Original Article

Primary decompressive craniectomy in neurocritical patients. a meta-analysis of randomized controlled trials, cohort and case-control studies

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Background: Primary decompressive craniectomy (DC) is increasingly used in certain neurosurgical pathologies. We have performed a systematic review and meta-analysis to study the results in terms of quality of life (QOL) and survival at 1 year of follow-up of patients undergoing this treatment.

Methods: Meta-analysis of randomized controlled trials, cohort and case-control studies.

Results: Fifteen studies (1,603 patients) were included (9 ischemic stroke, 3 trauma brain injury, 3 subarachnoid hemorrhage, none cerebral hemorrhage). None of the studies used specific QOL assessments. Eleven studies reported modified Rankin Scale and 4 Extended Glasgow Outcome Scale. DC reduces mortality or vegetative state (OR 0.21; 95% CI, 0.14–0.32) and the combined goal of mortality or moderate-severe disability (OR 0.35; 95% CI, 0.21–0.58) at 12 months in a malignant stroke of the middle cerebral artery (MCA). Patients ≤60 years, with infarctions ≥50% of MCA territory, without contralateral involvement, Glasgow Coma Score ≥6 and without bilateral fixed mydriasis, should be considered for early DC. However, international records indicate that a different population is being treated with DC. Those beneficial effects cannot be demonstrated in the other studied pathologies. As rule, the medical protocols do not include monitoring of oxygenation of brain tissue, cerebral microdialysis or electroencephalogram (EEG)-derived parameters.

Conclusions: The only clear current indication refers to certain select cases of malignant MCA infarction. Future studies should incorporate the evaluation of QOL, the institutional coverage and rehabilitation services, economic analysis, and impact of modern neuromonitoring techniques. Also, it seems that we should ensure that real clinical indications conform to those evaluated in clinical trials.

Keywords: Decompressive craniectomy (DC); meta-analysis; outcomes; critical care; stroke; trauma brain injury (TBI); subarachnoid hemorrhage

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Introduction

The first description on the use of decompressive craniectomy (DC) as a treatment for severe head trauma was published by Cushing in 1908, reporting a substantial reduction in the mortality of their patients (1). However, in the later decades, this treatment was not frequently used because many experts believed that the majority of survivors of DC were subsequently in a vegetative state or with severe disability (2). In the 1980s and 1990s, interest in DC was revitalized, and observational studies began to communicate good results (3,4). Virtually, all scientific literature consisting of randomized clinical trials (RCT), cohort and case-control studies on DC has been developed in the 21st century. *Table 1* summarizes some of the most recent meta-analyzes and systematic reviews on this topic (5-11)

Current guidelines for different neurocritical pathologies do not yet define a clear role for this treatment (12-16). Furthermore, RCTs are still being developed in which patients randomized to the control group are not submitted to DC [acute subdural hematoma: RESCUE-ASDH (17), subarachnoid hemorrhage (SAH): NCT02995928, intracerebral hemorrhage: NCT02258919 and NCT02135783]. Nonetheless, there seems to be an increased use of this treatment (18). The ORACLE Stroke Study (19) has been recently published, a paper in which the opinion of health professionals regarding the realization of DC in malignant middle cerebral artery (MMCA) infarction was reported. Although more than half of those responding to the survey would accept DC as a life-saving treatment, 90% of respondents would agree to consider a modified Rankin Scale (mRS) =4 as an unacceptable outcome, a situation in which the patient may be unable to walk unaided in addition to requiring assistance to attend bodily needs. It is necessary to emphasize that in the Japanese registry, 92% of the survivors were in this situation or worse at 3 months of follow-up (18). These data suggest that health professionals may have an excessive expectation of the benefits that a DC provides. More importantly, mRS is a scale that is not specifically designed to assess the quality of life (QOL) of survivors.

The present systematic review and meta-analysis was performed to determine whether craniectomy is effective in improving the survival and QOL expectancy or functional status of survivors when compared to conservative treatments in the treatment of neurocritical care patients.

Methods

A systematic search was conducted using MEDLINE, PubMed, EMBASE, Cochrane Library, Google Scholar, Science Direct and Web of Science until February 10th, 2018. This review included prospective RCTs, cohort and case-control studies regarding the effects of DC on patients with severe acute intracranial pathology potentially susceptible to this surgical treatment. We used different combinations of the following search keywords: traumatic brain injury, MMCA infarction, stroke, intracranial hypertension, cerebral hemorrhage, subdural hematoma, encephalitis, cerebral venous sinus thrombosis, subarachnoid hemorrhage, intracranial pressure (ICP), craniectomy, hemicraniectomy, decompressive, and medical management (Appendix 1: Search strategies). No language or data restrictions were applied.

Outcome: Our objective was to systematically analyze all articles that report on mortality and functional status of the cases at least 1 year after the insult.

The literature search was performed by two authors (J Muñoz and LC Visedo) who also compared their findings and selected articles to be reviewed by the rest of the authors. The data provided by each article were extracted and compared. Specifically, the variables determined were: number of cases, years of study development; country, number of centers participating in the study; inclusion and exclusion criteria; surgical technique of DC; medical protocol followed; functional or QOL scale with which the follow up was performed; mortality. Any discrepancies between the authors were resolved through review and consensus [Appendix 2: Checklist of PRIMA guideline for meta-analysis (20)].

Statistical study

Original data was abstracted from each study and used to calculate the pooled odds ratio (OR) and 95% confidence interval (95% CI) in order to compare DC and non-DC groups. We used the Review Manager 5.3 (21) and EPIDAT software (22). Heterogeneity analysis was performed using Cochrane's Q statistic and the graphic methods of Galbraith (23) and L'Abbe (24) for all the clinical trials. If the heterogeneity of each study was low or P>0.1, the fixed effect model was used (DerSimonian-Laird method); if the heterogeneity of each study was high or P<0.1, the random effects model was used. Meta-sensitivity and subgroup

Table 1 Decompressive craniectomy: recent systematic review and meta-analysis

Article, year	Disease	Studies included	Main results
Mohan Rajwani, 2017	MMCA	8 RCT, 4 M-A	In <60 years, DC within 48 hours of stroke onset < risk of death and major disability (mRS >3). In >60 years DC improved survival but the majority of survivors were left with major disability (mRS 4–5). DC performed more than 48 hours after symptom onset does not appear to be superior to best medical management
Streib, 2016	MMCA	6 RCT	Early DC resulted in an increased favorable outcome, defined as mRS ≤3
Back, 2015	MMCA	6 RCT	DC decreased mortality at the expense of increasing the proportion suffering from substantial disability (mRS 4–5) at the conclusion of follow-up
Barthélemy, 2016	Trauma brain injury	3 RCT, 9 observational studies	DC in specific populations does not offer GOS or mortality advantages compared with medical treatment Nonrandomized studies showed decreased mortality and increased GOS in patients aged ≤50 years when DC was performed <5 hours after TBI and with Glasgow Coma Scale score >5
Wang, 2015	Trauma brain injury	3 RCT	Whereas DC might effectively reduce ICP and shorten hospital stay in patients with TBI, its effect in decreasing mortality has not reached statistical significance
Zhang, 2016	Trauma brain injury: early *vs.* late DC	5 observational studies	Early DC may be more helpful to improve the long-term outcome of patients with refractory raised intracranial cerebral pressure after moderate and severe TBI
Alotaibi, 2017	Subarachnoid hemorrhage	15 observational studies	DC is associated with high rates of unfavorable outcome (mRS 4–6, GOS 1–3, eGOS 1–4) and death. Because of the lack of robust control groups in a majority of the studies, the effect of DC on functional outcomes versus that of other interventions for refractory intracranial hypertension is still unknown

MMCA, malignant middle cerebral artery infarction; ASH, acute subdural hematoma; RCT, randomized controlled trial; M-A, meta-analysis; DC, primary decompressive craniectomy; GOS, Glasgow Outcome Scale; eGOS, extended GOS; mRS, modified Rankin Scale.

analysis were used to explore the sources of heterogeneity between studies. Sensitivity analysis was performed based on the leave-one-out approach.

Subgroup analysis

A separate analysis of the studies was performed according to the pathology studied (MMCA infarction, cerebral hemorrhage, subdural hematoma, encephalitis, cerebral venous sinus thrombosis, subarachnoid hemorrhage) when it was possible to detect articles of the pathologies studied.

Quality and bias evaluation

Quality control was assessed using the Jadad scale for RCTs (25), and the Newcastle-Ottawa Scale for cohort and case-control studies (26). We evaluated publication bias and small study effects visually through funnel plots and statistically using Begg and Egger tests. A P value of <0.05 was considered statistically significant. RCTs were evaluated individually to estimate the risk of bias (27).

Results

We have found 15 studies that have analyzed 1,603 patients (884 controls) (*Table 2*). There was no study evaluating patients with cerebral hemorrhage, subdural hematoma, encephalitis or cerebral venous sinus thrombosis at one year after the DC. Nine studies reported ischemic stroke outcomes, 6 of which were RCTs (28-33), 2 cohort studies were performed on patients with MMCA (34,35) and 1 case-control study (36) reported on posterior fossa

Table 2 Characteristics of the studies included in the meta-analysis

Study, year of publication	Pathology/ functional scale	N, DC/ control	Type of study (Quality Index*)	Inclusion criteria	Exclusion criteria	Surgical technique	Medical protocol (control group)
DESTINY, 2007	Ischaemic stroke/mRS	17/15	Two-centre RCT [2]	≤60 years; MMCA ≤36 h; NIHSS ≥18 (dominant) or ≥20 (non-dominant); CT ≥2/3 MCA territory with basal ganglia involvement	Fixed pupils; previous mRS ≥2; Barthel ≤95; GCS ≤6; haemorrhagic transformation	At least 12 cm diameter DC; mean interval between infarction and surgery 24, 4 h	Standard care; ICP monitoring; no barbiturates
DECIMAL, 2007	Ischaemic stroke/mRS	20/18	Multicentric RCT [2]	≤55 years; MMCA ≤24 h; NIHSS ≥16; CT ≥50% of MCA territory	Contralateral infarction; previous mRS ≥2; severe comorbidity	Extensive DC; mean interval between infarction and surgery 20, 5 h	Standard care; no hypothermia; ICP monitoring discretional
HAMLET, 2009	Ischaemic stroke/mRS	32/32	Multicentric RCT [3]	≤60 years; MMCA ≤96 h; NIHSS ≥16 (right) or 21 (left), GCS ≤13; CT ≥2/3 of MCA territory	Hemispheric stroke; fixed pupils; alteplase ≤12 h; severe comorbidities	At least 12 cm diameter DC; time stroke-randomization 31 h	Standard care; ICP monitoring; no barbiturates
Slezins, 2012	Ischaemic stroke/mRS	11/13	One-centre RCT [3]	MMCA ≤48 h.; CT ≥50% MCA territory; infarct ≥145 mL; NIHSS ≥15	Fixed pupils; previous mRS ≤2	At least 12 cm diameter DC; mean interval between infarction and surgery 21 h	Standard care
Zhao, 2012	Ischaemic stroke/mRS	24/23	Multicentric RCT [3]	≤60 years; MMCA ≤48h; GCS ≤9 (motor + ocular); CT ≥2/3 of CMA territory	Previous mRS ≥2; GCS (motor + ocular) ≤6. One or two fixed pupils; contralateral infarct	At least 12 cm diameter DC	Standard care; ICP only in selected cases; no barbiturate; no hypothermia
DESTINY II, 2014	Ischaemic stroke/mRS	49/63	Multicentric RCT [2]	≥ 61 years; MMCA; NIHSS ≥14 (dominant) or ≥19 (non-dominant); TC 2/3 MCA territory with basal ganglia involvement	Fixed pupils; previous mRS ≥1 or Barthel ≤95; GCS ≤6	At least 12 cm diameter DC; time stroke-randomization 24, 6 h	Standard care; ICP monitoring discretional; no barbiturates; no hypothermia
Rai, 2014	Ischaemic stroke/mRS	36/24	Multicentric prospective cohort [6]	CT ≥50% MCA territory; NIHSS 16 GCS ≤13; clinical herniation signs	Fixed pupils; previous mRS ≥2; GCS ≤6	At least 12 cm diameter DC; mean delay to surgery from time of onset of symptoms 56 h	Standard care
Hao, 2015	Ischaemic stroke/mRS	31/188	One-centre retrospective cohort [6]	≤60 years; <48 h after stroke onset; CT ≥2/3 MCA territory; ≥5 mm midline shift	Previous mRS ≥2	No done	No done

Table 2 (*continued*)

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Study, year of publication	Pathology/ functional scale	N, DC/ control	Type of study (Quality Index*)	Inclusion criteria	Exclusion criteria	Surgical technique	Medical protocol (control group)
Kim, 2016	Ischaemic cerebellar stroke/mRS	28/56	Multicentric case-control [8]	GCS ≥9; no GCS score changes within 72 hours from onset; cerebellar infarction volume ratio between 0.25 and 0.33	No done	Preventive bilateral DC with the opening of the foramen magnum	Standard care; no steroids
DECRA, 2011	Trauma brain injury/ eGOS	73/82	Multicentric RCT [2]	≤60 years; ≤48 h; diffuse brain injury; GCS =3–8; ICP ≥25 mmHg ≥5 min at least twice during injury a 30 min period	Intracranial hemorrhage; medular injury; cardiac arrest; surgical subdural hematoma	Bifronto- parieto-temporal	ICP guided; ventriculostomy preferred
RESCUEicp, 2016	Trauma brain injury/ eGOS	194/179	Multicentric RCT [4]	≤65 years; ICP ≥25 mmHg for 1–12 h	Fixed pupils; injury that was deemed to be unsurvivable	Bifrontal DC 63%; unilateral DC 37%	ICP guided; hypothermy permitted; barbiturates 87%
Yu, 2015	Trauma brain injury/ eGOS	112/111	One-centre retrospective cohort [7]	≤60 years; GCS ≤8	Fixed pupils; medular injury; cardiac arrest	According to location	BTF Guidelines, ventriculostomy included; ICP monitoring
D'Ambrosio, 2005	Subarachnoid hemorrhage/mRS	12/10	One-centre case-control [4]	≤75 years; Hunt and Hess Grade IV or V; significant perisylvian or temporal lobe ICH; signs of brainstem compression	Significant brainstem infarction; hemicraniectomy performed to treat cerebral oedema	Hematoma evacuation and DC	Standard care; 50% aneurysm clipping; 30% coil embolization
Uozomi, 2014	Subarachnoid hemorrhage/eGOS	56/56	One-centre case-control [6]	Underwent either surgical clipping (7 patients) or endovascular coiling within 72 h; DC as judged by the treating neurosurgeon if sustained therapy-refractory ICP ≥20–25	Fixed pupils	Al least 12 cm diameter DC; ICP monitoring	ICP monitoring. Multimodal monitoring, microdialysis including. Barbiturates used
Zhao, 2015	Subarachnoid hemorrhage/mRS	24/14	Multicenter case-control [5]	≤75 years; surgical treatment of SAH WFNS IV–V with intracranial hematoma ≥30 mL	WFNS I–II; no surgical treatment (coils)	DC parieto-fronto-occipital (major medical complications 79%)	No done. No secondary DC (major medical complications 93%)

*, Quality Index: Jadad Scale (RCT; range, 0–5) and Newcastle-Otawa Scale (observational studies; range, 0–8). mRS, modified Rankin Score; RCT, randomized controlled trial; MMCA, malignant middle cerebral artery stroke; DC, decompressive craniectomy; MCA, middle cerebral artery; GCS, Glasgow Coma Score; Time to treat, mean time from symptom onset to treatment start; ICP, intracranial pressure; CT, cranial tomography; NIHSS, National Institutes of Health Stroke Scale; eGOS, extended Glasgow Outcome Scale; ICH, intracranial hemorrhage; WFNS, World Federation of Neurosurgical Societies.

ischemic infarction. Severe trauma brain injury (TBI) has been assessed by 2 RCTs (37,38) and a cohort study (39). Three case-control studies on DC have been published in subarachnoid hemorrhage (SAH) (40-42).

None of the studies used specific instruments to assess the QOL of the survivors. As a long-term functional evaluation criterion, 11 studies reported on the mRS and 4 the extended Glasgow Outcome Scale (eGOS). Therefore, the primary outcomes of our meta-analysis were: (I) overall mortality or vegetative state (mRS 5–6 or eGOS 1–2) and (II) mortality or moderate to severe disability on long time surveillance (mRS 4–6 or eGOS 1–4).

Patient selection

The majority of studies limit the age of indication of DC around 60 years. The DESTINY II study specifically studied older patients (33), and two observational studies on DC in SAH included patients up to 75 years of age (40,42). The patients included with MMCA stroke were cases with deterioration following an evolution of a few hours, although with moderate clinical repercussion, generally with Glasgow Coma Score (GCS) ≥6, absence of fixed pupils, and with a perfusion deficit of at least 50% of the territory of the MCA without contralateral involvement or 1/3 deficit in cerebellar infarcts. In the case of TBI, the presence of refractory intracranial hypertension was required in the two RCTs included, although in one for more than 15 minutes (≥20 mmHg, continuously or intermittently) within a 1-hour period (37) and in the other study up to 12 hours (≥25 mmHg) duration was permitted (38). In both studies even GCS =3 patients were allowed. The DECRA study included patients with reactive bilateral mydriasis (37), while the RESCUEicp excluded them (38).

Surgical technique

The standard surgical technique in the treatment of MMCA is a craniectomy of at least 12 cm in diameter. In the DECRA study (29) a larger craniectomy (a DC bifronto-parieto-occipital) was performed than that used in the RESCUEicp (30).

Medical protocol and neurocritical monitoring

In general, standard clinical practice guidelines were applied. Only two studies on MMCA infarction systematically monitored ICP (28,30), as in all the studies on patients with TBI (37,39). The case-control study of Uozomi was the only one in which multimodal monitoring techniques, including cerebral microdialysis, were systematically applied (41). Overall, barbiturates and hypothermia were excluded from treatments, with the exception of the RESCUEicp trial (38).

Outcomes

DC reduces mortality or vegetative state in MMCA stroke (OR 0.21; 95% CI, 0.14–0.32, RCT and observational studies) (*Figure 1*). DC also reduces the combined goal of mortality or moderate-severe disability at 12 months in MMCA stroke (OR 0.35; 95% CI, 0.21–0.58) (*Figure 2*). Those effects cannot be demonstrated in the treatment of refractory intracranial hypertension associated with cranial trauma (*Figures 1B*,*2B*). The sensitivity study of this meta-analysis does not establish a change in results by excluding the results of the DECRA study (37). Similarly, in SAH advantages with DC have not been found (*Figures 1C*,*2C*).

Quality and bias

Only one study reached the highest possible score (36). In general, the observational studies reached higher values than the RCTs. The small number of studies did not allow a sensitivity analysis based on methodological quality. Analysis of the funnel plot did not demonstrate the presence of publication bias (*Figure 3*). *Table 3* summarizes the assessment of the risk of bias in selected RCTs.

Ethics

As the data is all anonymised, so that there is no chance for a person's private medical information to leak, the ethical issues are strictly methodological. Therefore, no evaluation was requested by the Ethics Committee.

Discussion

Primary DC treatment has an indisputable rational basis: it is a question of offering the possibility of improved cerebral perfusion to patients with detrimental space occupying intracranial lesions. However, the reluctance to perform this procedure due to limitations regarding the QOL and functional situation of the survivors seems justified. Probably, the most relevant finding of our study is that Quality-Adjusted Life-Years (QALYs) and Disability-

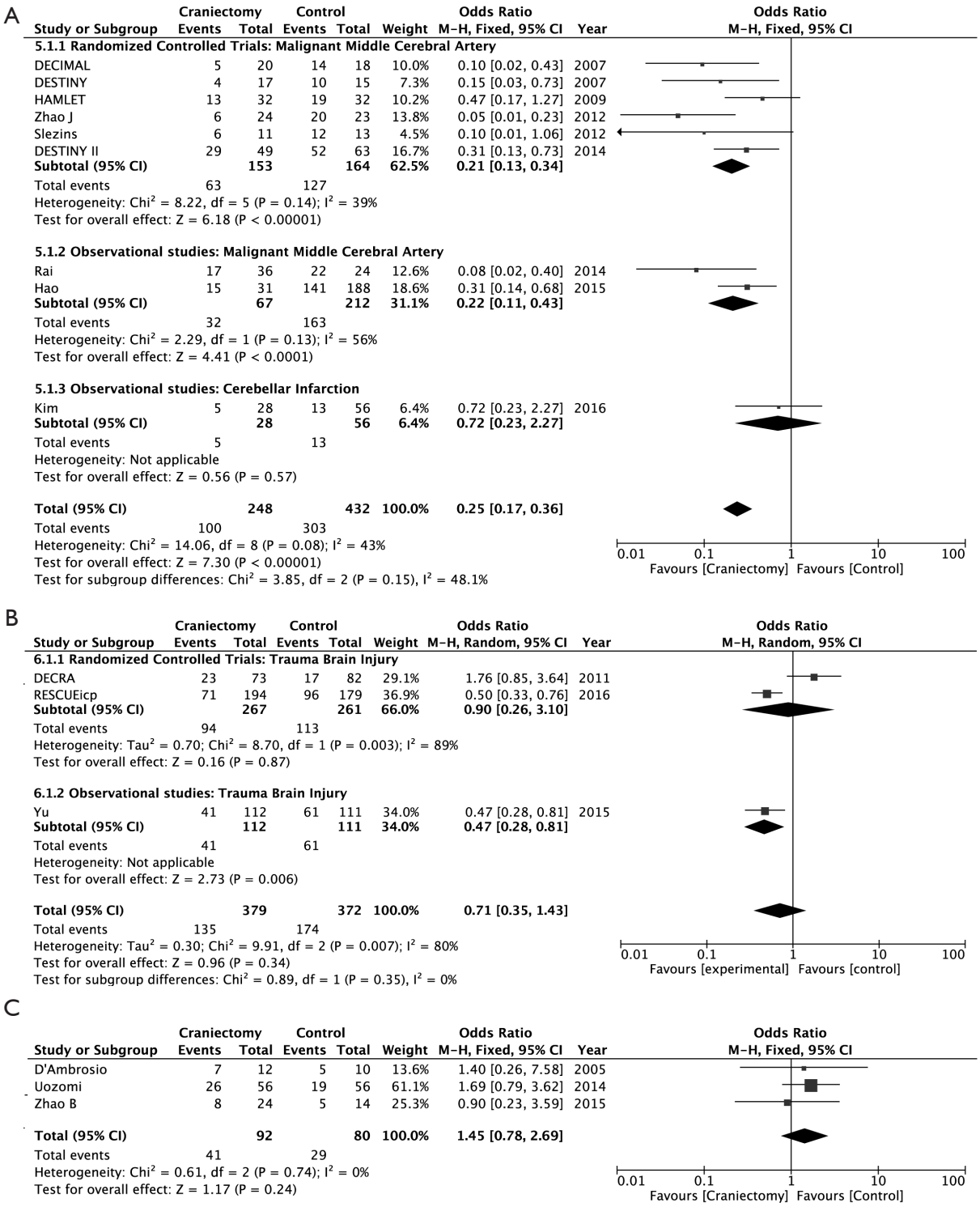

Figure 1 Results of the meta-analysis of decompressive craniectomy: mortality or vegetative state (mRS 5–6 or eGOS 1–2) at 1 year of evolution in: (A) ischemic stroke; (B) traumatic brain injury; (C) subarachnoid hemorrhage. Only the reduction of the combined end point is demonstrated in the case of ischemic strokes at the expense of a reduction in the mortality or vegetative state in the year of follow-up in the middle cerebral artery malignant stroke. mRS, modified Rankin Scale; eGOS, extended Glasgow Outcome Scale.

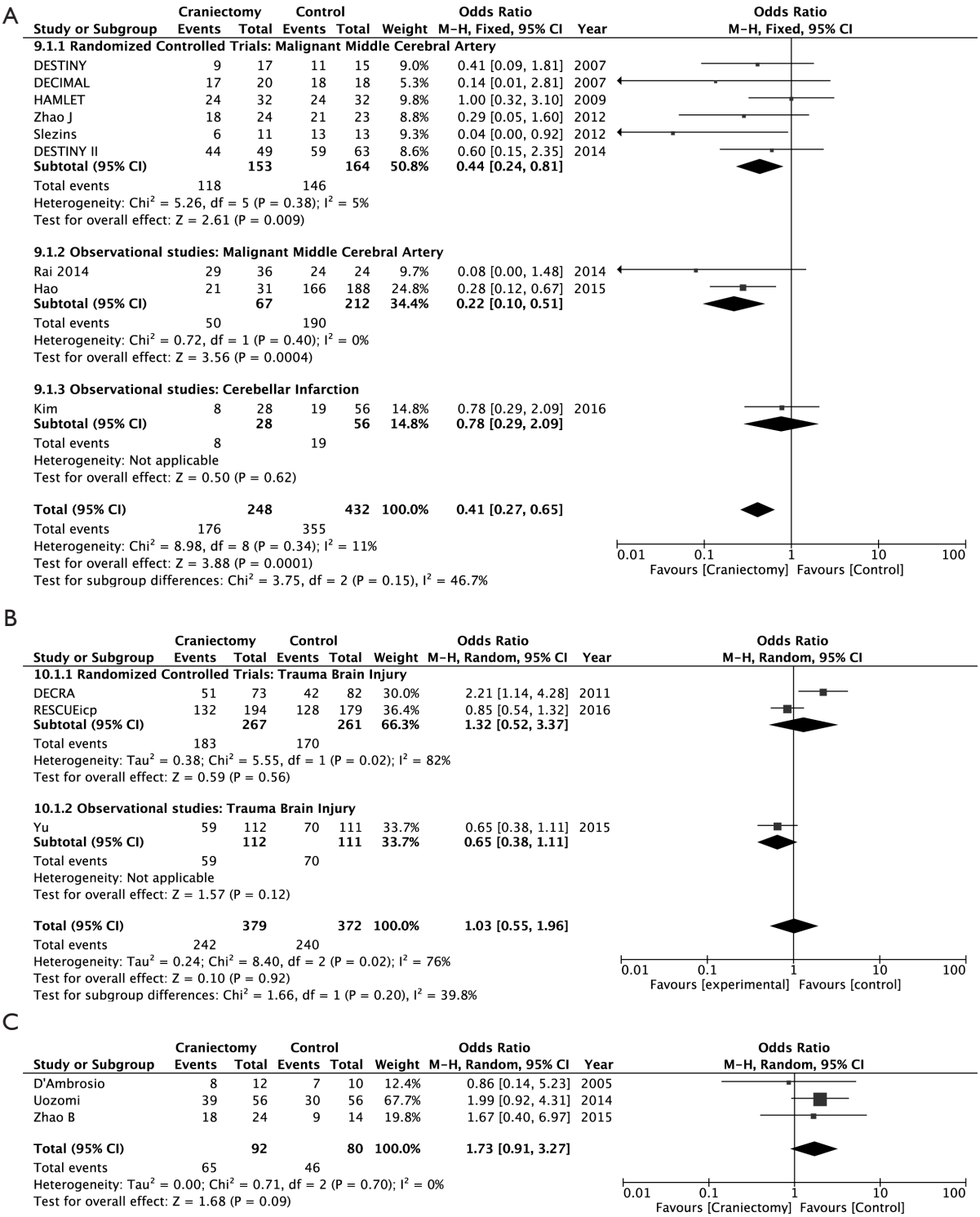

Figure 2 Results of the meta-analysis of decompressive craniectomy: mortality or moderate-severe disability (mRS 4–6 or eGOS 1–4) or at 1 year of evolution in: (A) ischemic stroke; (B) traumatic brain injury; (C) subarachnoid hemorrhage. Only the reduction of the combined end point is demonstrated in the case of ischemic stroke at the expense of a reduction in the mortality or moderate-severe disability in the year of follow-up in middle cerebral artery malignant stroke. mRS, modified Rankin Scale; eGOS, extended Glasgow Outcome Scale.

Adjusted Life-Years (DALYs) have not been applied in the analysis of the outcomes, burdens, and economic costs of DC on medium or long follow-up.

Stroke is the leading cause of disability in adults in Western society (43). Specific instruments and scales are increasingly needed to assess the outcomes of stroke treatment in a patient-centered fashion. Scales that measure neurological involvement, such as the National Institute Health Stroke Scale (NIHSS), the Scandinavian Neurological Scale of Stroke or the Canadian Scale, do not evaluate the QOL perceived by the survivors after a stroke. The mRS, the eGOS or the Barthel Index can be used to evaluate the outcomes of stroke treatment.

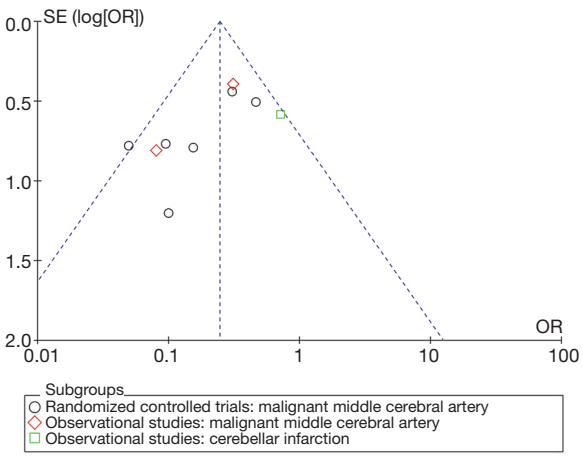

Figure 3 The funnel-graph analysis of studies on ischemic stroke does not detect the presence of publication bias. SE, standard error; OR, odds ratio.

However, these scales evaluate the physical aspects of stroke and leave aside other aspects such as memory, communication, thinking, emotions and social function (44). Some of the works published in the area of QOL and stroke have been developed with generic measures, such as the SF-36 health questionnaire (45) or the EuroQOL (46). Several QOL scales have also emerged specifically for ischemic stroke with recognized psychometric properties (47-52). The National Institutes of Health (NIH) consensus conference on the rehabilitation of persons with TBI (53) made two broad recommendations concerning QOL: (I) QOL predictors for persons with TBI, their families, and significant others should be studied, and (II) generic health-related QOL assessment instruments must be validated for use with persons with TBI, and TBI specific instruments must also be developed and validated. However, in our review only one study was identified that used specific estimates to evaluate DC. This study was not included in our meta-analysis as the follow-up was less than 1 year (54). An additional important point is that it maybe be questionable whether the so-called "retrospective consent" (the a posteriori acceptance of the functional situation) is really a demonstration of the adaptive capacity of humans (55).

The second remarkable finding from our review is the relative absence of the incorporation of advances in neuromonitoring of critically ill patients, both those submitted to DC and those treated conservatively, except for one case-control study (41). A recently published trial demonstrated a lower mortality in patients who had been treated with a strict standardized medical management protocol when compared with the medical management

Table 3 Risk of bias assessment for randomized controlled trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
DECIMAL	⊕	?	?	⊕	⊕	⊕	⊕
DESTINY	⊕	⊕	?	⊕	⊕	⊕	⊕
HAMLET	⊕	?	?	⊕	⊕	⊕	⊕
Zhao	⊕	⊕	?	⊕	⊕	⊕	⊕
Slezins	⊕	?	-	-	⊕	⊕	?
DESTINY II	⊕	?	?	⊕	⊕	⊕	⊕
DECRA	⊕	⊕	?	?	⊕	⊕	⊕
RESCUEicp	⊕	⊕	?	?	⊕	⊕	⊕

"⊕": low risk of bias; "-": high risk of bias; and "?": indicates unclear risk of bias.

arms in the other trials (56). It is true that in most studies the "best medical treatment" was applied, adjusted to the current guidelines. However, although the cost-effectiveness of these practices may be under study, what is striking is the lack of use of techniques quite common in the care of neurocritical patients, such as ICP, cerebral perfusion pressure, monitoring of brain tissue oxygenation, cerebral microdialysis or EEG-derived parameters (57).

Our study indicates that a primary DC of at least 12 cm. of diameter is a technique that is indicated in certain cases of MMCA stroke. Patients ≤60 years, with unilateral infarctions ≥50% of the MCA territory, treated in the first 24–36 hours of evolution, with a good previous functional situation and that when evaluated have a GCS ≥6 and do not present bilateral fixed mydriasis, should be considered for this treatment. DC not only reduces mortality in this group of patients, but also provides the prospect of a reasonable functional outcome in the survivors. In view of the protocols followed in the MMCA stroke, the postoperative monitoring of ICP should not be considered mandatory. If we admit that the scales used for the evaluation of DC are sufficient, with the already accumulated evidence, it would not be ethical to continue carrying out studies in which the control group is deprived of that treatment in MMCA stroke. Three recent reviews, which have also included studies with a shorter follow-up period, coincide with our results (5-7) (*Table 1*). Mohan Rajwani *et al.* especially emphasize that DC performed more than 48 hours after symptom onset does not appear to be superior to best medical management (5).

The real-world indication of DC in patients suffering an ischemic stroke seems, however, to be digressing from the theoretical indications. In the Japanese registry, patients older than 60 years accounted for more than 80% of DC, 26% of patients had a GCS <6, more than half of the patients had pre-surgical signs of midbrain compression and more than one third of cases were operated on despite more than 48 hours of evolution (18). A retrospective analysis of the national database of hospitalized patients in the United States between 2005 and 2008 has shown that 28% of the patients treated with DC were over 65 years (58). Other studies have shown that there is a growing tendency to increase the age of treated patients. Bhattacharya *et al.* have reported that the indication DC in patients over 60 years old varied from 30.4% of all hemicraniectomies in 2001 to 36.9% in 2009 (59). The most recent trial that analyzed this question, and which included the largest number of cases, is the DESTINY II trial (33), which studied patients ≥60 years. This RCT demonstrated improved survival, but showed that only a small minority of older patients survived without disability severe enough to require assistance with most bodily needs.

According to our review, the current evidence is inconclusive and does not support the performance of primary DC in trauma or hemorrhagic injuries outside research protocols. The three observational studies published to date on hemorrhagic strokes have been excluded from our study because the follow-up period was less than 1 year (60-62). However, the results concerning mortality or severe disability at 6 months did not show any improvements over what was observed in the control group (OR 0.74; 95% CI, 0.38–1.45). Neither in severe TBI nor in SAH this surgical treatment has been shown to reduce mortality or improve functional prognosis. Even in the case of SAH, there seems to be a tendency towards a deterioration in outcome. In a recent review of 13 observational studies, Alotaibi *et al.* also reported similar results (11) (*Table 1*).

The recent publication of the results of the RESCUEicp (38) trial has once again revitalized the controversy regarding the indication of DC. In this study, the craniectomy was evaluated in patients with severe TBI and refractory intracranial hypertension. The results reflect that, although DC reduces mortality, this treatment increases the probability of vegetative state or severe disability. In addition, it is was not found to be superior to conservative treatment with regards to the rates of moderate disability or good recovery, although these authors found that a substantial number of patients with severe disability at 6 months had improved to a better outcome in 1 year. This trial found improved results when compared to those reported previously in the DECRA trial, which was also performed in the context of severe head trauma (37). These results are consistent with the fact that the current evidence does not indicate that ICP monitoring is significantly superior to no ICP monitoring in terms of the mortality of TBI patients (63). Although Zhang *et al.* in a review of 5 observational studies suggest a favorable effect in cases where the intervention was performed earlier (10), two recent meta-analyses confirm that it has not been possible to find benefits in mortality or prognosis of these patients in the medium or long-term follow-up (8,9) (*Table 1*).

On the other hand, as a limitation, our study included trials with limited simple size. Small trials are more likely to report larger beneficial effects than large trials in critical care medicine, which could be partly explained by the lower methodological quality in small trials (64).

In our opinion, many aspects remain to be clarified with respect to the indications of a DC. It is necessary to evaluate the QOL of survivors with adequate validated instruments. Probably, the common mRS and eGOS should be substituted in future studies. It is also appropriate to monitor the institutional coverage and rehabilitation services offered to survivors for the long-term evaluation of results. We also believe that it would be advisable to maximize the available battery of monitoring and treatment of neurocritical patients. It is also necessary to incorporate economic analyses of the impact of this treatment. It is, of course, essential to control that the actual clinical indications of DC conform to those that are evaluated in clinical trials. It is necessary to try to offer the society and the relatives of patients simple, straightforward and impartial information regarding these aspects. This is especially true in order to avoid the interpretation of a DC as a "life or death" dilemma in a situation of pain and strong emotional tension. It may not be time for a moratorium, but we believe it is time for a re-evaluation of this treatment strategy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Appendix 1: Search strategies

Pathologies

Decompression OR Hemicraniectomy OR (decompres* AND (brain or crani* or surgery or surgical*)).

Craniocerebral Trauma [mh] OR Brain Edema [mh] OR Cerebrovascular Trauma [mh] OR ((head or cranial or cerebral or brain* or intra-cranial or inter-cranial) OR ("diffuse axonal injury" OR "diffuse axonal injuries") OR Stroke [mh] OR Stroke [tiab] ischemic stroke [mh] Or stroke [tiab] OR brain hemorrahag* [mh] or brain hemorrahag* [tiab] OR cerebral hemorrahag* [mh] or cerebral hemorrhag* [tiab] OR brain haemorrahag* [mh] or brain haemorrahag* [tiab] OR cerebral haemorrahag* [mh] or cerebral haemorrhag* [tiab] OR subarachnoid hemorrhag* [mh] OR subarachnoid hemorrhage* [tiab] OR subarachnoid haemorrhag* [mh] OR subarachnoid haemorrhage [tiab].

Prognosis

Glasgow Coma Score [mh] OR Glasgow Coma Score [tiab] OR GOS [mh] OR GOS [tiab] OR modified Rankin Scale OR mRH OR ("persistent vegetative state") OR ((unconscious* OR coma* OR concuss*).

Publications

Randomized controlled trials, cohorts and case controls studies

(clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials as topic[MeSH Terms] OR (clinical[Title/Abstract] AND trial[Title/Abstract]) OR random allocation[MeSH Terms] OR RCT OR therapeutic use[MeSH Subheading] OR MH random assignment OR TX randomised OR randomized OR randomly OR random order OR random sequence or randomly allocated or at random OR exp cohort studies/ OR cohort$.tw. OR controlled clinical trial.pt. OR epidemiologic methods/ OR exp case-control studies/OR(case$ and control$).tw. OR exp cohort analysis OR exp longitudinal study/ OR exp prospective study/ OR exp follow up/ OR cohort$.tw. OR exp case control study/ OR (case$ and control$).tw.

Specific Medline review and meta-analysis

1. Meta-Analysis as Topic; 2. meta analy$.tw.; 3. metaanaly$.tw.; 4. Meta-Analysis/; 5. (systematic adj (review$1 or overview$1)).tw.; 6. exp Review Literature as Topic/; 7. or/1-6; 8. cochrane.ab.; 9. embase.ab.; 10. (psychlit or psyclit).ab.; 11. (psychinfo or psycinfo).ab.; 12. (cinahl or cinhal).ab.; 13. science citation index.ab.; 14. bids.ab.; 15. cancerlit.ab.; 16. or/8-15; 17. reference list$.ab.; 18. bibliograph$.ab.; 19. hand-search$.ab.; 20. relevant journals.ab.; 21. manual search$.ab.; 22. or/17-21; 23. selection criteria.ab.; 24. data extraction.ab.; 25. 23 or 24; 26. Review/; 27. 25 and 26; 28. Comment/; 29. Letter/; 30. Editorial/; 31. animal/; 32. human/; 33. 31 not (31 and 32); 34. or/28-30,33; 35. 7 or 16 or 22 or 27; 36. 35 not 34.

Specific Embase review and meta-analysis

1. exp Meta Analysis/; 2. ((meta adj analy$) or metaanalys$).tw.; 3. (systematic adj (review$1 or overview$1)).tw.; 4. or/1-3; 5. cancerlit.ab.; 6. cochrane.ab.; 7. embase.ab.; 8. (psychlit or psyclit).ab.; 9. (psychinfo or psycinfo).ab.; 10. (cinahl or cinhal).ab.; 11. science citation index.ab.; 12. bids.ab.; 13. or/5-12; 14. reference lists.ab.; 15. bibliograph$.ab.; 16. hand-search$.ab.; 17. manual search$.ab.; 18. relevant journals.ab.; 19. or/14-18; 20. Data extraction.ab.; 21. selection criteria.ab.; 22. 20 or 21; 23. review.pt.; 24. 22 and 23; 25. letter.pt.; 26. editorial.pt.; 27. animal/; 28. human/; 29. 27 not (27 and 28); 30. or/25-26,29; 31. 4 or 13 or 19 or 24; 32. 31 not 30.

Specific CINAHL review and meta-analysis

1. Meta analysis/; 2. Meta analys$.tw.; 3. Metaanaly$.tw.; 4. exp Literature review/; 5. (systematic adj (review or overview)).tw.; 6. Or/1-5; 7. Commentary.pt.; 8. Letter.pt.; 9. Editorial.pt.; 10. Animals/; 11 Or/7-10; 12. 6 not 11.

Appendix 2: Checklist of PRISMA Guidelines for meta-analysis

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	2
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	Yes: Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	3
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	No
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	Table 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	6, Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (I) simple summary data for each intervention group; (II) effect estimates and confidence intervals, ideally with a forest plot	Figures 1&2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	Figures 1&2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15)	6 & Figure 3
Additional analysis	23	Give results of additional analyses, if done [e.g., sensitivity or subgroup analyses, meta-regression (see Item 16)]	Figures 1&2
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	6&9&10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	10&11
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	11