18–2.28, day 5: 1.05, 95% CI 0.85–1.29; Data S1: Figures S1 and S2) and secondary outcomes (Data S1: Tables S1 and S2). The sensitivity analyses also yielded similar results for the primary and secondary outcomes (Data S1: Table S3).

DISCUSSION

Our study in aSAH patients with clinical DCI shows that HTI results in a higher proportion of clinical improvement at day 1 after DCI; however, due to the spontaneous reversal of DCI symptoms in

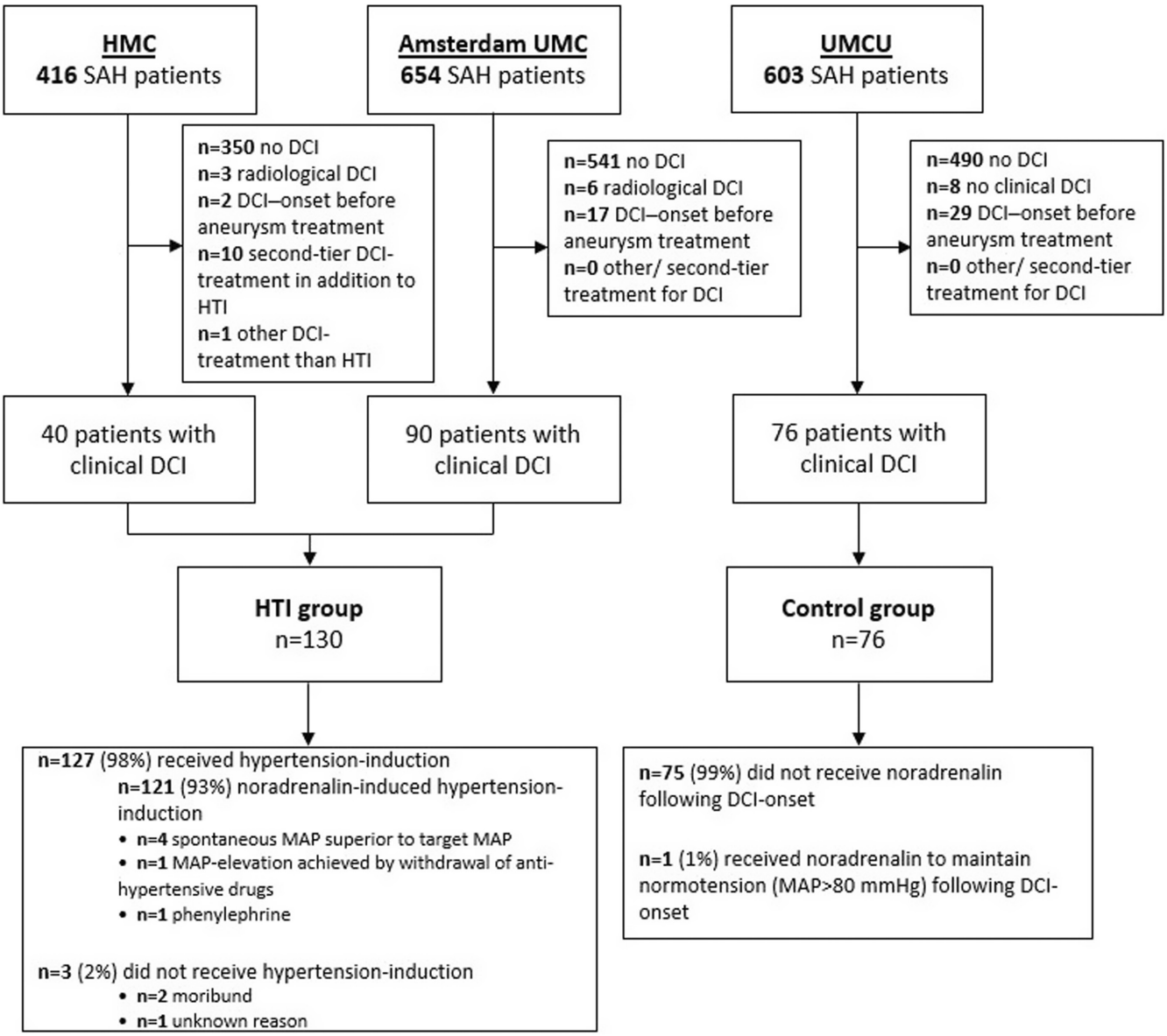

FIGURE 1 Flow chart of the selection procedure. DCI, delayed cerebral ischemia; HMC, Haaglanden Medical Center; HTI, hypertension induction; MAP, mean arterial blood pressure; SAH, subarachnoid hemorrhage; Amsterdam UMC, University Medical Centers; UMCU, University Medical Center Utrecht.

patients without HTI, no clinical benefit of HTI is observed at 5 days and 3 or 6 months after DCI. These results may explain current clinical equipoise, as the higher proportion of clinical improvement in patients treated with HTI on day 1 after DCI supports the anecdotal reports and clinical experience of "HTI believers", while the lack of long-term clinical benefit supports the opinion of "HTI disbelievers".

Former anecdotal success stories on reversal of DCI symptoms after application of HTI have resulted in worldwide application [4, 5] however, a beneficial effect on clinical outcome has never been shown by high-evidence controlled studies [13]. The HIMALAIA trial ($n=41$ participants), designed to elucidate this matter, was stopped prematurely due to too slow recruitment and a lack of effect on cerebral perfusion [20], and therefore was underpowered for primary outcome analysis on clinical outcome (aRR 1.0, 95% CI 0.6–1.8). Notably, serious adverse events occurred more often in patients treated with HTI (HTI group: 52%, control group: 25%) [13]. The results of the HIMALAIA trial were published including a systematic review, which showed no previous controlled studies on clinical efficacy and a high frequency of serious complications (2%–49%) in uncontrolled studies. We updated their search yielding 220 new studies, of which one study compared clinical outcome in DCI patients with and without HTI. This retrospective, comparative study showed that, in a subgroup of SAH patients without cerebral infarction at time of DCI onset, HTI reduced the occurrence of cerebral infarction and prevented poor clinical outcome [21].

In our study, HTI effectively increased the MAP and clinical improvement at day 1 occurred more often in the HTI group, which was quite similar to the results of the HIMALAIA trial. Our study

TABLE 2 Baseline characteristics in 206 patients with aneurysmal subarachnoid hemorrhage and clinical symptoms suggestive of delayed cerebral ischemia, of which 130 patients were admitted to hospitals with a strategy of hypertension induction (HTI) (HTI applied in $n=127$) and 76 patients admitted to a hospital without such a strategy (noradrenalin administered in $n=1$).

Characteristic	HTI group ($n=130$)	Control group ($n=76$)	*P*-value
Age, mean (SD)	55.6 (12.6)	59.0 (13.9)	0.08
Female	99 (76)	58 (76)	1.00
Comorbidities			
Cardiovascular	17 (13)	8 (11)	0.66
Diabetes mellitus	3 (2)	0 (0)	0.30
Hypertension	35 (27)	28 (37)	0.16
Hypercholesterolemia	15 (12)	8 (11)	1.00
Current smoker[a]	64 (52)	34 (56)	0.64
Antithrombotic agents			
Antiplatelet	15 (12)	8 (11)	1.00
Anticoagulation	3 (2)	2 (3)	1.00
Clinical condition on admission[b]			
Good (WFNS grade 1–3)	86 (67)	55 (72)	0.44
Poor (WFNS grade 4–5)	43 (33)	21 (28)	
Amount and distribution of SAH on initial non-contrast CT			
Fisher grade 1–2	5 (4)	1 (1)	0.42
Fisher grade 3–4	125 (96)	75 (99)	
Aneurysm location			
Anterior	110 (85)	64 (84)	1.00
Posterior	20 (15)	12 (16)	
Aneurysm size, mean (SD)	6.8 (3.5)	6.0 (3.0)	0.09
Aneurysm treatment modality			
Microsurgical	26 (20)	30 (40)	0.003
Endovascular	104 (80)	46 (61)	
Complications			
Rebleeding	30 (23)	14 (18)	0.48
Hydrocephalus	87 (67)	40 (53)	0.05
Treatment-related ischemia	11 (9)	13 (17)	0.07
Infective meningitis	18 (14)	6 (8)	0.26
Pneumonia	21 (16)	8 (11)	0.30
Seizures	26 (20)	7 (9)	0.05
Delirium	37 (29)	32 (42)	0.05
Length of stay[c] median (IQR), days	22.0 (18.0–33.0)	19.5 (16.0–27.0)	0.05

Note: 127 of 130 (99%) patients in the HTI group received HTI treatment, 1 of 76 (1%) patients in the control group was treated with noradrenalin to maintain normopressure. Data are numbers with percentages unless otherwise stated.

[a]$n=22$ missing.

[b]$n=1$ missing.

[c]$n=28$ missing.

Abbreviations: CT, computed tomography; HTI, hypertension induction; IQR, interquartile range; SAH, subarachnoid hemorrhage; SD, standard deviation; WFNS, World Federation of Neurological Surgeons.

additionally reports on clinical improvement at day 5. The increase in clinical improvement from day 1 to day 5 in the control group indicates that a substantial proportion of DCI symptoms resolve spontaneously. Since UMCU only uses a strategy of maintaining normovolemia and preventing hypotension, the observed increase in clinical improvement could possibly reflect the natural course of the disease, which suggests that the comparable clinical improvement at day 5 in the HTI group might not be attributable to increases in MAP.

Clinical outcome at 3 or 6 months after aSAH did not differ between our study's treatment groups, which is in line with the

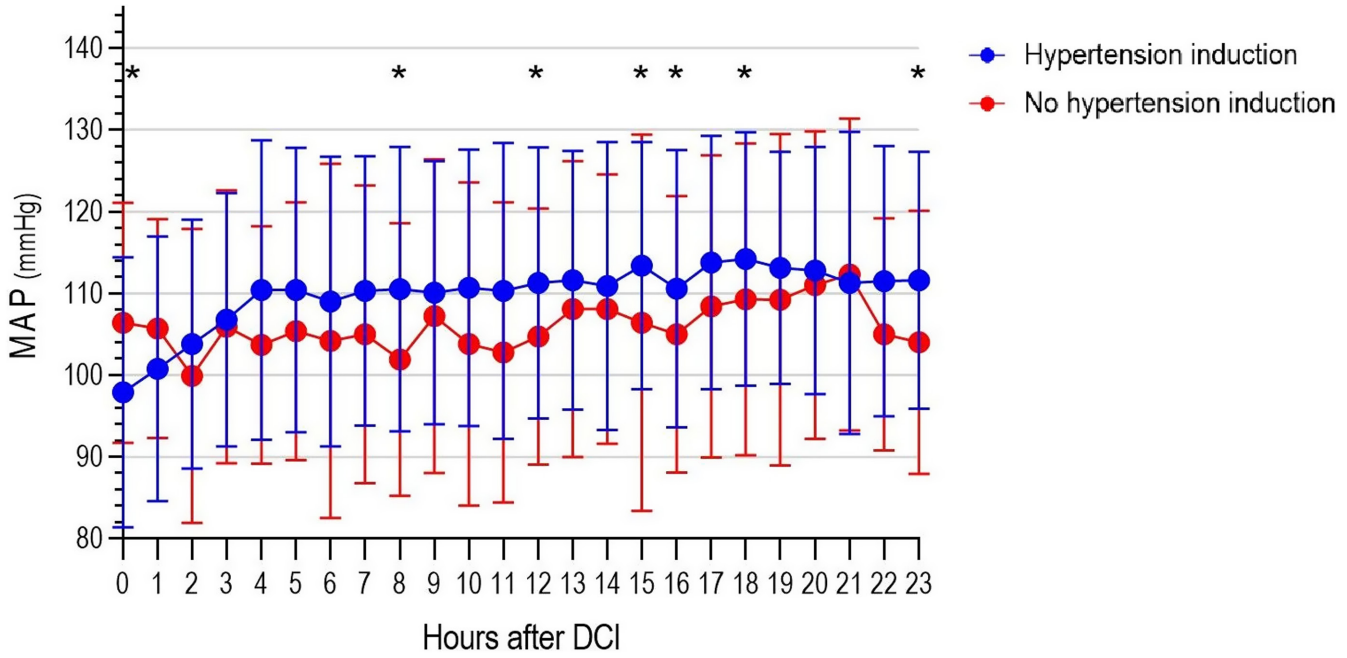

FIGURE 2 Hourly mean arterial blood pressure (MAP) (mean, standard deviation) during the first 24 h after delayed cerebral ischemia (DCI) onset in patients with and without hypertension induction according to the intention-to-treat principle. Asterix indicates significantly different MAP values between the HTI and control group ($p < 0.05$)

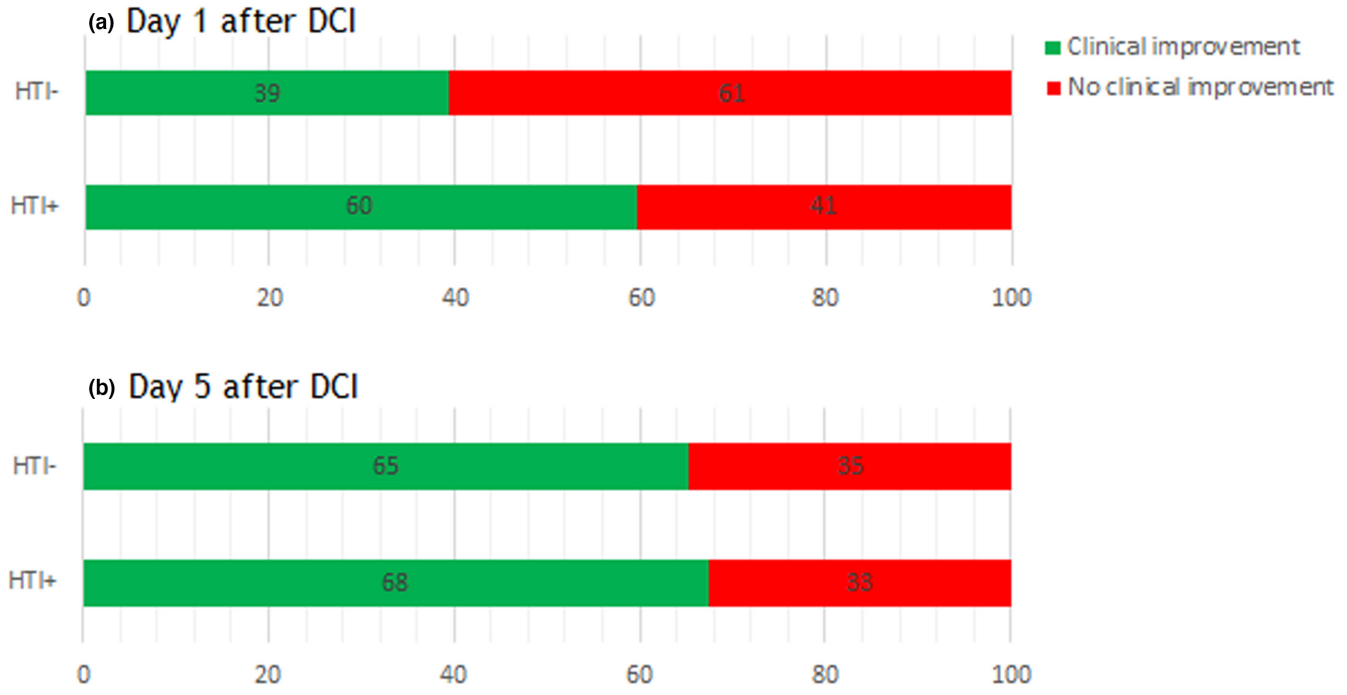

FIGURE 3 Intention-to-treat analyses for clinical response at day 1 (a) and day 5 (b) after delayed cerebral ischemia (DCI) in 197 (a) and 195 (b) patients with aneurysmal subarachnoid hemorrhage and clinical symptoms suspect of DCI. HTI, hypertension induction.

results of the HIMALAIA trial [13]. The results, however, are in contrast to the previously mentioned retrospective, comparative study in patients without cerebral infarction at the time of DCI onset [21]. As all three controlled studies were performed in the Netherlands, in part even using similar hospitals, the studies are unlikely to be subject to large differences in patient management. The combined results question the efficacy of HTI, at least as routine treatment for DCI.

The proportion of patients with clinical DCI seems low in our study (12% of spontaneous SAH patients), which could be explained by strict handling of the clinical definition of DCI, the exclusion of patients with a purely radiological diagnosis of DCI, of those receiving

TABLE 3 Intention-to-treat analyses for secondary outcomes in patients with aneurysmal subarachnoid hemorrhage and clinical delayed cerebral ischemia who were admitted to hospitals with a strategy of hypertension induction ($n=130$) or a hospital without such a strategy ($n=76$).

Secondary outcome	HTI group ($n=130$)	Control group ($n=76$)	RR (95% CI)
Cerebral infarction due to DCI,[a] *n (%)*	48 (38)	31 (42)	0.92 (0.65–1.30)
In-hospital mortality, *n* (%)	16 (12)	12 (16)	0.78 (0.39–1.56)
Poor outcome after 6 months,[b] *n* (%)	34 (39)	7 (44)	0.88 (0.48–1.63)
Poor outcome at follow-up,[c] *n (%)*	34 (40)	23 (32)	1.24 (0.81–1.90)

Note: 127 of 130 (99%) patients in the HTI group received HTI treatment; 1 of 76 (1%) patients in the control group was treated with noradrenalin to maintain normopressure.

[a]Seven missing due no to imaging after DCI onset. In 42 patients imaging was only performed at DCI onset without any later imaging.

[b]Analysis includes patients who participated in the ULTRA trial only ($n=88$ HTI group, $n=16$ control group).

[c]Analysis includes patients of UMCU (mRS at 3 months) and Amsterdam UMC (mRS at 6 months) only ($n=86$ HTI group, $n=72$ control group).

Abbreviations: CI, confidence interval; DCI, delayed cerebral ischemia; HTI, hypertension induction; mRS, modified Rankin Scale; RR, relative risk; UMC University Medical Center; UMCU, University Medical Center Utrecht.

therapeutic DCI treatments other than HTI, and of those with DCI onset prior to aneurysm treatment. Due to the lack of hard diagnostic criteria for DCI, definitions and proportions are known to vary in the literature. Several factors might have negatively affected a potential clinical response to HTI in our study. The MAP values during the first 24 h in the HTI group barely reached 115 mmHg and did not exceed a 10 mmHg difference when compared to the control group. In addition, the median time interval between DCI onset and noradrenalin administration was 5.8 h. Possibly, earlier treatment with increased intensity could have led to a larger number of patients with (perhaps persistent) clinical improvement. In the literature, 75%–100% of clinical improvement following HTI has been reported using noradrenalin, phenylephrine, or dobutamine [7, 22–25]. Most studies lacked details on the exact application and effect (in MAP values) of HTI, which complicates comparison. One study showed that the preferred vasopressor seems to be noradrenalin [23], which we used too. Another study showed clinical improvement in 7/8 (88%) patients and MAP increases of approximately 20 mmHg, compared to approximately 10 mmHg in our study [22]. However, whether the difference in MAP increases is associated with higher improvement rates is unknown. A possible benefit of HTI could be limited to a subgroup of DCI patients with certain patient characteristics, for example, pre-DCI neurological/cardiovascular condition, impaired autoregulation, or altered levels of brain injury, cerebral metabolism, or brain tissue oxygenation markers [21, 24, 26–29].

HTI is known to be associated with serious adverse events, including the occurrence of cardiac arrhythmia, pulmonary edema, hemorrhagic transformation of cerebral infarction, and intracranial (re)bleeding [13]. Other disadvantages of an additional or prolonged admission to an ICU are the higher risk of nosocomial infection and extensive health care costs [30]. Unfortunately, the retrospective design of our study and the difference in intensity of patient monitoring between both groups (ICU vs. neurological/neurosurgical ward) hampered reliable investigation into the occurrence of HTI-related complications. As our study does not show a long-term beneficial effect of HTI, the risk–benefit ratio would likely not have been supportive of HTI.

The lack of proof for the sustained benefit of HTI at day 5 and 6 months after DCI, especially in the presence of multiple reports on associated serious adverse events, should already be reason enough to reconsider HTI as a treatment of DCI. However, the worldwide application and clinical experience of immediate reversal of symptoms once HTI is started likely require more and high-level evidence to induce a paradigm shift, especially if it concerns a relatively young patient with severe neurological deficits. The observed spontaneous reversal of DCI symptoms in patients without HTI should be further investigated. Since conducting an RCT on HTI has proven to be difficult [31], research is likely limited to non-randomized studies. A potential next step may be a prospective, comparative study with standardized clinical outcome and adverse event assessments in hospitals with and without a strategy of HTI. Also, individual patient characteristics that may be associated with clinical response should be evaluated.

Strengths of this study are the blinded clinical improvement assessment, relatively large sample size, and multicenter design. Limitations are the retrospective, non-randomized design of the study, which could introduce selection bias and includes non-standardized treatment and primary outcome assessment [32]. The exclusion of patients with purely radiological DCI (without accompanying symptoms) might have created selection bias towards better-grade aSAH and less severely affected patients, as neurological assessment cannot be performed in unconscious patients. However, the treatment window for ischemic damage in these patients will frequently have elapsed once the radiological appearance of infarction is visible on CT imaging of the brain and radiological DCI is diagnosed. Consequently, in both HTI treatment centers in this study, patients without accompanying symptoms would generally not be considered for HTI. Therefore, exclusion of the patients with radiological DCI will likely not, or negligibly, have influenced the results on the efficacy of HTI. Also, patients who were treated with additional, endovascular, or intra-arterial DCI treatment at the HMC were excluded. As these patients generally are non-responders of HTI, this may also induce selection bias. To overcome this we performed a sensitivity analysis.

Potential confounding by the physician's decision to apply HTI or not was minimized by comparison at the hospital-level. In addition, we performed intention-to-treat, as-treated, and per-protocol analyses. Our primary outcome relies on non-numerical parameters reported in clinical records, which lack standardized clinical assessments and may be subject to scarce reporting by the treating physician. Subtle changes in neurological status are therefore prone to be missed. We unfortunately cannot tell whether this would have led to under- or overestimation of the observed effect. In the future, a prospective study could elucidate this. This study is prone to center-specific subtle differences in SAH care for which we could not correct.

In conclusion, the observed clinical benefit of HTI 1 day after clinical DCI was not sustained due to spontaneous reversal of DCI symptoms in the control group after 5 days. The 3–/6-month clinical outcome of HTI did not differ between the two both groups either. These data, in combination with the results of the HIMALAIA trial, imply that to not apply HTI in aSAH patients with clinical DCI may be considered; however, prospective studies confirming this assumption are desired.

AUTHOR CONTRIBUTIONS

Maud A. Tjerkstra: Conceptualization; investigation; formal analysis; writing – original draft; methodology; visualization; data curation. **Marcella C.A. Müller:** Investigation; data curation; conceptualization. **Bert Coert:** Investigation; data curation. **Friso W.A. Hoefnagels:** Investigation; data curation. **Mervyn D.I. Vergouwen:** Data curation; conceptualization. **Peter van Vliet:** Data curation; conceptualization. **Lizzy Ooms:** Data curation. **Arjen Slooter:** Data curation. **Wouter Moojen:** Data curation. **Korné Jellema:** Data curation. **Dagmar Verbaan:** Conceptualization; methodology; data curation; validation; supervision.

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CONFLICT OF INTEREST STATEMENT

M.C.A.M. reports a payment from Werfen for lectures and participates on the Data Safety Monitoring Board of the PACER trial, platelet transfusion before insertion of central venous catheters. P.V. is a paid lecturer for ICU nurse education at Leiden University Medical Center and has unpaid board membership of MuzIC, a Dutch organization that brings live music into intensive care units. All the other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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