Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data

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Summary

Background General anaesthesia (GA) during endovascular thrombectomy has been associated with worse patient outcomes in observational studies compared with patients treated without GA. We assessed functional outcome in ischaemic stroke patients with large vessel anterior circulation occlusion undergoing endovascular thrombectomy under GA, versus thrombectomy not under GA (with or without sedation) versus standard care (ie, no thrombectomy), stratified by the use of GA versus standard care.

Methods For this meta-analysis, patient-level data were pooled from all patients included in randomised trials in PuMed published between Jan 1, 2010, and May 31, 2017, that compared endovascular thrombectomy predominantly done with stent retrievers with standard care in anterior circulation ischaemic stroke patients (HERMES Collaboration). The primary outcome was functional outcome assessed by ordinal analysis of the modified Rankin scale (mRS) at 90 days in the GA and non-GA subgroups of patients treated with endovascular therapy versus those patients treated with standard care, adjusted for baseline prognostic variables. To account for between-trial variance we used mixed-effects modelling with a random effect for trials incorporated in all models. Bias was assessed using the Cochrane method. The meta-analysis was prospectively designed, but not registered.

Findings Seven trials were identified by our search; of 1764 patients included in these trials, 871 were allocated to endovascular thrombectomy and 893 were assigned standard care. After exclusion of 74 patients (72 did not undergo the procedure and two had missing data on anaesthetic strategy), 236 (30%) of 797 patients who had endovascular procedures were treated under GA. At baseline, patients receiving GA were younger and had a shorter delay between stroke onset and randomisation but they had similar pre-treatment clinical severity compared with patients who did not have GA. Endovascular thrombectomy improved functional outcome at 3 months both in patients who had GA (adjusted common odds ratio (cOR) 1·52, 95% CI 1·09–2·11, p=0·014) and in those who did not have GA (adjusted cOR 2·33, 95% CI 1·75–3·10, p<0·0001) versus standard care. However, outcomes were significantly better for patients who did not receive GA versus those who received GA (covariate-adjusted cOR 1·53, 95% CI 1·14–2·04, p=0·0044). The risk of bias and variability between studies was assessed to be low.

Interpretation Worse outcomes after endovascular thrombectomy were associated with GA, after adjustment for baseline prognostic variables. These data support avoidance of GA whenever possible. The procedure did, however, remain effective versus standard care in patients treated under GA, indicating that treatment should not be withheld in those who require anaesthesia for medical reasons.

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Introduction

Multiple observational studies have suggested that, in general, patients treated with endovascular thrombectomy under general anaesthesia (GA) have poorer outcomes than those treated without GA.[1] However, patients with more severe stroke or comorbidities might be more likely to be treated under GA, leading to the potential for confounding by indication. In MR CLEAN, sites specified their anaesthetic strategy prospectively and analysis of that trial found that the beneficial treatment effect of thrombectomy became non-significant in patients treated under GA.[2] These results could lead to a reluctance to convert from an awake procedure to GA in cases where patient agitation or challenging vascular anatomy are preventing optimal revascularisation. By contrast, three small single-centre randomised trials that

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Research in context

Evidence before this study

We searched PubMed for studies in any language examining the association of general anaesthesia (GA) with outcome in stroke patients undergoing endovascular thrombectomy between Jan 1, 2010, and May 31, 2017, using one of the terms "general anesthesia" OR "anesthetic" OR "sedation" with "thrombectomy". Multiple observational studies showed a worse outcome in patients treated under GA compared with patients who were not treated under GA. Individual randomised trials of thrombectomy versus standard care found conflicting results on the effect of GA, varying between abolition of the thrombectomy treatment effect in MR CLEAN and no effect in THRACE. Three single-centre randomised trials of GA versus conscious sedation found either no difference in functional outcome between groups or a slight benefit of GA.

Added value of this study

To our knowledge, these data from contemporary, high-quality randomised trials form the largest study to date of the association between GA and the benefit of endovascular thrombectomy versus standard care. We found that GA for endovascular thrombectomy, as practised in contemporary clinical care across a wide range of expert centres during the randomised trials, was associated with a worse outcome than that seen when avoiding GA, independent of patient comorbidities. Patients still benefited from thrombectomy compared with standard care when treated under GA.

Implications of all the available evidence

The requirement for GA when the airway is compromised or the patient is agitated, which threatens the quality of revascularisation, should not deter clinicians from pursuing endovascular thrombectomy. The contrast between this analysis and the recent randomised trials comparing GA with conscious sedation suggests that, when GA is medically necessary, close attention should be paid to minimising anaesthetic delays to commence the procedure and maintaining physiological parameters such as blood pressure. A multicentre randomised trial to definitively address these issues is warranted.

compared GA, which was done in accordance with strict protocols to maintain blood pressure, with conscious sedation, which made use of the same anaesthetic drugs at lower doses without intubation, did not detect a signal of harm, and functional independence was either no different or slightly increased in the patients who had GA.[3–5] We analysed the pooled individual patient data from all randomised trials of stent retriever thrombectomy versus standard care. Our aim was to assess the influence of anaesthetic strategy on the treatment benefit of endovascular thrombectomy in broader contemporary practice.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched PubMed for randomised trials published in any language between Jan 1, 2010, and May 31, 2017, comparing endovascular thrombectomy that was predominantly performed with stent-retrievers versus standard care in patients with anterior circulation ischaemic stroke. The PubMed search string was (("randomized controlled trial" [Publication Type]) AND ((thrombectomy[Title/Abstract]) OR (clot retrieval[Title/Abstract]) OR intra-arterial[Title/Abstract]) AND (stroke[Title/Abstract])). The highly effective reperfusion using multiple endovascular devices (HERMES) collaboration[6] pooled individual patient data from the MR CLEAN,[7] ESCAPE,[8] EXTEND-IA,[9] SWIFT PRIME,[10] REVASCAT,[11] PISTE,[12] and THRACE[13] trials. The HERMES executive committee (comprising representatives of each trial) confirmed that all eligible trials were included and contributed their trial data. There were no conflicts over study inclusion. SBro oversaw the creation of the unified database. All participants provided informed consent according to each trial protocol and each study was approved by the local ethics board. The meta-analysis was prospectively designed by the HERMES executive committee, but not registered, and the protocol is available in the appendix.

Data analysis

Data were contributed by the authors of all the trials meeting eligibility criteria and collated by independent statisticians. All data relevant to the analyses presented were part of each study's individual design and data collection and are part of the general HERMES database. No standardisation or translation of the fields used for analysis and reporting was necessary. After collation of data, key fields were compared with original results, including published data. No major discrepancies were found and minor discrepancies were resolved in collaboration with the study authors and investigators. Variability and heterogeneity was assessed by use of the I^2 estimate of heterogeneity (appendix). Risk of bias in the individual studies was assessed using the Cochrane handbook method.[14] The principal risk of bias was derived from differences among individual studies' methods and inclusion criteria. We used a one-stage approach, defined as the use of individual patient data with analysis including covariates and random study effects to appropriately incorporate any between-study differences.

In MR CLEAN, the steering committee gave no recommendations about anaesthetic management. Nevertheless, most centres adhered to a fixed protocol regarding the type of anesthetic management throughout the trial. In the other trials, the use of anaesthesia was at the discretion of the treating team on a case by case

basis, although two trials (ESCAPE and REVASCAT) discouraged GA when possible. Patients treated under GA (sedation with intubation) were identified and their baseline characteristics compared with patients who had treatment without GA who were managed with or without sedation and not intubated.

The primary outcome was the modified Rankin Scale (mRS) at 3 months, which was analysed using ordinal logistic regression to obtain the common odds ratio (cOR) with 95% CI, measured by I^2 statistics for three pairwise comparisons: GA versus no GA, GA versus control, and no GA versus control. Secondary outcomes were the proportion of patients reaching independence (mRS 0–2) and return to all usual activities (mRS 0–1) and the proportion with early neurological recovery defined as at least an eight-point reduction in National Institutes of Health Stroke Scale (NIHSS) or reaching 0–1 at 24 h. Safety outcomes were the proportion of patients who had died at 90 days, the proportion with symptomatic intracerebral haemorrhage (as defined by each trial) and the proportion with parenchymal haematoma (intracerebral blood clot with mass effect). The proportions of endovascular patients with vessel perforation and pneumonia were compared between GA and non-GA groups. Patient characteristics, including age, sex, baseline stroke severity (by use of NIHSS), non-contrast CT of ischaemic change of the affected hemisphere (by use of the Alberta stroke program early CT score [ASPECTS]); whether the patient presented directly to the treating centre; time of stroke onset, randomisation, and reperfusion; site of arterial occlusion, use of intravenous alteplase, or a past history of hypertension, hyperlipidaemia, diabetes mellitus, or smoking were extracted.

Regression analyses were adjusted for baseline prognostic factors including age, sex, NIHSS at baseline, ASPECTS, location of occlusion, treatment with intravenous alteplase (yes or no) and time to randomisation. Treatment was included as a variable with three levels: defined as GA, non-GA (including conscious sedation and no sedation), and controls. To account for between-trial variance we used mixed-effects modelling with a random effect for trials incorporated in all models. Additionally, as a prespecified sensitivity analysis, propensity scores were constructed by use of logistic regression with GA versus no GA as the outcome and using the same set of baseline variables as in the regression models. Propensities were then incorporated into the outcome model for the ordinal mRS score by sorting the propensity score from lowest to highest and dividing patients into five groups of equal size.[15] Statistical analyses were done in SAS software, version 9.3, and R, version 3.2.

Role of the funding source

An unrestricted grant was provided to the University of Calgary by Medtronic who had no role in study design, the collection, analysis or interpretation of data, the writing of the report or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Seven randomised trials were identified from 65 studies returned by our search. All 1764 patients in these seven trials were included in our analysis, of whom 871 participants were randomly assigned to endovascular thrombectomy and 893 participants to standard medical care. After exclusion of 74 patients from the thrombectomy group (72 who did not undergo the procedure and two who had missing data on anaesthetic strategy), 236 (30%) of 797 endovascular patients were treated under GA (figure 1). Details of the individual trials are provided in the appendix. At baseline, patients treated under GA were younger and had shorter time from stroke onset to randomisation than those treated without GA (table 1). Baseline clinical stroke severity (according to NIHSS) and affected hemisphere were not significantly different between anaesthesia groups. GA was used in 113 (29%) of 394 right hemisphere stroke patients and 119 (30%) of 392 left hemisphere stroke patients; 11 patients had missing hemisphere data. Patients treated under GA were more likely to receive alteplase and had a lower rate of diabetes.

At 3 months, the patients who had endovascular treatment had significantly greater odds of improved functional outcome in covariate-adjusted analysis in both GA (common odds ratio [cOR] 1·52, 95% CI 1·09–2·11, p=0·014) and non-GA (cOR 2·33, 95% CI

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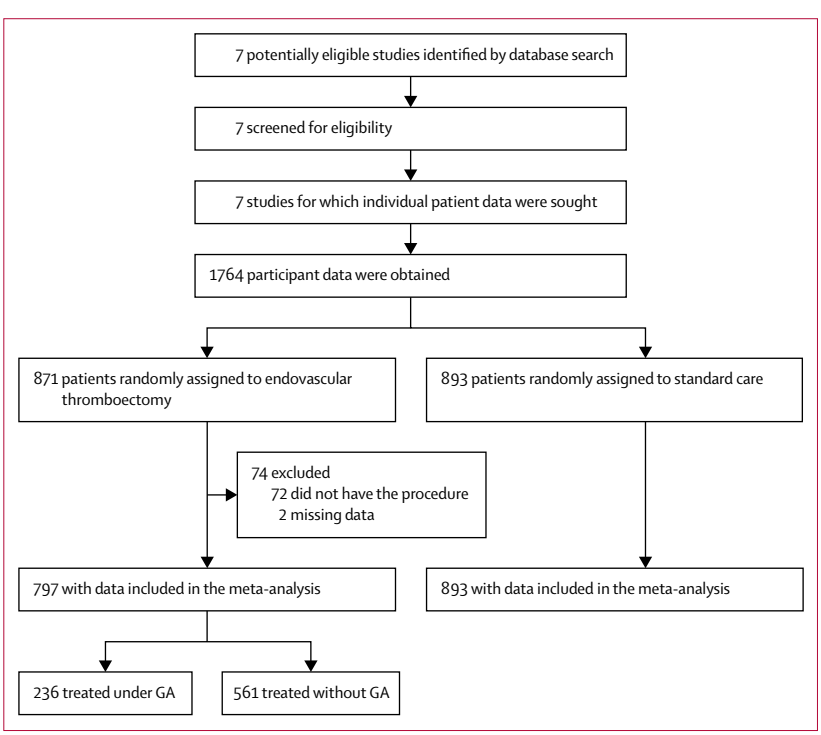

Figure 1: **Study selection**

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See Online for appendix

	All standard care (n=893)	All patients receiving endovascular therapy (n=871)	GA (n=236)	No GA (n=561)	p-value GA *vs* no GA
Age, years	65·7 (13·5)	65·5 (13·5)	63·8 (14·0)	66·3 (13·3)	0·015
Sex					
Female	421/891 (47%)	412 (47%)	101 (43%)	273 (49%)	0·14
Male	470/891 (53%)	459 (53%)	135 (57%)	288 (51%)	0·14
NIHSS at baseline	17 (13–21)	17 (14–20)	18 (15–21)	17 (14–20)	0·09
ASPECTS	8 (7–9)	8 (7–9)	7 (6–8)	8 (7–9)	0·0005
Left hemisphere affected	442/881 (50%)	424/856 (50%)	119/232 (51%)	273/554 (49%)	0·64
Directly admitted to treating centre	668/888 (75%)	678/869 (78%)	178 (75%)	432/559 (77%)	0·57
Onset to randomisation, min	184 (140–250)	181 (141–241)	179 (137–238)	184 (144–246)	0·04
Randomisation to reperfusion, min	NA	92 (61–128)	105 (80–149)	85 (51–118)	<0·0001
Onset to reperfusion, min	NA	291 (231–357)	302 (246–357)	288 (222–358)	0·57
Site of arterial occlusion	..	..	..	..	0·13
ICA occlusion	227 (25%)	215 (25%)	59 (25%)	144 (26%)	..
M1 occlusion	537 (60%)	536 (62%)	141 (60%)	343 (61%)	..
M2 occlusion	64 (7%)	67 (8%)	15 (6%)	47 (8%)	..
Unknown	64 (7%)	53 (6%)	21 (9%)	27 (5%)	..
Alteplase administered	809 (91%)	763 (88%)	218 (92%)	473 (84%)	0·002
Hypertension	523/890 (59%)	465/867 (54%)	119/234 (51%)	315 (56%)	0·18
Hyperlipidaemia	351/873 (40%)	300/846 (36%)	69/232 (30%)	202/548 (37%)	0·06
Diabetes mellitus	156/889 (18%)	131/867 (15%)	21 (9%)	102/560 (18%)	0·0009
Smoking	300/820 (37%)	298/788 (38%)	85/218 (39%)	183/504 (36%)	0·503

Data are mean (SD), median (IQR), or n (%). Denominators have been provided where they differ from the group n. NIHSS is a standardised neurological examination for which the score ranges from normal (0) to death (42). ASPECTS reflects the extent of early ischaemic change on the CT brain; 10 is normal, 0 shows involvement of the entire middle cerebral artery territory. GA=general anaesthesia. NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta stroke program early CT score. ICA=internal carotid artery. M1=first segment of middle cerebral artery (pre-bifurcation). M2=second segment of middle cerebral artery (from bifurcation to the circular sulcus of the insula in the Sylvian fissure).

Table 1: **Baseline characteristics of endovascular patients treated under GA versus without GA and those who received standard care**

1·75–3·10, p<0·0001) groups versus standard medical care; table 2, figure 2). There was no heterogeneity in the effect of GA on outcome between studies, although the small numbers limit power for this analysis. The odds of improved outcome using non-GA versus GA were significantly greater in ordinal analysis of the mRS, after adjustment for baseline prognostic factors (cOR 1·53 95% CI 1·14–2·04, p=0·0044). For every 100 patients treated under GA versus no GA, 18 patients would have worse functional outcome, including ten who would not achieve functional independence. The propensity-stratified analysis generated similar results for patients treated without GA compared with those treated under GA (cOR 1·44, 95% CI 1·08–1·92, p=0·012). Secondary outcomes followed similar trends (table 2).

The rate of symptomatic intracerebral haemorrhage did not differ between endovascular patients treated under GA, those treated without GA, or patients who received standard medical care. 75 (13%) of 561 patients who received thrombectomy without GA died compared with 153 (17%) of 884 who received standard medical care (p=0·066), and 41 (17%) of 236 who received thrombectomy under GA (table 2); nine patients in the standard care group had missing 90-day follow-up data. Pneumonia occurred in a similar proportion of patients who received GA versus those who did not (27 [11%] of 236 *vs* 47 [8%] of 561, p=0·18), although the reported incidence of pneumonia was significantly different between studies (p=0·0006), which is likely to indicate differences in definition or in capture of adverse events. Vessel perforation occurred in one (<1%) of 236 patients who had thrombectomy under GA versus nine (2%) of 561 patients who had the procedure without GA (p=0·30).

The proportion of patients with successful reperfusion after the procedure (modified Treatment in Cerebral Infarction 2b/3)—ie, achieved reperfusion of at least 50% of the affected territory—did not differ between patients who received GA and those who did not (160 [75%] of 213 *vs* 386 [76%] of 507, p=0.78). The time interval between randomisation and reperfusion was significantly greater in patients who had GA versus patients who did not have GA (median 105 min *vs* 85 min, p<0·0001). However, there was an imbalance in the time from stroke onset to randomisation, which was median 5 min shorter in the GA group (p=0·042) and the difference in total onset to reperfusion time between both groups was therefore not significant (median

	Standard care (n=893)	Endovascular thrombectomy with GA (n=236)	Endovascular thrombectomy without GA (n=561)	GA *vs* standard care*		No GA *vs* standard care*		No GA *vs* GA*	
				Effect size OR (95%CI)	p value	Effect size OR (95%CI)	p value	Effect size OR (95%CI)	p value
Primary outcome									
Functional outcome at 90 days (mRS)†	4 (2–5)	3 (2–4)	2 (1–4)	..	..	..	..	..	..
Covariate adjusted common odds ratio	..	..	..	1·52 (1·09–2·11)	0·014	2·33 (1·75–3·10)	<0·0001	1·53 (1·14–2·04)	0·0044
Propensity-score stratification common odds ratio	..	..	..	1·42 (1·09–1·84)	0·0084	2·21 (1·65–2·95)	<0·0001	1·44 (1·08–1·92)	0·012
Secondary outcomes									
Independent functional outcome (mRS 0–2)	268/877 (31%)	94/234 (40%)	282 (50%)	1·62 (1·16–2·26)	0·0050	2·72 (1·99–3·72)	<0·0001	1·65 (1·14–2·38)	0·0078
Excellent functional outcome (mRS 0–1)	146/877 (17%)	53/234 (23%)	177 (32%)	1·53 (1·02–2·31)	0·041	2·72 (2·00–3·69)	<0·0001	1·68 (1·12–2·52)	0·013
Early neurological improvement (NIHSS reduction ≥8 points or reaching 0–1 at 24 h)‡	204/857 (24%)	86/226 (38%)	293/550 (53%)	2·02 (1·36–3·00)	0·0005	3·92 (2·73–5·62)	<0·0001	1·75 (1·23–2·48)	0·0020
Safety									
Death within 90 days	153/884 (17%)	41 (17%)	75 (13%)	1·01 (0·67–1·52)	0·96	0·73 (0·52–1·02)	0·066	0·71 (0·44–1·14)	0·15
Symptomatic intracerebral haemorrhage§	31/877 (4%)	10/228 (4%)	21/556 (4%)	1·19 (0·56–2·51)	0·65	1·14 (0·62–2·10)	0·68	0·95 (0·41–2·19)	0·90
Parenchymal haematoma	86/842 (10%)	32/223 (14%)	61/533 (11%)	1·38 (0·86–2·22)	0·19	1·25 (0·72–2·16)	0·42	0·97 (0·60–1·58)	0·90

Data are median (IQR) or n (%). GA=general anaesthesia. OR=odds ratio. mRS=modified Rankin scale. NIHSS=National Institutes of Health stroke scale.ASPECTS= Alberta stroke program early CT score. *Adjusted for age, sex, baseline stroke severity, site of occlusion, intravenous alteplase treatment, ASPECTS, and time from onset to randomisation. †mRS ranges from normal (0) to death (6). Analysis combined mRS 5 & 6. ‡NIHSS score ranges from normal (0) to death (42), an 8-point reduction is highly clinically significant. §As defined by source trial.

***Table 2*: Outcomes in patients treated with standard care versus endovascular thrombectomy with or without GA**

302 min *vs* 288 min, p=0·57, table 1).

Finally, we assessed bias between studies and found little to no bias for all studies except THRACE, which used unblinded assessment of day 90 functional outcome (appendix).

Discussion

Patients treated under GA had poorer outcomes compared with those treated without GA, after adjustment for baseline characteristics. The magnitude of this effect was clinically significant—for every 100 patients treated under GA versus those who were treated without GA, 18 patients would have worse functional outcome, including ten who would not achieve functional independence However, a significant benefit of endovascular thrombectomy over standard care was retained in patients treated under GA.

The randomised trials differed in their proportion of patients treated under GA but the experience in the REVASCAT[11] and ESCAPE[8] studies, which discouraged GA, was that less than 10% of patients who had anterior circulation stroke had an absolute requirement for GA. MR CLEAN previously reported that GA was associated with marked attenuation of treatment effect.[2] It is possible that the lower rate of revascularisation in MR CLEAN[7] attenuated the potential treatment benefit compared with EXTEND-IA[9] and SWIFT PRIME.[10] However, the THRACE trial[13] reported no difference in outcomes in patients treated with or without GA despite a similar effect size to MR CLEAN.

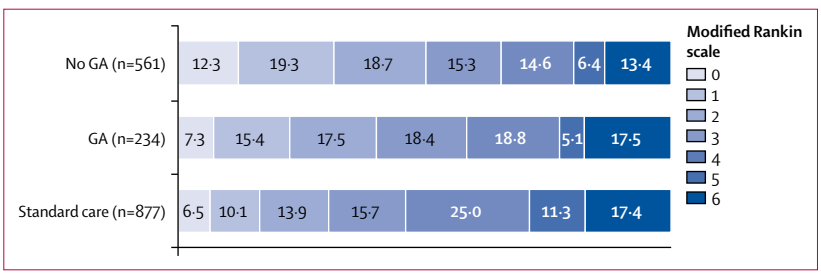

***Figure 2*: Distribution of modified Rankin Scale**
3-month outcomes in patients treated with endovascular thrombectomy under GA or without general anaesthesia (no GA) versus the standard medical care group. GA=general anaesthesia.

The method of GA in these randomised trials was entirely at the discretion of the treating team and there were no formal protocols specifying anaesthetic agents, blood pressure targets, or other aspects of physiological management. This is in contrast to the highly protocol-specified approach to both GA and conscious sedation in the SIESTA,[3] ANSTROKE,[4] and GOLIATH trials.[5] In particular, strict attention to maintaining systolic blood pressure at more than 140 mmHg throughout the procedure (including during anaesthetic induction) might have been crucial to preserving collateral blood flow to the ischaemic penumbra and preventing a harmful effect of GA. There were also specified criteria to prevent hyperventilation or hypoventilation.

Each of the GA versus conscious sedation randomised trials also used the same medications in both treatment groups, the difference being lower dose and absence of intubation in the conscious sedation group. This finding contrasts with results from this individual patient data meta-analysis of HERMES trials[7–13] in which treatment in the no GA group varied between no sedative medication at all and use of sedatives and anaesthetic agents but without intubation. The use of local anaesthetic agents at the arterial puncture site without any sedative agent, which is routine at many institutions, might have different implications for patient outcome compared with conscious sedation as described in the recent randomised trials.[3–5] Different anaesthetic agents could also vary in their protective or harmful effects on the ischaemic brain, among other hypothetical differences between approaches.[16] The details of the medications given in the HERMES patients were not available for this analysis.

Although the main reasons given for using GA are procedural safety and securing the airway, there was no significant difference in the rate of vessel perforation or pneumonia between patients who had GA and those who did not. Our data therefore do not support GA as a safer approach to treatment and show the general technical safety of endovascular thrombectomy. There are potential advantages of avoiding GA, including the ability to assess neurological status during the procedure, reduced intensive care requirements after the procedure and reduced costs. In our individual patient data meta-analysis of the HERMES trials, GA was also associated with a delay in reperfusion. However, this was not the case in the randomised trials,[3–5] in which a slight delay to start the procedure in patients who had GA (on average <10 min) appeared to be offset by shorter procedural time. This might be plausible if reduced patient movement allows more efficient roadmap techniques. However, the three centres that did the randomised trials of GA achieved exceptionally fast anaesthetic induction that might not be common practice at most institutions.

The main limitation of this study is that the choice to treat patients with or without GA was not randomised, and the differentiation between medically-required GA versus elective GA was not recorded in the trial databases. The important prognostic variables of age and time from stroke onset to randomisation favoured the GA group. We used two different methods of adjustment for baseline imbalances (multivariate regression and propensity-score stratification), which gave consistent results. Nonetheless, for both methods, the possibility of unmeasured confounding remained. The anaesthetic practices in the HERMES trials were not pre-specified by protocol and were not recorded in detail but are likely to have been substantially more variable than the recent single centre randomised trials comparing patients who receive GA versus those who do not. However, this also represents a strength of our study as results are likely to be generalisable to current clinical practice. The risk of bias in component trials was overall assessed to be low.

In conclusion, the pooled data from this meta-analysis suggest that the use of GA for endovascular thrombectomy, as practised in contemporary clinical care across a wide range of expert centres during the randomised trials, is associated with worse outcomes compared with the avoidance of GA, independent of patient comorbidities. Patients still benefited from thrombectomy compared with standard care when treated under GA. Therefore, the requirement for GA because of airway compromise or agitation that threatens the quality of revascularisation should not deter clinicians from pursuing endovascular thrombectomy. The contrast between the HERMES data and the recent randomised trials[3–5] comparing GA with conscious sedation suggests that, when GA is medically necessary, close attention should be paid to minimising delays to anaesthetic induction and procedure commencement and maintaining physiological parameters such as blood pressure. A multi-centre randomised trial to definitively address these issues is warranted.

Contributors

BCVC prepared the first draft of the report based on an analysis plan agreed by the HERMES Executive Group (BCVC, MG, DWJD, AMD, SBra, PW, AD, CBLMM, FG, KWM, JLS, TGJ, MDH, and PJM) who also contributed to study interpretation. SBro did the statistical analyses. All authors participated in patient enrolment, data collection, critically reviewed the report, and approved the final version. FG, KWM, RJvO, JLS, TGJ, MDH and PJM contributed equally.

Declaration of interests

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frequency;[5] a practical formula for dose calculation is necessary. SCIg should be less costly than IVIg but, considering that the IgG total dose is higher than that of IVIg and the cost of pumps, infusion setups, and training, it might not be.

Finally, everything will come down to preference: 1 day per month IVIg infusion in outpatient centres or at home (as done currently) or four weekly home self-infusions (finger strength permitting) in two to eight parallel sites of 50 mL each, lasting 1–2 h? Time will tell. The preference data from immunodeficient children[7,8] are not applicable to adults with CIDP, who require not only more IgG than do children but also adequate finger strength to self-administer the infusions. Patients with CIDP commonly have distal muscle weakness, so in these cases, another person would need to give the infusions.

Future studies should examine whether SCIg exerts effective immunomodulation as IVIg does,[4] is helpful as an induction therapy, or can eliminate the wearing off effect seen at the end of each IVIg cycle, ensuring a steady-state IgG concentration; studies should also investigate whether or not a formula combining IVIg with SCIg is advantageous. Notwithstanding the extraordinary help in alleviating the symptoms of CIDP that IVIg (and now SCIg) provides, its efficacy in only 75% of patients with CIDP mandates the need, not so much for an alternative route of administration of the IgG, but for new immunotherapies to benefit the other 25%.

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HERMES: a helpful messenger in the anaesthesia for thrombectomy debate?

The effectiveness of endovascular treatment in patients with anterior circulation ischaemic stroke due to large artery occlusion is firmly established, although optimal anaesthesia for the procedure remains contentious. Studies have suggested that endovascular treatment under general anaesthesia (GA) is associated with a worse outcome than when treatment is done without GA. However, because patients with more severe stroke and comorbidities are more likely to receive GA, there is potential for confounding by indication. Additionally, few trial reports have contained details of anaesthetic techniques or drugs, leaving many unanswered questions.

In *The Lancet Neurology*, Bruce Campbell and colleagues (for the HERMES collaborators),[1] address the role of GA in endovascular mechanical thrombectomy with the meta-analysis of individual patient data from seven trials.[1] The primary outcome was the modified Rankin scale (mRS) at 90 days in each of the standard medical care group and the GA and non-GA thrombectomy groups, adjusted for baseline prognostic factors. Patients who had their thrombectomy without GA had significantly better outcomes (2·33, 95% CI 1·75–3·10, p<0·0001) than those who had the procedure under GA (1·52, 95% CI 1·09–2·11, p=0·014), even after adjustment for

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baseline characteristics (covariate-adjusted common odds ratio 1·53, 95% CI 1·14–2·04, p=0·0044). The magnitude of effect was clinically significant; for every 100 patients treated under GA versus non-GA, 18 patients would have worse functional outcome, including ten who would not achieve independence. Although patients still benefited from thrombectomy compared with standard care, the authors concluded that GA should be avoided whenever possible.

This makes stark reading and supports the findings of previous observational studies.[2] However, although this analysis is the largest to date and includes data from high-quality randomised trials, it remains a meta-analysis of pooled data. None of the included trials were designed to investigate the effect of GA on outcome and its use was not randomised. Reviewing individual trial protocols, formal anaesthetic protocols are not specified, nor are criteria for the use of GA in individual patients. The drugs chosen and the use of GA varied both between and within individual trials.

An association between GA and adverse outcome is entirely plausible. The effect of anaesthesia on the neurological outcome, especially in the oldest and youngest populations, is the subject of much recent debate.[3] However, GA is not a single entity. There are numerous anaesthetic drugs with very different properties not only in terms of putative neuroprotective or neurotoxic properties but also in terms of their effects on physiological parameters. Episodes of hypotension, hypocapnia or hypercapnia, or excessive depth of anaesthesia might further compromise an already ischaemic brain. Consequently, it is important to know the individual drugs used and for detail to be provided on intraprocedural variables such as blood pressure, respiratory parameters, or depth of anaesthesia.

Even the definition of what constituted GA in these seven pooled trials is unclear. The non-GA group comprised both patients who had conscious sedation and local anaesthesia alone. The ability to perform thrombectomy without any sedation implies a more cooperative patient, potentially making a favourable outcome more likely in the non-GA group. It would be interesting to have a direct comparison of GA versus conscious sedation, excluding the local anaesthesia group.

The effect and use of GA varied widely between individual trials. The use of GA was actively discouraged and was only used in 6·8% of patients in the REVASCAT trial,[4] possibly resulting in a worse functional outcome in this group. In the MR CLEAN[5] and THRACE[6] trials, GA was used more frequently (36% of patients in MR CLEAN and 49% of patients in THRACE). However, although MR CLEAN reported a 51% decrease in treatment effect with GA, there was no effect on outcome in THRACE. It is difficult to explain such differing effects of GA between trials.

The findings in the study by Campbell and colleagues are also in contrast with those of the SIESTA,[4] ANSTROKE,[5] and GOLIATH[6] trials, which did not show an advantage of conscious sedation over GA in endovascular thrombectomy.[4–6] These trials defined the GA group, specified anaesthetic drugs used, and had strict blood pressure targets. The ANSTROKE investigators hypothesised that the anaesthesia technique would have no effect on outcome if hypotension was avoided. Patients were randomly allocated to GA or conscious sedation, with strict blood pressure control (systolic blood pressure 140–180 mmHg) and normoventilation. There was no difference between GA and conscious sedation groups in mRS at 3 months and no difference in early neurological recovery, infarction volume, anaesthetic use, or neurointerventional complications. Although these are small single centre trials, the results are encouraging in terms of minimising adverse effects of GA when there is careful anaesthesia and strict haemodynamic control. It would be interesting to see these results included in the meta-analysis.

Safe and effective implementation of endovascular thrombectomy has had many major challenges. Unfortunately, despite the size and the inclusion of such high-quality trials within this meta-analysis, there remains insufficient information about the type of anaesthesia used and intraprocedural variables to give a definitive answer regarding the effect of GA on functional outcome. The authors acknowledge these problems and advocate a multicentre randomised trial. This is now imperative, but must include all disciplines involved in the management of these patients. Until then, decisions regarding choice of anaesthesia should be made on an individual patient basis.

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Subthalamotomy for Parkinson's disease: back to the future?

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MRI-guided focused ultrasound is a novel method for creating thermic ablations in the thalamus or basal ganglia without opening the skull. The method uses focused sonic energy and real-time MRI thermography of brain temperature to control lesion size and location precisely. This is a principle advantage over gamma-knife radiosurgery, which is another incision-free lesioning technique but induces radionecrosis that is difficult to control and develops within months of the procedure. In July, 2016, the US Food and Drug Administration approved MRI-guided focused ultrasound for unilateral thalamotomy for treatment of medically refractory and disabling essential tremor. The efficacy and relative safety of the procedure have been proven in several clinical trials,[1,2] with outcomes in essential tremor comparable to the benefit of conventional radiofrequency thalamotomy or thalamic deep brain stimulation.[3]

In *The Lancet Neurology*, Martínez-Fernández and colleagues[4] now report the results of a small pilot study of MRI-guided focused ultrasound for unilateral subthalamotomy in Parkinson's disease. The subthalamic nucleus is a delicate target for lesioning because of the risk of hemichorea-ballism and only became accessible for surgical interventions in the 1990s, when advances in deep brain stimulation technology allowed a reversible and adaptable neuromodulation.[5] Deep brain stimulation is now the mainstay of functional stereotactic neurosurgery, with proven efficacy and safety in numerous controlled studies, and can be applied bihemispherically, whereas bilateral lesions in basal ganglia or thalamus are associated with a risk of permanent neurological sequelae such as dysarthria. Why would one reverse history and return to a lesional procedure, albeit it a technically fancy one? Although deep brain stimulation technology has evolved in recent years, the systems still have the same principle design: a brain electrode is connected via an extension cable to a pulse generator, which is implanted in the subclavicular or abdominal region. Hardware-associated problems are not uncommon, and pain