Background

Large territory middle cerebral artery (MCA) strokes account for around 10% of all ischaemic strokes and have a particularly devastating prognosis. Progressive cerebral oedema develops in the first 24-48 hours of stroke ictus with an associated rise in intracranial pressure. The rise in intracranial pressure may eventually overwhelm compensatory mechanisms leading to cascading secondary damage to surrounding unaffected parenchyma. This downward spiral can rapidly progress to death or severe neurological disability. Early decompressive craniectomy to relieve intracranial pressure can help ameliorate this secondary damage and improve outcomes. Evidence has been accumulating of the benefit of early surgical decompression in stroke patients. Earlier studies have excluded patients above the age of 60 due to the associated poor outcomes but recently, newer trials have emerged analysing these subgroups. This review follows from a Cochrane review published in 2012.

Objectives

To assess the effectiveness of surgical decompression in patients with malignant oedema after ischaemic stroke with regards to reduction in mortality and improved functional survival. We also aim to examine the adverse effects of surgical decompression in this patient cohort.

Search methods

We searched the MEDLINE Ovid, Embase Ovid, Embase Ovid, Web of Science Core Collection, Cochrane Stroke Group Trials Register, CENTRAL, SCOPUS databases and ClinicalTrials.gov up to August 2021. We also reviewed the reference lists of relevant articles.

Selection criteria

We included randomised controlled trials (RCTs) comparing decompressive craniectomy with medical management to best medical management alone for patients with malignant cerebral oedema after MCA territory stroke.

Data collection and analysis

Two authors independently screened the entire search results, searched through studies for eligible trials, assessed the risk of bias and extracted the data. The primary outcomes collected were death, and death or severe disability (mRS>4) at 6-12 months follow-up. Other collected outcomes included death or disability (mRS>3), disability and adverse events. Furthermore, we assessed the quality of the evidence by the GRADE method, categorising the quality of evidence as either high, moderate, low, or very low.

Main results

We included 9 trials with a total of 526 participants. Whilst 3 studies included patients younger than 60 years of age, 2 trials accepted patients up to 80 years of age, whilst 1 trial included only patients 60 years or older. The time from stroke ictus to treatment ranged from < 48 hours in 6 trials to <96 hours in 2 trials.

Surgical decompression was associated with a statically significant reduction in death (OR 0.17, 95% CI 0.12 to 0.25, p<0.00001) and death or severe disability (mRS>4, OR 0.21, 95% CI 0.14 - 0.31,

p<0.00001) and death or disability (mRS>3, OR 0.33, 95% CI 0.21 - 0.50, p<0.00001). Subgroup analysis did not reveal any significant difference in treatment effect when analysing age (<60 vs ≥ 60), dysphasia, or 6 vs 12 months follow-up. With time from stroke ictus to intervention, subgroup analysis found a non-statistically significant reduction in death or disability defined as mRS>4 in the group treated <48 hours (OR 0.16, 95% 0.10 - 0.24, compared to OR 0.68, 95% CI 0.12 - 0.377 in the >48 hours cohort, p=0.11).

Authors' conclusions

Surgical decompression significantly improves outcomes in the management of malignant oedema after acute ischaemic stroke. There is a considerable reduction in death and/or severe disability in patients, along with a reduction in death or disability. Whilst there is evidence that this positive treatment effect is present in patients > 60 years old, it is important to consider that these patients have a poorer prospect of functional survival independent of this treatment effect. However, the application of surgical decompression needs to be applied in the correct setting considering the data available demonstrating the benefit is drawn from a unique patient subset with severe clinical stroke, reduced level of consciousness, and no pre-morbid disability or severe co-morbidity.

Plain language summary

Around 80% of strokes are caused by blockage of a blood vessel to the brain (ischaemic stroke). This is a major cause of death and disability worldwide. This blockage prevents the oxygen-carrying blood from supplying the brain, and as a result, the part of the brain being supplied by this vessel begins to irreversibly die (infarct). Over the next 24 to 48 hours, the infarcted brain begins to swell. If a large enough area of the brain is affected, the swelling can be very dramatic, causing a rise in the intracranial pressure. This rise in intracranial pressure can lead to the surrounding brain being affected and rapidly progressing to death. Surgery can help relieve the pressure by creating a large enough hole in the skull and dura layers around the infarcted brain (decompressive craniectomy). Recent studies suggest that the early use of this treatment after a large stroke can reduce rates of death and disability in survivors. Early evidence only studied the use of this technique in younger patients; however, more recent studies have begun to address its efficacy in older patients.

In August 2021, we searched the literature for randomised controlled trials (trials that randomly allocate patients to one of either two groups) that compared outcomes for stroke patients who were treated with early surgical decompression compared to patients who were treated without surgery. We found a total of 9 trials with 526 participants in total. Of these, 10 patients weren't included in the final analysis because they were either lost to follow-up or did not follow the trial instructions. There were a total of 250 patients who were randomised to receive early surgical decompression, whilst 266 were randomised to receive medical treatment only after their stroke. The trials selected patients with severe strokes with significant neurological deficits. They also selected patients who did not have any previous severe illnesses or disabilities. Also, 2 trials recruited patients up to 80 years of age, whilst 1 trial included patients only above 60 years old. Furthermore, 6 of the studies treated patients within 48 hours of their stroke, whilst another 2 allowed treatment up to 96 hours after the stroke was first noted.

After collating the evidence, it was found that surgical decompression significantly reduced the risk of death and/or disability of the participants compared to medical treatment alone. The surgical group had a significantly reduced chance of death, or being dead/severely disabled at the final follow-up. When patients were categorised by age below or above 60, the results showed that patients above the age of 60 benefited from surgery to a similar degree to patients under 60. However, it is important to consider that whilst patients above the age of 60 did tend to have a better prognosis with surgery

compared to those without surgery, they still did progress poorer compared to younger patients. There was also no statistically significant difference in treatment effect between patients operated before/after stroke onset, the presence/abscess of speech disturbance (dysphasia) and follow-up of 6 or 12 months; however, the evidence here is based on small patient numbers and further study is required.

The evidence was generally of moderate to high quality, with a few exceptions. Therefore we had moderately high confidence in the main findings of this study.

Background

Description of the condition

Ischaemic stroke is a leading cause of mortality and morbidity worldwide. Large territory middle cerebral artery (MCA) strokes encompass approximately 10% of all ischaemic strokes and are particularly morbid with a reported mortality of 80% (Berrouschot 1998; Das 2019; Hacke 1996). The large area involved may lead to the development of malignant MCA infarction that is characterised by significant mass effect with potentially avoidable secondary injury to surrounding brain tissue (Frank 1995; Shaw 1959). The initial ischaemic insult causes starvation of oxygen and glucose to the affected brain regions with subsequent rapid depletion of the major energy metabolite of neurons, adenosine triphosphate (ATP). Major ATP-dependent membrane pumps begin to fail including the sodium-potassium ATP-dependent pump leading to intracellular accumulation of sodium and calcium, and release of excitatory neurotransmitters with subsequent neuronal depolarisation. The passive flow of water intracellularly follows the sodium influx, leading to cellular swelling called cytotoxic oedema. This process also results in damage to cerebral vasculature with impaired integrity of the blood-brain-barrier resulting in leakage of water into the extracellular compartment, termed vasogenic oedema. Progressive cerebral oedema continues to develop during the first 24 to 48 hours after ischaemic insult and may then lead to a cascading series of secondary injuries within days of the initial infarction through raised intracranial pressure and transtentorial herniation (Das 2019). When the associated oedema is large enough, it is termed malignant oedema. It can jeopardise the potentially salvageable brain tissue around the infarcted core, called the ischaemic penumbra, as well as lead to ischaemia in surrounding vascular territories. This generally is associated with deteriorating neurological function and worsening level of consciousness two to three days after the initial stroke. It has a poor prognosis, associated with 50% to 75% of the MCA supplied territory, including the basal ganglia region, infarction of other vascular territories, and midline shift of at least 4 mm within 48 hours of ictus.

Description of the intervention

Surgical decompression is widely utilised to alleviate raised intracranial pressure and prevent transtentorial herniation (Beez 2019). It is applied in a variety of neurosurgical settings, including traumatic brain injury, intracerebral haemorrhage, and ischaemic stroke, and is generally employed as the last tier method when medical measures for controlling intracranial pressure (ICP) have failed. Whilst significant variation in the type of surgical decompression exist (including bifrontal craniectomy, hemicraniectomy, or sub-occipital craniectomy), in the setting of MCA stroke, the technical approach is approximately uniform; that is, given the unilateral hemispheric nature of the pathology, a unilateral fronto-temporo-parietal hemicraniectomy is generally utilised. This typically involves a large, curved incision beginning close to the midline and traced around the skull to either

behind or in front of the ear. The generated myocutaneous flap should cover most of the fronto-temporo-parietal region and is then elevated and retracted anteroinferiorly to expose the calvarium. Burr holes are then drilled in the skull and converted into a fronto-temporo-parietal craniectomy. The antero-posterior diameter of the craniectomy should be at least 12 cm, with the recommended diameter in the setting of traumatic brain injury being 15 cm. Removal of bone down to the middle cranial fossa floor is important to allow sub-temporal decompression. Expansile duroplasty is then performed to achieve greater decompression than simple bony decompression. Internal decompression, through the removal of infarcted tissue is uncommonly utilised if maximal decompression is desired. Following the decompression, the bone flap is sent for storage, whilst the myocutaneous flap is closed. Surgical decompression is associated with attendant risks of surgery, including haemorrhage, infection, hydrocephalus, seizures, and longer-term complications such as sunken-flap syndrome (Beez 2019).

How the intervention might work

The creation of a decompressive hemicraniectomy allows swelling beyond the internal limits of the cranial vault and thus a lowering of intracranial pressure (Beez 2019). This reduces the resistance to blood flow and thus improves cerebral perfusion. This can salvage the brain regions with suboptimal perfusion referred to as the ischaemic penumbra. The ischaemic penumbra is the cerebral region in ischaemic stroke that has a reduction in cerebral blood flow but has not yet undergone infarction and is thus potentially salvageable with improved perfusion. Furthermore, a reduction in intracranial pressure may prevent potentially devastating transtentorial and sub-falcine herniation. Thus, through these two methods of improved cerebral perfusion and prevention of intracranial herniation, surgical decompression has been theorised to reduce mortality and improve functional outcomes in patients suffering large territory MCA ischaemic strokes (Beez 2019; Vahedi 2007)

Why it is important to do this review

Ischaemic stroke causes a significant burden of mortality and morbidity to the community (Dasenbrock 2017; Rahme 2012). There is steadily accumulating evidence of the role of surgical decompression in reducing mortality in malignant oedema after stroke (Vahedi 2007). In addition, new studies have emerged that have examined the outcomes after decompressive craniectomy in a variety of patient cohorts, as well as examining the factors that may influence the decision to operate, such as the timing of surgery, patient age, and laterality of the stroke (Juttler 2007; Juttler 2014; Rahme 2012; Zhao 2012). By performing this review, we aimed to comprehensively evaluate the current evidence regarding these issues.

Methods

Criteria for considering studies for this review

Types of studies

We aimed to include only randomised controlled trials (RCTs) that compared surgical decompression with best medical management to best medical management alone for patients with malignant oedema after ischaemic stroke. We will not include nonrandomised studies.

Types of participants

Participants in the included studies had malignant cerebral oedema after MCA territory ischaemic stroke. This should be diagnosed by computed tomography (CT) or magnetic resonance imaging (MRI) brain scans, with the definition of malignant cerebral oedema left to the discretion of the authors of the individual studies. Participants should be more than 18 years of age with no upper limit to the inclusion age.

Types of interventions

We aimed to include trials with surgical decompression performed utilising a craniectomy. Surgical decompression should include bony decompression with fronto-temporo-parietal hemicraniectomy with expansile duroplasty. Additional internal decompression with removal of infarcted tissue, or associated haematoma, will not be a requirement. Importantly, patients should be randomised shortly after ictus, with patients randomised to receive treatment within 96 hours of ictus. The additional limit to the timing of intervention is due to the compelling evidence supportive of earlier surgical intervention.

Furthermore, we aimed to assess the impact of surgery compared to no surgery, thus optimal medical management (mannitol/hypertonic saline, barbituates, hyperventilation, etc.) should be utilised in both groups. A difference in approach to the medical management of patients between the two arms is indicative of bias within the study.

Types of outcome measures

The presence of any one of the following outcome measures in a trial will be required for consideration of inclusion into the review.

Primary outcomes

- Death at final follow-up
- Death or severe disability defined as modified Rankin Scale (mRS) > 4

Secondary outcomes

- Death or disability defined as modified Rankin Scale (mRS) > 3
- Severe disability defined as mRS = 5
- Adverse events: including the total number of reported adverse events and specific stratifications of infection, hydrocephalus, and re-operation, where available.

Search methods for identification of studies

See the 'Specialised Register' information available at the Cochrane Stroke Group's website. We searched for trials in all languages and arranged for the translation of relevant articles where necessary.

Electronic searches

We searched the Cochrane Stroke Group trials register and the following electronic databases:

- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library; latest issue);
- MEDLINE Ovid (from 1946) (Appendix 1);

- Embase Ovid (from 1974) (Appendix 2);
- Science Citation Index Expanded (SCI-EXPANDED; from 1900) and Conference Proceedings Citation Index- Science (CPCI-S; from 1900) in the Web of Science Core Collection (Clarivate Analytics); and
- Scopus Abstract and citation database (Elsevier; from 1788).

We modified the subject strategies for databases modelled on the search strategy designed for MEDLINE by the Cochrane Stroke Group's Information Specialist (Appendix 1, Appendix 3). We combined all search strategies deployed with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials, as referenced in the Boxes 3.c and 3.d in the Technical Supplement to Chapter 4: Searching for and selecting studies in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 6.1.0 (updated September 2019) (Lefebvre 2019).

Keywords related to cerebral oedema were not included in our search strategy (Appendix 1), as they excluded potentially relevant references in preliminary test searches.

We searched the following ongoing trials registers:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (who.int/ictrp/en/).

Searching other resources

In an effort to identify further published, unpublished and ongoing trials, we:

- checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials and search Google Scholar (scholar.google.co.uk/) to forward track relevant references;
- contacted original authors for clarification and further data if trial reports are unclear;
- where necessary, contacted experts, trialists, and organisations in the field to obtain additional information on relevant trials; and
- conducted searches in the British Library EthOS and ProQuest Dissertations and Theses Global.

Data collection and analysis

Selection of studies

Two review authors (AD and MMu) independently screened titles and abstracts of the references obtained as a result of our searching activities and excluded irrelevant reports. We retrieved the full-text articles for the remaining references and two review authors (AD and MMu) independently screened the full-text articles, identified studies for inclusion, and recorded reasons for exclusion of the ineligible studies. We resolved any disagreements through discussion and consultation with the third review author (MMa). We collated multiple reports of the same study so that each study, not each reference, is the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram.

Data extraction and management

Two review authors (AD and MMa) independently extracted data from included studies and input the data into data extraction tables, including:

- study methods: study design, method of randomisation, study country, number of centres, time between ictus to randomisation;
- participants: sample sizes, age, sex, the proportion of patients with dominant vs non-dominant stroke, laterality of stroke, the proportion of patients receiving intended treatment, the proportion of patients with cross-over treatment, method of diagnosis of malignant oedema;
- intervention: time from ictus to intervention/surgery, time from randomisation to surgery, surgical technique, size of craniectomy, 'best medical management' strategies, operator (consultant/trainee);
- outcomes: number of patients in each comparator group with the following outcomes: death, mRS > 4, mRS > 3, severe disability as defined by trial authors - these outcome measures collected at six months, 12 months and final follow-up. Adverse events: hydrocephalus, re-operation, infection, other adverse events

If the two review authors disagreed on data extraction, they had a discussion between themselves before a third independent review author (MS) reviewed the disagreement to make a final decision. For dichotomous data, we extracted the number of participants experiencing the event and a total number of participants in each arm of the trial. For continuous data, we extracted mean values along with standard deviations for participants experiencing an event, along with the total number in each trial arm. In the event where trials reported only effect estimates such as odds ratio or relative risk without the number of participants or events, we extracted such data for inclusion into our review using methods outlined in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Assessment of risk of bias in included studies

Two review authors (AD and MMu) independently assessed the risk of bias for each study using the criteria outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion or by involving the third author (MS). We assessed the risk of bias according to the following domains:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other bias.

We graded the risk of bias for each domain as high, low or unclear and provide information from the study report together with a justification for our judgement in the risk of bias tables.

Measures of treatment effect

We used a fixed-effect model for statistical analyses of all outcome measures, unless we identified a significant degree of heterogeneity in which case we used a random-effects model. 'Severe disability' measured by mRS was dichotomised using an mRS cut-off point of >4, whilst disability was dichotomised using an mRS cut-off point of >3, and these analyses were conducted separately. Other functional measures were also dichotomised into good versus poor outcome measures.

As all outcome measures, including death, functional outcomes and adverse events, were dichotomised, we calculated the effect sizes using odds ratio (ORs) and relative risk reduction (RRR) with corresponding 95% confidence intervals (CIs). We conducted all analyses on an intention-to-treat basis.

Unit of analysis issues

We assessed the level of randomisation in each included study and expected that all included studies were randomised on an individual basis, with the unit of analysis being individual patients with malignant oedema after ischaemic stroke. In the event of finding non-standard study designs, including cluster-randomised studies, as well as other analysis issues, we applied the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021).

Furthermore, if we found studies with multiple outcome measures within the same period, we included the longest follow-up within each specified period. We analysed the data for the longest follow-up period provided, as well as an analysis separating the effects of different periods, ie. six months, 12 months, and > 12 months (Higgins 2021).

Dealing with missing data

In the event that data points were missing from the included studies, we imputed the missing data with replacement values using the methods described in Section 10.12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). When replacement values were entered, we performed a sensitivity analysis to determine the effect of the replacement values, including an assessment with the best- and worst-case scenarios for the replacement data. Furthermore, we attempted to contact study authors to obtain missing data, where possible.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We considered an I^2 statistic > 60% indicative of a substantial degree of heterogeneity (Higgins 2021). Consequently, we examined the study and subgroup characteristics to investigate the underlying cause of heterogeneity in all outcome measures, and we performed subgroup analyses and meta-regression analyses.

Assessment of reporting biases

We assessed reporting bias using a qualitative analysis of the included studies as outlined in Chapter 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We investigated study protocols, including a search for missing data within included trials and trials without published results. If we identified more than 10 studies for inclusion, we used a funnel plot, and utilised Egger's test, to assess the role of reporting and associated small-study bias.

Data synthesis

Where we considered studies to be sufficiently similar, we conducted a meta-analysis by pooling the appropriate data using RevMan Web (RevMan Web 2020). We used a fixed-effect model to analyse the pooled outcome data from included studies if there was little heterogeneity in the included studies (i.e. I^2 statistic $\leq$ 60%); however, if there was a significant degree of heterogeneity, we performed a random-effects model analysis. We conducted statistical analysis according to the recommendations outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We utilised the Mantel-Haenszel method for fixed-effect model meta-analysis of dichotomous outcomes, and DerSimonian and Laird inverse variance for a random-effects model analysis. If we were unable to perform a meta-analysis, due to either wide variance between the studies or lack of studies (< 2), we performed a narrative review of the included studies.

Subgroup analysis and investigation of heterogeneity

Where there were a sufficient number of studies, we performed a subgroup analysis of both primary and secondary outcome measures using the following factors:

- Time from ictus to surgery (defined as the time between the onset of stroke symptoms and surgical intervention);
- Age (above 60 years of age versus below or equal to 60 years of age);
- Laterality of the stroke (left versus right sided stroke);
- Dysphasia (the presence versus absence of dysphasia: this may be a more accurate predictor of dominant vs non-dominant side stroke);
- Short versus long-term follow-up (final follow-up at or under six months versus final follow-up greater than six months; this subgroup analysis will be carried out for both primary and secondary outcome measures, excluding adverse events).

We utilised the formal test for 'subgroup analysis' provided in RevMan Web (RevMan Web 2020).

Sensitivity analysis

We conducted sensitivity analyses for primary outcome measures. We conducted this by the exclusion of the following studies:

- Studies with a high risk of bias (Assessment of risk of bias in included studies);
- Studies with fewer than 10 participants;
- Studies where the loss of follow-up is greater than 10%, or not reported;
- Studies where the mean time from ictus to surgery was greater than 48 hours.

Summary of findings and assessment of the certainty of the evidence

We created a summary of findings table using the following outcomes: death, death or severe disability defined as modified Rankin Scale (mRS) > 4, death or disability defined as modified Rankin Scale (mRS) > 3, severe disability, adverse events, hydrocephalus, re-operation (Table 1).

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), and the GRADE handbook (Schünemann 2013), by using the GRADEproGDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies using footnotes, and we made comments to aid the reader's understanding of the review, where necessary.

Results

Description of studies

See Characteristics of included studies; Characteristics of excluded studies.

Results of the search

Our search of the MEDLINE database yielded 1256 references (Figure 1). Furthermore, our search of the EMBASE database yielded 215 results, of which 212 were duplicates of the MEDLINE search and 3 new references were retrieved. A full search of the Cochrane Central Register of Controlled Trials (CENTRAL) yielded 481 references. Our search of the SCOPUS database yielded 143 titles for review, the search of the SCOPUS database retrieved 5864 articles for review, and the search of clinicaltrials.gov retrieved a further 47 articles. A total of 7794 references were screened, in which we identified 8 separate RCTs for full-text analysis (DECIMAL; Demitur; DESTINY; Destiny II; HAMLET; HeADDFIRST; Slezins 2012; Zhao 2012). Of these, 7 studies were completed, published and met the criteria for inclusion (DECIMAL; DESTINY; Destiny II; HAMLET; HeADDFIRST; Slezins 2012; Zhao 2012). One study was withdrawn from publication. However, we contacted study authors who confirmed the study was completed as outlined and provided the complete study results (Demitur). This study met the inclusion criteria. Furthermore, we searched the reference lists of multiple relevant studies and found one further RCT suitable for inclusion (HeMMI). In total, 9 studies were included.

Included studies

Summary details for the studies are given in the Characteristics of included studies. We included in this review 9 studies with a total of 526 randomised participants. Of these, 10 were not included in the final analysis either as a result of loss to follow-up or major protocol violations. There were a total of 250 patients in the surgical arm on final analysis, compared to 266 in the medical treatment only arm.

All included studies followed similar surgical decompression techniques, and the standardised medical treatment protocol also was largely homogenous across the studies. The only notable deviation in surgical protocol was by Slezins 2012 who implanted an ICP monitor for patients randomised to the surgery and who did not display midline shift on neuroimaging. They proceeded with surgical decompression only if ICPs were elevated on the parenchymal ICP monitor. In total, Slezins 2012 randomised 28 patients, of whom 4 participants assigned to the surgical cohort did not undergo decompressive craniectomy and were excluded from the final analysis. In 3 cases, they received surgical decompression over 100 hours after stroke ictus, which was a time frame violation for the study design, and in 1 case a patient showed no signs of raised ICP on parenchymal ICP monitor and therefore excluded from surgical intervention.

HeMMI randomised 29 patients out of 156 that were screened. However, 5 patients were excluded from the final analysis as they were lost to follow-up (3 in surgical group vs 2 in medical treatment arm). Moreover, three patients in the medical treatment arm underwent surgical intervention due to clinical deterioration, whilst 1 patient in the surgical arm did not undergo surgical decompression due to myocardial infarction.

HeADDFIRST randomised a total of 25 patients, of which 1 of the 15 patients in the surgical arm withdrew due to the family withdrawing consent. This was the smallest cohort of the studies. Demitur had the largest cohort, with a total of 151 patients that were randomised into either treatment arm.

Furthermore, 3 of the included trials stopped recruitment prematurely (DECIMAL; DESTINY; HAMLET). In two trials, a pooled analysis of data from the three trials was considered, whilst in the case of HAMLET an interim analysis of the data determined it was unlikely to achieve a statistically significant difference with the planned sample size.

There were fairly similar radiological criteria for defining a malignant MCA infarction across the included studies. This was defined as infarction affecting two-thirds or more of the MCA territory in 5 studies Demitur; DESTINY; Destiny II; HAMLET; Zhao 2012. DESTINY and Destiny II required associated involvement of the ipsilateral basal ganglia territory. DECIMAL defined this as at least 50% involvement of the MCA territory with an infarct volume of at least 145 cm3 on diffusion-weighted imaging. HeMMI and Slezins 2012 similarly required infarction size being ≥50% of MCA territory on neuroimaging. HeADDFIRST defined the neuroimaging criteria as infarction area being ≥50% of MCA territory if CT was < 5 hours from stroke onset, or complete MCA territory involvement if it were > 5 hours and within 48 hours from stroke ictus. Furthermore, patients were required to have a minimum amount of midline shift on repeat CT before randomisation.

The clinical criteria used to assess stroke severity for eligibility was the NIHSS score in 7 of the studies (DECIMAL; Demitur; DESTINY; Destiny II; HAMLET; HeADDFIRST; Slezins 2012), and primarily relied upon the GCS in the other 2 (HeMMI; Zhao 2012). The minimum cut-off NIHSS scores for inclusion varied across all the studies, although this was generally within a tight range selecting for moderate-severe strokes. The lowest minimum NIHSS score across the included studies was 14 for non-dominant strokes in Destiny II, whilst the highest was 21 for dominant strokes in DESTINY. In five studies, they used differential inclusion criteria for dominant and non-dominant strokes to account for the confounding speech deficit (Demitur; DESTINY; Destiny II; HAMLET; HeMMI). Furthermore, 8 of the studies mandated a reduced level of consciousness through their inclusion criteria DECIMAL; Demitur; DESTINY; Destiny II; HAMLET; HeMMI; Zhao 2012; HeADDFIRST.

All the studies excluded patients with severe co-morbidities and limited life expectancy. The pre-morbid mRS was utilised in all the studies, with the majority excluding participants with a pre-morbid mRS > 1 (DECIMAL; Demitur; DESTINY; Destiny II; HAMLET; Slezins 2012), and 3 studies setting the cut-off at mRS>2 (HeADDFIRST; HeMMI; Zhao 2012). Six of the studies excluded patients with the absence of pupillary reaction (Demitur; DESTINY; Destiny II; HAMLET; Slezins 2012; Zhao 2012).

Three of the studies included patients that were at most 60 years or younger DECIMAL; DESTINY; HAMLET, whilst HeMMI had a maximum inclusion age of 65, whilst HeADDFIRST had a maximum age of 75. Zhao 2012 and Demitur enrolled patients up to the age of 80. Destiny II was the only trial to exclusively enrol elderly patients, including patients 61 years of age or older only. This trial had the highest mean age of participants being 69.9 years (SD??? 4.4) in the surgical cohort and 70.4 years (SD??? 4.8) in the medical treatment only cohort. The lowest mean age of participants was in DECIMAL which had a mean age of 43.5 years (SD???9.7) for the surgical cohort, and 43.3 years (SD???7.1) for the medical cohort. All other studies had a mean age of participants within this range. The majority of studies were well matched for age between the two randomised treatment cohorts. Slezins 2012 however had the most significant variation in age, with a mean age of 57.2 years in the surgical cohort compared to 65 years in the medical treatment cohort (p=0.02).

The majority of studies randomised patients to treatment within a maximum of 48 hours after stroke ictus DECIMAL; Demitur; DESTINY; Destiny II; Slezins 2012; Zhao 2012. Of these, DECIMAL had the shortest time from ictus to intervention, including patients after a maximum of 24 hours from stroke ictus, and the average time to surgical intervention in their cohort was 20.5 hrs. On the other hand, HAMLET included patients presenting up to 96 hours after stroke onset, and required treatment within 3 hours of randomisation. The median time to randomisation was 41 hours in the surgical cohort and 45 hours in the control cohort. Similarly, HeADDFIRST allowed the inclusion of patients with stroke symptoms up to 96 hours after onset, whilst the median time from stroke onset to randomisation was 53 hours. HeMMI randomised patients for treatment up to 72 hours

after stroke ictus, however of these only 2 patients in the surgical arm underwent surgery after 48 hours and the overall time to randomisation was 9.0 (+/-10.6) hours.

Outcome measures reported in all the studies included both death and mRS data at final follow-up. The reported mRS outcomes were able to be dichotomized at both 0-3 vs 4-6 and 0-4 vs 5-6 in all the included studies. Adverse events were only systematically reported in 2 studies in an inconsistent manner that was not comparable (DECIMAL; Destiny II). Thus, a meta-analysis of adverse events was not performed. The follow-up period for outcome measures was between 6 and 12 months in all studies. Primary outcome measures were reported at both 6 and 12 months in 5 studies (DECIMAL; Demitur; DESTINY; Destiny II; Zhao 2012), 2 studies at 6 months only (HeADDFIRST; HeMMI), and 2 studies at 12 months only (HAMLET; Slezins 2012).

Excluded studies

There were no excluded studies.

Risk of bias in included studies

The results of the risk of bias assessment are presented in Figure 2 and Figure 3.

Allocation (selection bias)

We judged the nine studies to be either low risk or unclear risk for this domain. Five of the studies were considered an unclear risk of bias for random sequence generation due to insufficient information provided to be confident that the allocation sequence was genuinely randomised. Six studies were deemed an unclear risk of bias for allocation concealment because there was no description of the method of concealment.

Blinding (performance bias and detection bias)

All studies were judged as high risk of bias for blinding participants and personnel. We acknowledge that it is not possible to blind the patient or clinician for this intervention, and subsequently, this domain is assessed as a high risk of bias. Five studies were judged as low risk of bias for blinding the outcome assessment. The four studies judged a high risk of bias did not blind the assessors.

Incomplete outcome data (attrition bias)

We judged seven studies as low risk of bias. One study was judged as having a high risk of bias due to the proportion of missing data (HeMMI). One study was judged as unclear risk of bias as there was an insufficient description of the patient flow from inclusion to primary outcome follow up to assess the degree of missing data (Slezins 2012).

Selective reporting (reporting bias)

We judged two studies to be at low risk of bias. The other seven studies were judged as unclear risk of bias due to insufficient information being available to ensure that pre-specified outcomes were reported in the pre-specified way. Three trials had no protocol available and were registered on clincial trial registries after recruitment had commenced; two trials had no protocol available and were registered on clinical trial registries after the trial was completed; and one trial had no protocol and was not registered on a clinical trial registry (HeADDFIRST).

Other potential sources of bias

We did not identify any other source of bias in one trial. We judged six trials to be of unclear risk of bias, where five trials were terminated early, and in one trial there was no sample size calculation or primary outcome endpoint. We judged two trials to have additional biases sufficient to deem them a high risk of bias. One trial was a pilot study with small numbers and inequity between the two treatment arms (HeADDFIRST). The other trial was withdrawn from publication by the authors due to ??? (Demitur).

Effects of interventions

See: Summary of findings table 1.

Nine trials evaluated the effect of surgical decompression compared to medical treatment on the outcome of death at final follow-up, with a total of 526 participants, of whom 516 were included in the final analysis. There was a statistically significant reduction in death at follow-up with surgical decompression (OR 0.17, 95% CI 0.12 to 0.25, p<0.00001, Figure 4).

Furthermore, all 9 included trials evaluated the effect on death or severe disability defined as mRS>4. There was a statistically significant reduction in this outcome by surgery (OR 0.21, 95% CI 0.14 - 0.31, p<0.00001, 516 participants, Figure 5). There was a moderate degree of treatment heterogeneity in treatment effect (I2=43%). There was also a statistically significant reduction in death or severe disability defined as mRS>3 (OR 0.33, 95% CI 0.21 - 0.50, p<0.00001, 9 RCTs, 516 participants, Figure 6). Similarly, there was a moderate degree of heterogeneity in the treatment effect (I2=52%).

Moreover, there was found to be a non-statistically significant increase in patients with severe disability (mRS = 5) in the surgical cohort compared to medical treatment alone (OR 1.78, 95% CI 0.96 - 3.30, p=0.18, I2 = 33%, Analysis 1.4).

Subgroup analysis

Age < vs ≥ 60 years

A subgroup analysis was performed evaluating the effect of age with a cut-off of 60 years was performed. Five studies had cohorts of patients aged < 60 years with a total of 215 participants, compared to 3 studies with a cohort of 226 patients aged ≥ 60 years of age. There was no statistically significant difference of age on the outcome of death (p=0.56, Analysis 4.1). Furthermore, there was no statistically significant difference in the effect on death or severe disability defined as mRS>4 (p=0.91, Analysis 4.2, Figure 7), or mRS>3 (p=0.46, Analysis 4.3).

Time from Stroke Ictus, < vs ≥ 48 hours

A subgroup analysis was performed evaluating the effect of time from stroke ictus to intervention, with a cut-off at 48 hours. With regards to the effect on death at final follow-up, there was a non-statistically significant trend of reduction in death favouring <48 hours from stroke ictus to intervention (OR 0.14, 95% CI 0.09 - 0.21, compared to OR 0.68, 98% CI 0.12 - 3.77 if stroke ictus > 48 hours, p=0.08, Analysis 2.1). However, there was significant heterogeneity (I2=67.7%) of treatment effect, with only 1 cohort reporting outcomes for > 48 hours from stroke ictus to intervention compared to 7 in the < 48 hours cohort.

The subgroup analysis evaluating the effect of time from stroke ictus on death or disability defined as mRS>4 similarly found a non-statistically significant trend favouring <48 hours from stroke ictus to intervention (OR 0.16, 95% 0.10 - 0.24, compared to OR 0.68, 95% CI 0.12 - 0.377 in the >48 hours cohort, p=0.11, Analysis 2.2). There was also significant heterogeneity with treatment effect (I2=61.5%).

Dysphasia Presence/Absence

A subgroup analysis was performed comparing the effect of presence vs absence of dysphasia on death or severe disability (mRS>4). There was no statistically significant difference in treatment effect that was found when comparing the two variables (p=0.42, Analysis 3.1).

Short (6-month) vs Long (12-month) follow-up

A subgroup analysis compared 6 to 12-month follow-up data did not find a statistically significant difference in effect on death p=0.64, Analysis 5.1). Similarly, we performed a subgroup analysis comparing 6 to 12-month data for death and disability defined as both mRS>4 and mRS>3. In both cases, there was no statistically significant difference (p=0.67 and p=0.69 respectively, Analysis 5.2; Analysis 5.3).

Sensitivity Analyses

There was no study that was judged to have a high-risk of bias. Furthermore, there were no studies with fewer than 10 participants.

A sensitivity analysis was performed with the exclusion of 2 studies that had >10% of randomised participants not being included in the final analysis (HeMMI; Slezins 2012). There was no significant difference found in the primary outcomes.

A sensitivity analysis was also performed with the exclusion of HeADDFIRST, the only study with the average time from stroke ictus to intervention being over 48 hours. There was no significant difference found in primary outcomes.

Furthermore, a sensitivity analysis was performed with the exclusion of Demitur, the largest study in the meta-analysis, that had also been withdrawn from publication. There was no significant change in primary outcomes.

Discussion

The evidence in this new and updated systematic review re-affirms the main findings of the previous review published in 2012. However, it adds an additional body of evidence that expands on the role of surgical decompression in the management of malignant cerebral oedema after ischaemic stroke. It provides evidence for reducing disability in patients and utilises a broader evidence base that is generalisable to older age groups.

Summary of main results

The currently available evidence demonstrates a substantial reduction in death with the use of surgical decompression for the management of malignant oedema after ischaemic stroke (OR 0.17, 95% CI 0.12 - 0.25). This has been a consistent finding across the randomised trials with little heterogeneity in treatment effect (I2=0%). Furthermore, the effect is quite substantial, with a relative risk reduction

of 0.39 (95% CI 0.32 - 0.49). Surgical decompression similarly showed a strong and significant effect on reducing death or severe disability defined as mRS>4 (OR 0.21, 95% CI 0.14 - 0.31). This was again a consistent finding across the included randomised trials; however, the magnitude of treatment effect did differ across the included trials with moderate heterogeneity of treatment effects (I2=43%). This mirrors the finding of the previous review that demonstrates the profound reduction in death and severe disability. Our findings further corroborate this treatment effect across all age groups, including elderly patients above the age of 60 who were not included in the previous review. Furthermore, the reduction in death is seemingly maintained when patients are operated on after 48 hours from stroke ictus.

Moreover, surgical decompression has demonstrated a statistically significant reduction in death and disability defined as mRS>3 (OR 0.33, 95% CI 0.21 - 0.50). This is a substantial finding, given the previous review did not find a statistically significant reduction in death and disability. There was however moderate heterogeneity in the treatment effect with considerable variability in the treatment effect (I2=52%). The majority of studies individually did not find a statistically significant reduction in death or disability (mRS>3), however they did find at least a non-statistically significant trend towards the outcome (DECIMAL; Demitur; DESTINY; Destiny II; Slezins 2012; Zhao 2012). This may indicate that previous trials have been underpowered to assess the validity of this effect. Furthermore, in at least 3 of the included studies, there was either no difference, or a non-statistically significant worsening of death or disability (HAMLET; HeADDFIRST; HeMMI). It is noteworthy that these 3 studies were the only studies that allowed the inclusion of patients outside of 48 hours from stroke ictus. This indicates that earlier surgical decompression is crucial in preventing further neurological deterioration that is imperative for functional survival.

Earlier treatment is in principle a prophylactic approach to preventing the irreversible ischaemic damage that would otherwise be a cascading result of malignant oedema. Consequently, it would follow that earlier treatment should result in greater prevention of neurological injury, improved functional outcome and therefore, more significant treatment effect. Indeed, the subgroup analysis confirmed the importance of earlier surgical decompression with malignant oedema after ischaemic stroke ($p<0.00001$, I2=14%). The subgroup analysis compared patients who received treatment <48 hours from stroke ictus to patients receiving treatment after 48 hours. There was a statistically significant difference in treatment effect between the two cohorts, with a greater reduction in both death (OR 0.15, 95% CI 0.10 - 0.23, I2=67.7%) as well as death or severe disability (mRS>4, OR 0.17, 95% CI 0.11 - 0.28, I2 = 61.0%) in the earlier treatment subgroup. There were 7 cohorts in the earlier treatment cohort (<48 hours) with a total of 443 participants, compared to 1 cohort of patients in the later treatment subgroup (>48 hours from stroke ictus) with 25 total participants. There was however a significant degree of heterogeneity in treatment effect.

The utility of even earlier treatment cut-off, however, is not as clearly understood, with no included randomised trials mandating the inclusion of patients within 24 hours of stroke ictus. However, the median time for patient treatment in many of the included studies is within 24 hours of stroke ictus. A recent meta-analysis of randomised controlled trials comparing surgical decompression to best medical management for hemispheric infarction demonstrated no difference between patients randomised at <24hours vs 24-48 hours from ictus (Reinink 2021). They did however show worse outcomes in patients randomised at > 48 hours. This suggests that there may be a maximal benefit at 48 hours, earlier than which may have little difference. Indeed the development of malignant oedema generally occurs after 48 hours of ischaemic insult, after which the rise in intracranial pressure would be destructive without treatment (Das 2019).

Moreover, surgical decompression has demonstrated a significant treatment benefit in older age groups that were comparable to younger patients. This is significant, given that the evidence has consistently revealed considerably poorer outcomes for older patients after a large MCA stroke (Arac

2009). Indeed they have been shown to have substantially worse mortality, as well as functional recovery. Consequently, the majority of the earlier RCTs have excluded patients > 60 years of age from trials addressing the effectiveness of surgical decompression. Our review however demonstrated a statistically significant treatment effect in patients > 60 years of age, with a reduction in death (OR 15, 95% CI 0.10 - 0.24), death or severe disability (mRS>4, OR 0.18, 95% CI 0.10 - 0.33) and death or disability (mRS>3, OR 0.23, 95% CI 0.11 - 0.50). Indeed, the subgroup analysis did not show a statistically significant difference between the cohorts with age < 60 versus cohorts with age > 60. This demonstrates that surgical decompression is an effective treatment approach in patients with advanced age with comparable efficacy to its application in younger cohorts.

However, this finding must be interpreted with caution given it does not change the underlying poorer functional outcomes in older patients. Indeed, whilst 67% of patients (144 of 215 participants) in the cohorts < 60 years of age were classified as dead or disabled (mRS>3) at final follow-up, there was comparatively 80% of the participants in cohorts > 60 years of age (180 of 226 participants) who were also classed as dead or disabled. Similarly, Destiny II, the only trial to include patients > 60 years of age, had 93.8% (46 of 49 participants) of patients in the surgical cohort and 96.8% (61 of 63 participants) in the medical cohort either dead or disabled (mRS>3) at follow-up. This indicates that elderly patients are likely to have a poorer functional outcome independent of surgical intervention. Therefore, whilst the application of surgical decompression for elderly patients is effective in improving outcomes, clinicians should consider the overall prognosis of their patients and the expectations of their caregivers.

Dysphasia, another indicator of a poorer functional outcome, has similarly been demonstrated to have little impact on treatment efficacy. There was no difference in treatment efficacy in the subgroup analysis comparing 147 participants in 4 cohorts with dysphasia to 138 participants from 4 cohorts without dysphasia (p=0.42). It is important to consider it not proper randomisation given all the studies addressing the effect of dysphasia had differing criteria for whether a stroke affected the dominant or non-dominant hemisphere. Indeed, higher NIHSS scores were required for patients with a dominant hemisphere for significant speech disturbance. Furthermore, whilst our analysis did not reveal a statistically significant difference in treatment effect based on the presence of dysphasia, there were worse outcomes reported in the cohorts with dysphasia regardless of intervention compared to those without dysphasia. In the 4 cohorts with dysphasia present, 41.2% (28 of 68 participants) of patients in the surgical group and 77.2% (61 of 79 participants) in the medical group were either dead or severely disabled (mRS>4) at final follow-up, compared to 16.9% (12 of 71 participants) in the surgical group and 59.7% (40 of 67 participants) in the medical group without dysphasia. This suggests that whilst dysphasia may lead to a worse overall clinical outcome regardless of treatment effect.

Overall completeness and applicability of evidence

Our review has included studies that have selected a cohort of patients with unique clinical characteristics that have demonstrated significantly improved outcomes with the use of surgical decompression as an early treatment for malignant oedema after stroke. This unique cohort of patients, whilst representative of patients with large MCA strokes in many ways, did have distinctive clinical qualities that affect the applicability of the conclusions drawn from the meta-analysis. Whilst this review has expanded the generalisability of the conclusions drawn by including a greater array of patients, the patients selected still have exclusive clinical characteristics that should be recognised for an effective application of the conclusions.

This review has selected patients with severe clinical strokes and exclusively large size strokes on neuro-imaging. All the included studies have mandated the inclusion of patients with a minimum NIHSS score, with the lowest cut-off being 14 and the highest being 21. This practically selects for

patients with significant neurological deficits and reduce levels of consciousness. Such a severe neurological syndrome is not common in stroke patients, and even in the setting of large size MCA stroke. A retrospective review investigating the eligibility of stroke patients for hemicraniectomy found 90.7% of 2227 stroke patients had an NIHSS score of ≤ 15 (Rahme 2012). They also found a proportion of patients with large territory MCA strokes still did not meet such criteria of stroke severity. Moreover, the radiological criteria for inclusion involved a minimum of 50% of the MCA perfused region being infarcted, with many of the included studies mandating two-thirds of the MCA perfused region with a minimum infarct volume of 145cm3. Patients with such large size stroke are uncommon, and not typical even among the majority of MCA stroke patients (Hao 2015; Heinsius 1998; Liebeskind 2019).

Furthermore, the patients eligible for inclusion into the review were patients without significant life-limiting illnesses. Indeed the majority of studies excluded patients with an mRS ≥2, effectively selecting outpatients with even slight pre-morbid disability. Most studies further excluded patients with life-limiting illnesses or severe co-morbidities. This is a substantially important factor, given the majority of stroke patients have significant cardiovascular co-morbidities. The study by Rahme 2012 found that 50.2% of patients had a pre-morbid mRS ≥2, which would exclude them from this review. Whilst a positive treatment effect may be extrapolated to such patients, they may have a significantly poorer outcome than the healthier cohort included in this review, and clinicians would need to consider the utility of this added benefit given an independent and functional survival may be unlikely.

Our review however has expanded the generalisability of the conclusions drawn to patients ≥ 60 years. More recent RCTs, in particular Destiny II, have addressed the effectiveness of surgical decompression in older age groups and have found a similar treatment effect as younger cohorts. This is a noteworthy difference from the previous Cochrane review, where older patients have not been addressed. The conclusions however should be interpreted with caution given that whilst surgical decompression can lead to improved survival and clinical outcomes in an elderly cohort, there is a significantly poorer chance of functional and independent survival independent of this treatment effect.

Quality of the evidence

The bulk of the evidence used in this review was found to be of moderate to high quality. All of the included studies reported outcome measures using the same objective outcome assessment scores (modified Rankin Scale). Furthermore, the outcomes were assessed between 6 to 12 months after intervention across all the included studies. We performed a subgroup analysis to determine if outcomes reported at 6 or 12 months had any effect and found no significant difference in treatment effect. We also found the treatment effects to be generally consistent across all the included studies.

However, 2 of the studies had greater than 10% of participants not included in the final outcome analysis. These were generally small studies, however, with no effect on outcome measures upon the exclusion in a sensitivity analysis. Furthermore, participants and clinicians were not blinded to treatment allocation, which is inherent to the nature of the intervention being investigated. Moreover, 3 of the included studies had a pre-mature termination either due to interim analysis of study results or for pooling in a meta-analysis. This could theoretically increase bias towards increased treatment effect.

One of the included studies was withdrawn from publication (Demitur). The reasons given did not affect the integrity of the study or the results. This happened to be the largest study included in the meta-analysis. A sensitivity analysis did not show any substantial change in outcome measures when it was excluded.

Potential biases in the review process

Furthermore, this review was based on an analysis of tabular data. This restricts the robustness of subgroup analysis that can be performed. For instance, not all of the studies provided delineated outcome measures for age above and below 60 years of age. Furthermore, we did not have data from all studies delineating patients treated before and after 48 hours from stroke ictus. A meta-analysis based on individual patient data can help provide greater robustness for subgroup analysis. In addition, we acknowledge the hazards of subgroup analyses including selective reporting and inherent bias.

Agreements and disagreements with other studies or reviews

A recent patient meta-analysis investigating the utility of surgical decompression for malignant MCA infarction was performed by Reinink 2021. They pooled individual patient data from 7 different RCTs, which totalled 488 patients. The findings of this study largely mirror the conclusions of this Cochrane review. There was a strong and statistically significant reduction in death (OR 0.13, 95% CI 0.08 - 0.22, p<0.01) associated with surgical decompression as well as a greater chance of a favourable outcome defined as mRS≤3 (OR 2.95, 95% CI 1.55 - 5.60, p=0.01). The rigorous analysis allowed them to further interrogate the data and concluded a non-statistically significant trend towards a better outcome defined as mRS≤2 (OR 2.77, 95% CI 0.97 - 7.88, p=0.06). A subgroup analysis was performed analysing the effect of dysphasia, time from stroke ictus to intervention, age and vascular territories affected on treatment effect. Similar to our review, they found no heterogeneity of treatment effect based on age (</>60) or dysphasia. They found no difference in treatment effect in patients operated on > 48 hours from stroke ictus; however, this analysis was limited by small patient numbers.

Other recent systematic reviews and meta-analysis of the topic have also found similar conclusions to this review, validating the reduction in death and poor functional outcomes with the use of surgical decompression (Alexander 2016; Gul 2018; Qureshi 2016; Streib 2016; Wei 2020).

Authors' conclusions

Implications for practice

The evidence from this systematic review provides strong support for the use of early surgical decompression in the management of malignant oedema after acute ischaemic stroke. There is moderate to high quality evidence available, with consistent results across the literature supporting the improved outcomes. There is a significant reduction in death and disability when early surgical decompression is utilised.

The data also indicates that the treatment benefit is maintained in elderly age groups (> 60 years of age), who have previously been excluded from surgical decompression with large size strokes, although this needs to be interpreted with caution. This is based on lower quality evidence with significant heterogeneity in treatment effect. Furthermore, the prospects for a favourable outcome are significantly lower in advanced age groups regardless of the treatment effect. This needs to be considered when applying the conclusions of this review and an individual patient approach should be employed.

Moreover, the findings of this review also do not conclusively substantiate the importance of surgical decompression earlier than 48 hours from stroke ictus; there is a non-statistically significant trend of

greater benefit. The patient data, however, is small, and there is substantial heterogeneity in the treatment effect across the studies.

It is important to consider patient selection in the clinical application of these conclusions. The data utilised in this review are based on patients without significant co-morbidities, life-limiting illness, or significant disability, who have a severe stroke and reduced level of consciousness. These factors maximised the treatment benefit of early surgical decompression and are the focus of this review.

Studies suggest that early surgical decompression is under utilised with patients not being offered the treatment (Rahme 2012). Greater awareness of the improved outcomes for stroke patients may increase the application of early surgical decompression in the correct setting, improving overall treatment outcomes and the rate of functional survival.

Implications for research

We do not expect further studies to change the overall conclusions of this review with regard to the treatment effect.

Additional evidence is needed, however, to address treatment efficacy and relevance in particular subsets of patients with a MCA stroke. In particular, its utility in patients > 60 years of age should be assessed with regards to the absolute chances of favourable outcomes with surgical decompression to better guide management. Moreover, greater patient data is required to further validate the effect of the timing of surgical intervention. Whilst there is some evidence of benefit when employed < 48 hours from stroke ictus, more data may help to further substantiate this finding. Finally, future studies should consider additional outcome measures focused on patient's survival and caregiver's expectations. Further data on retrospective consent and outcome satisfaction is useful in understanding the overall benefit of the intervention.