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ORIGINAL RESEARCH

A decrease in blood pressure is associated with unfavorable outcome in patients undergoing thrombectomy under general anesthesia

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ABSTRACT

Background Up to two-thirds of patients are either dependent or dead 3 months after thrombectomy for acute ischemic stroke (AIS). Loss of cerebral autoregulation may render patients with AIS vulnerable to decreases in mean arterial pressure (MAP).

Objective To determine whether a fall in MAP during intervention under general anesthesia (GA) affects functional outcome.

Methods This subgroup analysis included patients from the MR CLEAN trial treated with thrombectomy under GA. The investigated variables were the difference between MAP at baseline and average MAP during GA (ΔMAP) as well as the difference between baseline MAP and the lowest MAP during GA (ΔLMAP). Their association with a shift towards better outcome on the modified Rankin Scale (mRS) after 90 days was determined using ordinal logistic regression with adjustment for prognostic baseline variables.

Results Sixty of the 85 patients treated under GA in MR CLEAN had sufficient anesthetic information available for the analysis. A greater ΔMAP was associated with worse outcome (adjusted common OR (acOR) 0.95 per point mm Hg, 95% CI 0.92 to 0.99). An average MAP during GA 10 mm Hg lower than baseline MAP constituted a 1.67 times lower odds of a shift towards good outcome on the mRS. For ΔLMAP this association was not significant (acOR 0.97 per mm Hg, 95% CI 0.94 to 1.00, p=0.09).

Conclusions A decrease in MAP during intervention under GA compared with baseline is associated with worse outcome.

Trial registration number NTR1804; ISRCTN10888758; post-results.

BACKGROUND

Although the efficacy of mechanical thrombectomy in patients with acute ischemic stroke (AIS) has been proved in multiple studies,[1–7] two out of three treated patients are functionally dependent or dead (score on the modified Rankin Scale (mRS) >2) at 90 days.[3] It is unclear whether the use of general anesthesia (GA) in thrombectomy for AIS interacts with treatment effect. A recent meta-analysis found less favorable outcome in patients treated under GA.[8] In a post hoc analysis of the Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands (MR CLEAN) cohort the significant treatment effect present in the total study population was also found in patients treated under local anesthesia, but not in patients treated under GA.[9]

Blood pressure levels during intervention could influence neurologic outcome in patients treated under GA. The large vessel occlusion required for thrombectomy in AIS that causes an AIS might also cause a loss of cerebral autoregulation.[10] As a result, decreases in mean arterial pressure (MAP) might reduce cerebral blood flow, with subsequent further neurological deterioration.

This study aims to assess the association of a drop in blood pressure during intervention under GA compared with that at baseline with functional outcome in the MR CLEAN study.

METHODS

Patients and data

We performed a post hoc analysis of the MR CLEAN trial. In MR CLEAN, patients were randomized between usual care and usual care with additional IA treatment in those with confirmed proximal anterior circulation AIS. The inclusion and exclusion criteria for the MR CLEAN trial have been reported earlier.[11] The decision about the type of anesthetic management during intervention was left to the discretion of the MR CLEAN centers and treating physicians. However, the majority of centers had a fixed protocol during the trial.[9] No specific recommendations were provided by the steering committee about blood pressure management. Only patients treated under GA had peri-interventional blood pressure measurements available. Patients treated with endovascular therapy under GA were included in this subgroup analysis if their data satisfied the following quality criteria: 1. baseline blood pressure was available; 2. blood pressure data could be read/extracted from the anesthesia report; 3. the induction anesthetic was listed in the report, and; 4. one blood pressure registration had been made every <10 min during anesthesia (one gap of 15 min was allowed). This last interval was chosen as the intervals between the reported blood pressure measurements varied

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greatly between centers: from continuous arterial blood pressure measurements to measurements every 3, 5, or even 8 min.

Baseline data (eg, National Institute of Health Stroke Scale (NIHSS) at presentation, time from onset to randomization, and baseline Alberta Stroke Program Early CT Score (ASPECTS)) were extracted from the MR CLEAN database. The baseline blood pressure was a single brachial measurement at admission to the emergency department at the recruiting center. Specific data concerning the anesthetic management during the intervention were extracted from the available anesthesiology reports. All data from the anesthesiology reports were collected from the start of anesthetic induction until awakening. In cases of prolonged anesthesia after the intervention, data collection stopped at the end of the intervention. Extracted data included the type of induction and maintenance anesthetic, blood pressure levels during the intervention, and use of blood pressure elevating medication (eg, norepinephrine). When both invasive and non-invasive blood pressure measurement was made, invasive measurement was used for data collection as this continuous measure could be more readily extracted at the proposed intervals. When a single systolic or diastolic measurement was missing, the value directly following the missing value was imputed.

From the systolic and diastolic blood pressure measurements (SBP and DBP, respectively), the MAP was calculated using the formula MAP=DBP+1/3(SBP−DBP). As our main measure of blood pressure decrease, we used ΔMAP: the difference between baseline MAP and the average of all MAP values collected during GA at intervals of approximately 10 min. Also, to assess the significance of large, small drops in MAP, ΔLMAP was used: the difference between MAP at baseline and the single lowest MAP during GA (figure 1). To correct for the baseline blood pressure level, both variables were also analyzed as a percentage of MAP at baseline. For all patients included in this analysis, written informed consent from patients or their representatives was obtained before randomization in the MR CLEAN study.

Statistical analyses

Our primary outcome measure is the score on the mRS at 90 days. This scale ranges from 0 ('no symptoms') to 6 ('dead'). Ordinal logistic regression is used to assess the association of the decrease in blood pressure with a shift towards better outcome on the mRS. The mRS was inversely coded (ie, level 0 corresponds to mRS 6) so that a common OR (cOR) below 1 constitutes a drop in blood pressure that is associated with worse functional outcome. To adjust for known baseline prognostic variables as defined in the MR CLEAN protocol,[11] the models include age, the baseline score on the NIHSS, history of atrial fibrillation, history of diabetes mellitus, previous stroke, presence of an internal carotid artery terminus occlusion, and time from onset to randomization.

Anesthetic agents are known to induce varying degrees of systemic hypotension .[12] Therefore, a univariable linear regression analysis was performed to see whether the type of anesthetic (propofol vs others) was associated with ΔMAP. As a longer procedure duration could yield more hypotensive events, its association with ΔMAP was determined in a similar manner. All statistics were performed with R (R foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/; used packages: Ordinal v2015.6-28, http://CRAN.R-project.org/package=ordinal/; Foreign v0.8-63, http://CRAN.R-project.org/package=foreign; Tableone v0.7.3, http://CRAN.R-project.org/package=tableone; ggplot2 v2.2.0, http://CRAN.R-project.org/package=ggplot2).

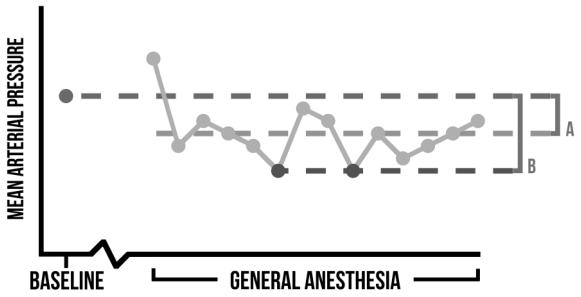

Figure 1 Schematic representation of the used blood pressure variables. The dot top left represents the baseline mean arterial pressure (MAP). Its level is represented by the upper dashed line. The line with dots represents the MAP values measured approximately every 10 min during general anesthesia (GA). Their average value is represented by the middle dashed line. The lowest dots and the lowest dashed line represent the lowest MAP value during GA. A represents the difference between baseline MAP and the average MAP during GA (ΔMAP). B represents the difference between baseline MAP and the lowest MAP during GA (ΔLMAP).

RESULTS

Patients and characteristics

Eighty-five patients underwent endovascular therapy under GA in the MR CLEAN trial. Six of those were converted from local anesthetic management, probably owing to increased movement. For this study, 15 patients were excluded because of partly or completely missing anesthesiology reports. Another 10 patients were excluded because the available data did not meet the predefined quality criteria. The remaining 60 patients were treated in nine different hospitals. Their characteristics are listed in table 1.

Table 1 Patient characteristics

Characteristics	Value
Number of patients	60
Age, median (IQR)	66 (54–76)
Time from onset to randomization (min), median (IQR)	204 (156–262)
Sex, male, n (%)	35 (58.3)
Medical history, n (%)*	
Atrial fibrillation	22 (36.7)
Diabetes mellitus	7 (11.7)
Hypertension	24 (40.0)
Ischemic stroke	12 (20.0)
Myocardial infarction	7 (11.7)
Occlusion location on admission CTA, n (%)	
A2	1 (1.7)
ICA-T	15 (25.0)
M1	39 (65.0)
M2	5 (8.3)
Admission NIHSS, median (IQR)	18 (14–20)
Admission ASPECTS, median (IQR)†	8.0 (7.5–10)
Admission blood pressure values (mm Hg), median (IQR)	
SBP	140 (126–155)
DBP	80 (70–90)
MAP	100 (92–110)

*Percentages may add up to more than 100 owing to comorbidity.
†As one patient had an A2 occlusion, ASPECTS is available for 59 patients.
ASPECTS, Alberta Stroke Program Early CT Score; CTA, CT angiography; DBP, diastolic blood pressure; ICA-T, internal carotid artery terminus; MAP, mean arterial pressure; NIHSS, National Institute of Health Stroke Scale; SBP, systolic blood pressure.

Data concerning anesthetic management are summarized in table 2.

Propofol was used most often to induce anesthesia (n=45, 75%) and sevoflurane was the compound most used to maintain anesthesia (n=40, 66.7%). In four cases midazolam was administered as premedication (dose <5 mg) for induction with propofol (n=3) or propofol and esketamine (n=1), and in one case as inducing anesthetic (9 mg dose) combined with etomidate. Blood pressure elevating medication was administered in 54 of 60 (90%) patients, but there was considerable variation in the type and combination. Thirty-six of the 54 (66.7%) patients received norepinephrine. The median number of blood pressure measurements extracted from the anesthetic data was 11 (IQR 8–13) and the median procedure duration (groin puncture to end of procedure/sheath removal) was 69 min (IQR 47–96, data available for 59 of 60 patients). For four patients it was unclear whether the reported blood pressure was invasively or non-invasively measured, in 11 patients only invasive blood pressure measurements were available, and in 22 only non-invasive brachial measurements. For 23 patients, both non-invasive and invasive measurements were recorded during anesthesia, and measurements were extracted according to our prespecified methodology (ie, invasive when available). The median ΔMAP was 17 mm Hg (IQR 6–28) and ΔLMAP 36 mm Hg (IQR 21–53).

Table 2 Intraprocedural anesthetic data

Anesthetic data	Value
Number of patients	60
Inducing Anesthesia, n (%)*	
Esketamine	1 (1.7)
Etomidate	8 (13.3)
Midazolam	5 (8.3)
Propofol	45 (75.0)
Thiopental	7 (11.7)
Maintenance anesthetic, n (%)*	
None listed	3 (5.0)
Isoflurane	1 (1.7)
Propofol	20 (33.3)
Sevoflurane	40 (66.7)
Type of blood pressure elevating medication administered, n (%)*	
Ephedrine	30 (50.0)
Norepinephrine	36 (60.0)
Phenylephrine	30 (50.0)
None	6 (10.0)
Type of analgesic administered, n (%)*	
Acetominophen	6 (10.0)
Alfentanil	1 (1.7)
Fentanyl	4 (6.7)
Lidocaine	12 (20.0)
Metamizol	1 (1.7)
Morphine	1 (1.7)
Remifentanil	11 (18.3)
Sufentanil	42 (70.0)
None listed	2 (3.3)
Blood pressure values during GA, mm Hg, median (IQR)	
SBP	119 (106–130)
DBP	64 (59–71)
MAP	81 (77–91)
Lowest intraprocedural MAP	60 (55–69)
ΔMAP, median (IQR)	
mm Hg	17 (6.0–28)
as % of admission blood pressure	17 (7.8–26)
ΔLMAP, median (IQR)	
mm Hg	36 (21–53)
as % of admission blood pressure	39 (23–49)

*Percentages may add up to more than 100 owing to combined administration of medication.
DBP, diastolic blood pressure; GA, general anesthesia; MAP, mean arterial pressure; SBP, systolic blood pressure; ΔLMAP, difference between baseline and lowest MAP during GA; ΔMAP, difference between baseline and average MAP during GA.

Blood pressure decrease and outcome

For all patients, their score on the mRS at 90 days and their respective ΔMAP values are summarized in figure 2. The results of the ordinal regression analyses are summarized in table 3.

A greater ΔMAP was associated with worse outcome (adjusted common OR (acOR) 0.95 per point mm Hg decrease, 95% CI 0.92 to 0.99).

This finding shows that for every 10 mm Hg difference between baseline MAP and average MAP during GA the odds of a shift toward better outcome on the mRS are 1.67 times lower. For the ΔLMAP no statistically significant association was found after the adjustment for baseline prognostic variables (acOR 0.97 per mm Hg, 95% CI 0.94 to 1.00, p=0.09). For the adjusted analyses, findings were consistent when the variables were adjusted for the level of baseline MAP by expressing the size of the difference as the percentage of baseline MAP. No significant association was found between the use of propofol as an induction (β=−8.49, 95% CI −18.00 to 1.01) or maintenance (β=−4.98, 95% CI −13.85 to 3.90) anesthetic and ΔMAP. There was also no association between the procedure duration and ΔMAP (β=0.02, 95% CI −0.09 to 0.13).

DISCUSSION

In this post hoc subgroup analysis in patients who received mechanical thrombectomy under GA during the MR CLEAN trial, we found that a decrease in peri-interventional MAP was associated with a worse functional outcome.

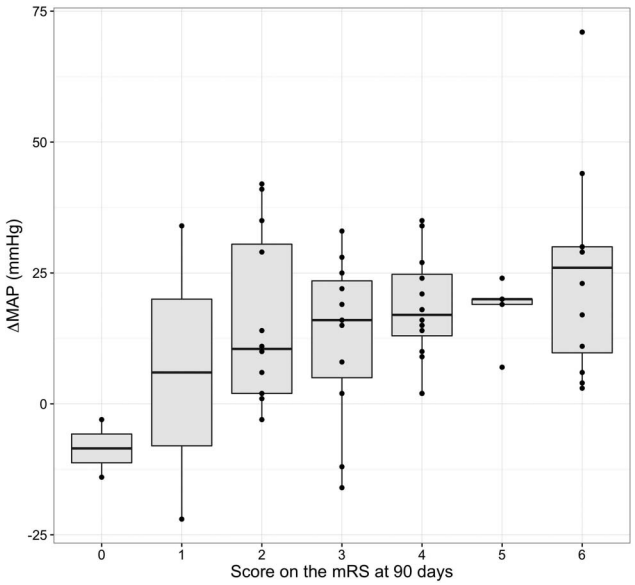

Figure 2 The association of the difference between baseline mean arterial pressure (MAP) and average MAP during GA (ΔMAP) with the score on the modified Rankin Scale (mRS) at 90 days. The dots represent individual patients. The boxes depict the median (black bar) with the IQR.

Table 3 Association of lower blood pressure during general anesthesia compared with baseline with a shift in the direction of better outcome on the modified Rankin Scale (mRS)

	Likelihood of a shift towards better outcome on mRS					
Variables	cOR	95% CI	p Value	acOR	95% CI	p Value
ΔMAP, per unit mm Hg	0.96	0.93 to 0.99	0.01	0.95	0.92 to 0.99	0.01
As percentage of baseline MAP	0.96	0.92 to 0.99	0.01	0.95	0.92 to 0.99	0.01
ΔLMAP, per unit mm Hg	0.97	0.95 to 1.00	0.03	0.97	0.94 to 1.00	0.09
As percentage of baseline MAP	0.97	0.94 to 1.00	0.09	0.98	0.95 to 1.02	0.43

acOR, adjusted common OR (adjusted for age, history of diabetes mellitus, atrial fibrillation and previous stroke, presence of ICA-T occlusion, time from onset to randomization and baseline National Institute of Health Stroke Scale); cOR, common OR; GA, general anesthesia; ICA-T, internal carotid artery terminus; MAP, mean arterial pressure; ΔLMAP, difference between baseline and lowest MAP during GA; ΔMAP, difference between baseline and average MAP during GA.

While anesthetic management during IA therapy for AIS and the role of hemodynamic management therein has been discussed frequently,[8 12–16] few studies have specifically investigated the association of blood pressure with outcome in this setting. Our findings suggest that prolonged episodes of lower MAP compared with baseline during GA are potentially deleterious. Conversely, we found no significant association with outcome of the single largest MAP drop during GA after adjustment. Previous studies examined the occurrence of such single extreme blood pressure values. One did find significant associations with outcome,[17] while others could not.[18 19] Another study investigating both patients under conscious sedation and GA found lower minimum diastolic blood pressures in patients with worse outcome.[20] In a population consisting of both patients treated under GA and local anesthesia, a lowest systolic blood pressure of <140 mm Hg was found to be associated with poor outcome.[21] The Society for Neuroscience in Anesthesiology and Critical Care recommends hemodynamic management with a systolic blood pressure >140 mm Hg.[22] However, in patients with a subarachnoid hemorrhage, who have a similar loss of autoregulation in the brain, no significant association of hypotension with outcome was observed.[23]

As shown in our study, the use of a single extreme blood pressure variable (ie, the lowest MAP during GA) could not reproduce the same association as found when an averaged value of the intraprocedural MAP was used. Other studies also illustrate the dependency of results on the chosen variable.[17 20] Therefore, the equivocal findings in the literature can partly be attributed to severe heterogeneity between studies in the investigated blood pressure variables.

Patients included in this study presented with a median admission systolic blood pressure of 140 mm Hg. Therefore, 50% of included patients had admission blood pressure levels lower than the minimum level recommended by the Society for Neuroscience in Anesthesiology and Critical Care.[22] Blood pressure levels were higher for patients not treated under GA in MR CLEAN (mean systolic blood pressure of 149 mm Hg),[9] or patients in the intervention arm of other trials (median systolic blood pressures of 142–150 mm Hg).[2 4 5] However, these levels are still low in comparison with the finding that 76% of patients with AIS presented with a systolic blood pressure of >140 mm Hg.[24] We have no clear explanation for the low systolic blood pressure observed in this study. However, other baseline characteristics were very similarly distributed in comparison with the intervention arm of MR CLEAN.[3] Also, the majority of MR CLEAN centers had a fixed protocol for the type of anesthetic management used. Blood pressure levels dropped even further during GA in our study. This can probably be attributed to a lack of awareness about the optimal anesthetic management for a treatment that was novel at the time inclusion in the MR CLEAN trial started.

This is the first study to assess the association of the difference between baseline MAP and average MAP during GA with continuous mRS. We specifically chose the MAP instead of the systolic or diastolic blood pressure as we feel it best approximates the perfusion pressure in the brain. As discussed above, the use of average intervention MAP is less prone to be influenced by measurement errors and short MAP fluctuations. Furthermore, the use of continuous mRS is likely to be more detailed than a dichotomized outcome variable as it takes the whole disability scale into account.

The study does have several limitations.

First, as this is a post hoc subgroup analysis, its results should be interpreted with caution, as the original study was not powered for these analyses.

Second, the multicenter design of MR CLEAN resulted in heterogeneous anesthesia data that had to be homogenized to make it suitable for analysis, as well as a large number of missing anesthesiology reports. This consequently led to a high exclusion rate (25 of 85 patients) to satisfy our predefined quality criteria.

Third, as reported earlier and seen in figure 2, only a few patients treated under GA in MR CLEAN were functionally independent after 3 months.[9] Therefore at the lower end of the mRS spectrum only few blood pressure data are available. This also prevented us from determining a reliable estimate of a blood pressure threshold for poor outcome.

Fourth, the baseline blood pressure variable is based on a single measurement and is therefore more prone to measurement error.

Fifth, as blood pressure levels during GA for most patients were lower than the currently advised minimum of 140 mm Hg systolic, it was not possible to examine whether adherence to this minimum blood pressure level was beneficial.[22]

Sixth, while the average MAP during intervention is more precise than a single extreme value, it does not take into account blood pressure variability.

Seventh, the comparison of baseline non-invasively measured blood pressure and intraprocedural invasive blood pressure measurements might have reduced the precision of the study. As shown in a large retrospective study, brachial measurements underestimate hypertensive blood pressure levels and produce higher values at the lower end of the spectrum.[25] As hypertension is common in patients presenting with an AIS,[24] this discrepancy might result in an underestimation of smaller drops in blood pressure in patients in whom intraprocedural invasive blood pressure measurements were extracted. Further, in the patients in whom both invasive and non-invasive measurements

were collected this might have led to imprecise estimation of the true average MAP.

Eighth, patients in this study were not randomized to GA or alternative managements. Thus one cannot exclude the presence of any bias toward worse outcome.

Finally, the small sample size led to the inclusion of more variables in the regression models than the 10 events per variable that rule of thumb would allow. We deviated from this rule of thumb to allow for adequate correction for potential confounders, as was justified by Vittinghoff and McCulloch.[26]

The management of blood pressure is also of great importance for patients not treated under GA. Complex, u-curved relationships with outcome have been observed in patients with AIS, [27 28] illustrating the delicate line between hyperperfusion predisposing to extensive cerebral edema, and hypoperfusion predisposing to infarct growth. Further, falls in blood pressure also seem to predispose to worse outcomes in patients undergoing intervention under conscious sedation.[29] In this light, one might even postulate that the lack of difference in outcome between the GA and conscious sedation groups in the recently published Sedation versus Intubation for Endovascular Stroke TreAtment (SIESTA, NCT02126085) trial can partly be explained by the lack of difference in blood pressure levels between the trial arms.[30]

The SIESTA trial was the first completed trial investigating the place of GA in thrombectomy, and we await the results of at least two more: General Or Local Anesthesia in IA THerapy (GOLIATH, NCT02317237),[31] and Sedation Versus GA for Endovascular Therapy in Acute Stroke—Impact on Neurological Outcome (ANSTROKE, NCT01872884). Post hoc analyses of their prospectively collected blood pressure data would yield more clarity about the association of blood pressure with outcome in and outside of a GA setting, and would provide some necessary guidance to improve outcome for patients with AIS even further.

CONCLUSION

Decreased MAP during intervention under GA compared with baseline is associated with worse outcome. However, prospective and systematically collected data are necessary to confirm this association.

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Contributors KMT collected and cleaned data for this study, wrote the statistical analysis plan, analyzed the data, and drafted and revised the paper. He is guarantor. OAB implemented the MR CLEAN trial in the Netherlands, collected and cleaned the data for the trial and this study, and revised the draft paper. RVI, JV, and VMCW-vdS helped with the collection of data for this study and revised the draft paper. MWH and JMC revised the draft paper. HFL helped with the statistical analysis plan and revised the draft paper. RJvO, WHvZ, DWJD, AvdL and YBWEMR designed the MR CLEAN trial, implemented the trial in the Netherlands, oversaw data collection, and revised the draft paper of this study. HAM helped with the statistical analysis plan and drafted and revised the draft paper. CBLMM designed the MR CLEAN trial, implemented the trial in the Netherlands, oversaw data collection, planned this study, and drafted and revised the paper. The MR CLEAN investigators (listed in the appendix) collected the data for the MR CLEAN trial.

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