JPRAS Open 20 (2019) 1–18

Contents lists available at ScienceDirect

JPRAS Open

journal homepage: www.elsevier.com/locate/jpra

Review

# Surgical intervention for chronic migraine headache: A systematic review

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A R T I C L E I N F O

*Article history:*
Received 17 December 2018
Accepted 6 January 2019
Available online 16 January 2019

*Keywords:*
Migraine
Migraine surgery
Chronic migraine

A B S T R A C T

*Aims:* Migraine is a global phenomenon, affecting more than 10% of the world's population. It is characterized by unilateral headache that may be accompanied by vomiting, nausea, photophobia and phonophobia. Some patients with chronic migraine respond to extra-cranial botulinum toxin type A injection, although the benefits observed are temporary. The rationale for surgical trigger site deactivation is to achieve lasting symptomatic improvement or permanent relief from migraine.
*Methods:* We performed a PRISMA-compliant systematic review of clinical studies evaluating surgical intervention for migraine by searching Ovid MEDLINE and EMBASE databases from inception to June 2017. Studies were independently screened by two authors. Data were extracted on study characteristics, migraine outcomes, adverse events and recurrence. The quality of evidence was assessed using the GRADE approach. The review

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https://doi.org/10.1016/j.jpra.2019.01.002

protocol was prospectively registered on the PROSPERO database (CRD42017068577).
*Results:* The search strategy identified 789 articles; of them, 18 studies (4 RCTs and 14 case series) were eligible for analysis. Surgical interventions were heterogeneous and variably involved peripheral nerve decompression by myectomy or foraminotomy, nerve excision, artery resection and/or nasal surgery. All studies reported significant reductions in migraine intensity, frequency, duration and composite headache scores following surgery. Study heterogeneity precluded formal meta-analysis. Where reported, adverse event rates varied markedly between studies. The quality of included studies was consistently low or very low.
*Conclusion:* There is insufficient evidence to support the effectiveness of any specific surgical intervention for chronic migraine, especially with regard to permanent relief; however, all included studies report improvements in key outcomes following migraine surgery. A definitive, well-powered RCT with objective surgical and patient-reported outcome measures and robust adverse event reporting is required.



## Introduction

Migraine headache is a global phenomenon and affects more than 10% of the world's population.[1] It is the most common brain disorder and is characterised by moderate to severe unilateral headache that may be accompanied by vomiting, nausea, photophobia and phonophobia.[1,2] It is more common than both diabetes mellitus and asthma.[3,4] Women are more than twice as likely to suffer with migraine than men, and it is more common in students and urban residents.[1] Approximately one third of migraine sufferers are not helped by standard therapies.[5,6] The economic effect of migraine is significant, surpassing $13 billion per year in the United States alone, predominantly through the cost of medicines and time off work.[7]

Patients experiencing headache on more than 15 days per month – where at least eight of these headache days meet the criteria for migraine or respond to migraine-specific therapy – may be diagnosed with chronic migraine.[8] It is estimated that between 1.3% and 2.4% of the general population suffers from chronic migraine and its additional socioeconomic and disability sequelae.[9–12]

A cohort of chronic migraine patients responded to a botulinum toxin type A injection administered into specific anatomic extra-cranial locations. In the standard paradigm, the majority of these injection sites are agnostic to the specific headache location in any one patient – although up to eight further injections may then be given using a 'follow the pain' strategy. The PREEMPT studies provide evidence supporting the effectiveness of both botulinum toxin and placebo injections for chronic migraine, with greater improvement in the intervention group, in terms of headache days per month and improved health-related quality of life.[13–16]

The extra-cranial migraine trigger site concept differs from traditional concepts of migraine pathogenesis, in that it describes the mechanical compression of an extra-cranial peripheral nerve by localised muscle activity, which usually corresponds to the area of onset of the headache. Numerous extra-cranial trigger sites have been described in the literature around the cranio-facial regions, posterior head and neck and nose.[17–21] Consistent aberrant peripheral signalling through intermittent nerve compression is thought to initiate centrally mediated migraine activity.[22,23] Botulinum toxin injections at extra-cranial trigger sites cause paralysis of the surrounding muscle tissue and hence temporarily de-activate that specific trigger site. It is associated with low complication rates, but it can only provide temporary relief.[13] Patients with chronic migraine responsive to botulinum toxin at certain trigger sites may therefore be candidates for surgical intervention – especially if botulinum toxin therapy becomes less effective over time or is associated with unwanted side effects.

A variety of surgical options for chronic migraine have been proposed, including peripheral nerve decompression by myectomy or foraminotomy, nerve excision, artery resection and/or nasal surgery. The premise of surgical deactivation of trigger sites through these methods is to ameliorate migraine symptoms and achieve permanent deactivation of the trigger site.[17,24–26]

### *Rationale*

The effectiveness of surgical intervention for chronic migraine has been asserted by a number of primary clinical studies.[26–29] However, to date, there has been no critical evaluation of the quality of the evidence for migraine surgery or whether the available evidence supports its effectiveness. Furthermore, the risk of adverse events is unclear. This systematic review of surgical interventions for chronic migraine provides an objective assessment of the evidence and a descriptive analysis of its effectiveness and adverse outcome rates.

### *Objectives*

1. To evaluate the quality of evidence for the efficacy of surgical intervention for chronic migraine.
2. To determine the effect of surgical intervention on migraine intensity, frequency, duration and migraine headache index (MHI) outcomes through pooled descriptive analysis.
3. To determine the risk of adverse events and migraine recurrence following surgical intervention for chronic migraine.

## Methods

The objective of this review was to assess the literature on surgical intervention for migraine with a focus on identifying and evaluating outcome measures and adverse events in accordance using the methodology described in the Cochrane Handbook of Systematic Reviews of Interventions, where applicable.[30] This review has been performed in accordance with the PRISMA statement.[31] A comprehensive review protocol was prospectively registered on the PROSPERO database (CRD42017068577).

### *Search methods*

Studies were identified thorough a systematic literature search of all records in Ovid MEDLINE and Ovid EMBASE from database inception to June 2017. The primary author (JCRW) completed both 'free-text term' and 'MeSH term' searches by combining variations of the keywords 'migraine' and 'surgery' using Boolean operators.[20] Only English language articles were considered. The search results were merged, and duplicate citations were discarded. Titles and abstracts were screened in duplicate, and studies unrelated to the research objective were discarded. The full text of each shortlisted paper was read in full by each author independently to assess its eligibility for inclusion. The final list of included studies was compared and discussed between all authors. The bibliographies of included papers and previous reviews were examined to ensure all relevant studies had been considered. Any disparities regarding inclusion of articles were resolved by consensus with reference to the pre-specified inclusion criteria. Published data from included studies were scrutinised for reporting of outcomes. If relevant data were not available for extraction, authors were contacted by email with a specific data request.

### *Criteria for selecting studies*

Study selection criteria were defined during the protocol stage and included all clinical studies of surgical intervention for chronic migraine. Two authors (JCRW and JL) used a pre-specified, bespoke inclusion/exclusion Excel sheet to independently assess eligibility of studies. Case reports, letters, editorials, anatomical studies and literature reviews were excluded. Study participants were adults undergoing surgical intervention for chronic migraine, diagnosed according to the International Classification of Headache Disorders (ICHD) criteria or International Headache Society (IHS) guidelines where possible.[32,33] Studies of patients with headache other than migraine (including familial hemiplegic migraine, supraorbital rim syndrome and cluster headache) were excluded. Studies were included if they reported on any outcomes following surgery for migraine surgery, including operative outcomes, patient-reported outcomes, recurrence rates and adverse outcomes. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[34]

### *Data extraction*

Data collection and analysis were performed in accordance with the Cochrane Handbook of Systematic Reviews of Interventions where applicable.[30] Data were extracted onto a pre-designed electronic form and included location of study, study design, sample size, age of participants, medical comorbidity, migraine characteristics, presence of aura and length of post-operative follow-up. Outcome data were extracted for migraine-specific outcomes, composite headache scores, patient-related outcomes, migraine recurrence and adverse events. Our primary outcome was reduction in migraine severity, based on continuous interval outcome measures and assessed on a visual analogue scale. Secondary outcomes included migraine frequency, migraine duration and composite headache index scores, as well as adverse event and recurrence rates. Two authors (JCRW and JL) extracted the data in duplicate and independently checked the data set for accuracy.

### *Statistical analysis*

We performed simple descriptive statistics for patient demographics. We used a narrative synthesis to summarise the identified surgical and patient-related outcomes with reference to variations in outcome definitions. Pooled rates were calculated for outcomes described by three or more studies to give overall descriptive estimates of effects of surgery and adverse events. Formal meta-analysis was not undertaken because of poor reporting of baseline data, intervention heterogeneity and inconsistent outcome reporting.

## Results

### *Search strategy*

Our search strategy identified a total of 789 research articles, 97 of which were potentially relevant to the research question. Of these 97 articles, 46 were read in full and 25 were deemed eligible for inclusion.[19,24,25,27–29,35–53] Data were immediately available for extraction from 18 study reports.[19,24,25,27–29,42–53] The authors of the remaining seven studies were contacted with additional requests including, as a minimum, baseline demographic data and absolute pre- and post-operative migraine headache variables.[35–41] None of the authors were able to provide these data; these studies were excluded and data were extracted from the remaining 18 studies (Figure 1, Table 1). Details of the excluded studies are shown in Supplementary Table 1. In total, 18 study reports were included from 17 distinct primary studies.

### *Study characteristics*

The included studies were published between 1962 and 2017. Twelve studies were from research groups in the USA, four from Europe (UK, Italy, Greece and Austria), one from Taiwan and one from Iran. Thirteen of the studies were published in plastic surgery journals, two in craniofacial/maxillofacial journals, one in a neurology journal and two in general journals. The median sample size was 35, with a range of 9–229 participants. Fourteen studies were retrospective observational

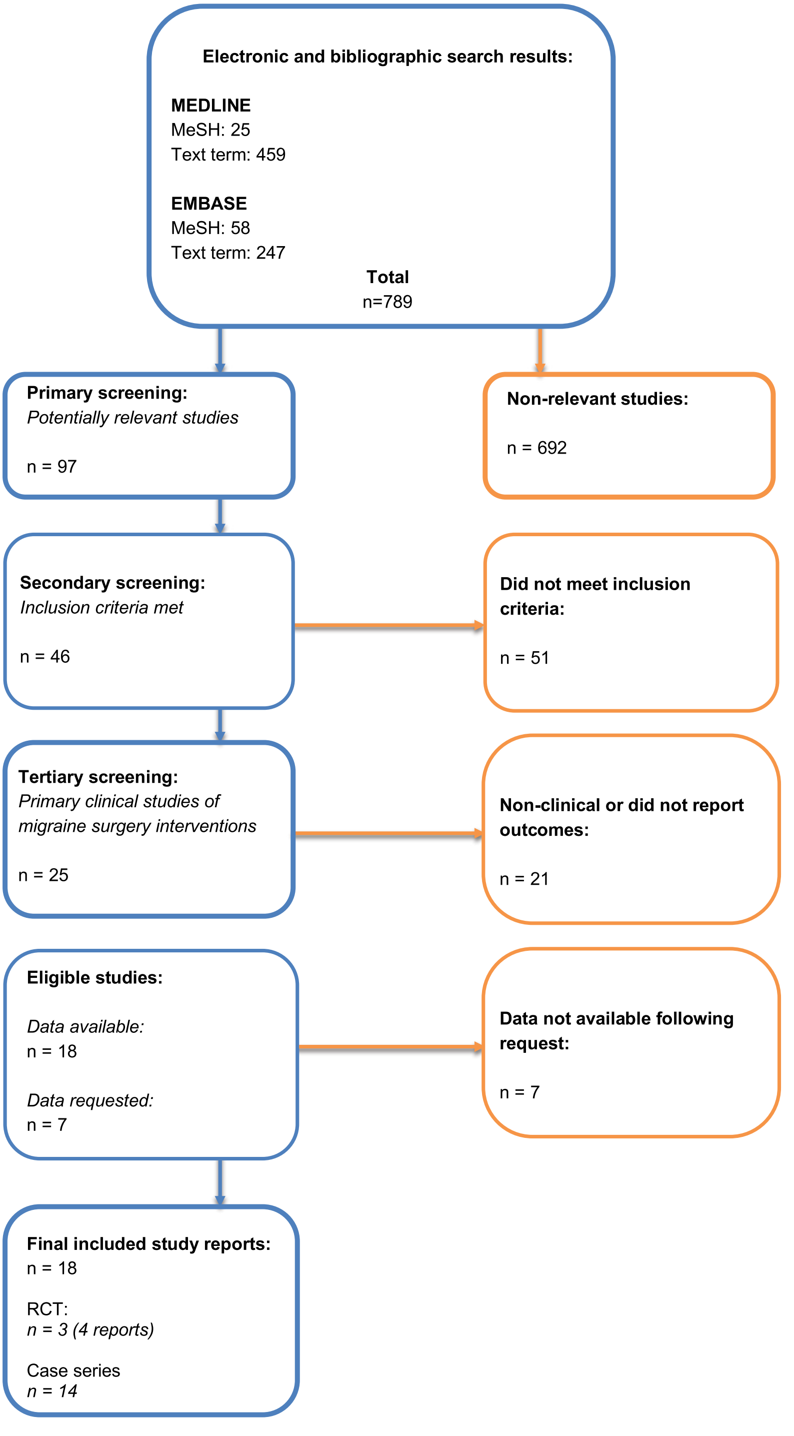


**Figure 1.** PRISMA flowchart of study attrition.

**Table 1**
Characteristics of included studies.

| | Primary Author & Year* | Title | Journal | Country | Study Design | Surgical Intervention** | Intervention Type | Number of Patients | Number of Patients (Subgroup) | Age (SD/range)*** | Male:Female Ratio | Follow-up (mean, months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Knight 1962 | Surgical Treatment of Migraine | Proceedings of the Royal Society of Medicine | UK | Case series | Unilateral superior cervical sympathectomy | Nerve (sympathectomy) | 10 | -<br>- | 43.4 (14.8) | 3:1 | - |
| 2 | Rapidis 1976 | The Therapeutic Result of Excision of the Superficial Temporal Artery in Atypical Migraine | Journal of Maxillo-Facial Surgery | Greece | Case series | Superficial temporal artery excision | Artery (excision) | 8 | -<br>- | 35.0 (9.9) | 1.6:1 | - |
| 3 | Behin 2004 | Surgical treatment of patients with refractory migraine headaches and intranasal contact points | Cephalalgia | USA | Case series | Decompression of intranasal contact points using turbinectomy, ethmoidectomy, septoplasty and maxillary antrostomy | Nose | 21 | -<br>- | 45 (21-73) | 1:1.4 | - |
| 4 | Dirnberger 2004 | Surgical Treatment of Migraine Headaches by Corrugator Muscle Resection | Plastic and Reconstructive Surgery | Austria | Case series | Glabellar myectomy | Muscle (resection) | 60 | -<br>- | 49.7 (13.9) | 1:4.6 | 12.8 |
| 5 | Poggi 2008 | Confirmation of Surgical Decompression to Relieve Migraine Headaches | Plastic and Reconstructive Surgery | USA | Case series | Multiple trigger site deactivation using any combination of the following: glabellar myectomy with zygomaticotemporal nerve excision and/or occipital nerve decompression | Muscle (resection) and nerve excision | 18 | -<br>- | 41.0 (8.6) | 1:9 | 16 |
| 6 | Ducic 2009 | Indications and Outcomes for Surgical Treatment of Patients with Chronic Migraine Headaches Caused by Occipital Neuralgia | Plastic and Reconstructive Surgery | USA | Case series | Greater occipital nerve excision with/without lesser occipital nerve excision | Nerve excision | 206 | -<br>- | 45.0 (2.9) | 1:4.4 | - |
| 7 | Guyuron 2005 | Comprehensive Surgical Treatment of Migraine Headaches | Plastic and Reconstructive Surgery | USA | RCT | Multiple trigger site deactivation using any combination of the following: glabellar myectomy, zygomaticotemporal nerve excision, occipital nerve decompression and/or septoplasty with turbinectomy | Muscle (resection), nerve (excision) and nose surgery | 108**** | 89 | 43.6 (21-63) | 1:12 | 60 |
| | Guyuron 2011 | Five-Year Outcome of Surgical Treatment of Migraine Headaches | | | | Control - no intervention | | | 19 | | | |
| 8 | Janis 2011 | Validation of the Peripheral Trigger Point Theory of Migraine Headaches: Single-Surgeon Experience Using Botulinum Toxin and Surgical Decompression | Plastic and Reconstructive Surgery | USA | Case series | Multiple trigger site deactivation using any combination of the following: glabellar myectomy, zygomaticotemporal nerve excision, occipital nerve decompression and/or septoplasty (with/without turbinectomy) | Muscle (resection), nerve (excision) and nose surgery | 24 | -<br>- | 44.4 (23.2-66.5) | 1:23 | 55 |
| 9 | Chepla 2012 | Clinical Outcomes following Supraorbital Foraminotomy for Treatment of Frontal Migraine Headache | Plastic and Reconstructive Surgery | USA | Case series | Glabellar myectomy with supraorbital foraminotomy | Muscle (resection) and foraminotomy | 86 | 43 | 42.5 (1.5) | 1:42 | 12 |
| | | | | | | Glabellar myectomy | | | 43 | 46.5 (1.9) | | |
| 10 | Chmielewski 2013 | The Role of Occipital Artery Resection in the | Plastic and Reconstructive | USA | Case series | Greater occipital nerve decompression with occipital artery resection | Nerve (decompression) | 170 | 55 | 45.9 | 1:8 | 12 |

(continued on next page)

**Table 1** (*continued*)

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Surgical Treatment of Occipital Migraine Headaches | Surgery | | | Greater occipital nerve decompression | and artery (resection) | | 115 | 44.6 | | |
| 11 | Lee 2013 | The role of the third occipital nerve in surgical treatment of occipital migraine headaches | Journal of Plastic, Reconstructive and Aesthetic Surgery | USA | Case series | Greater occipital nerve decompression with third occipital nerve resection | Nerve (decompression) and nerve (excision) | 229 | 111 | 44.7 | 1:8 | 6 |
| | | | | | | Greater occipital nerve decompression | Nerve (decompression) | | 118 | 45.3 | | |
| 12 | Gferer 2014 | Nonendoscopic Deactivation of Nerve Triggers in Migraine Headache Patients: Surgical Technique and Outcomes | Plastic and Reconstructive Surgery | USA | Case series | Multiple trigger site deactivation using any combination of the following: glabellar myectomy, zygomaticotemporal nerve excision, occipital nerve decompression and/or auriculotemporal nerve and artery excision | Muscle (resection), nerve (excision) and nerve (decompression) and artery (excision) | 35 | - | 46.1 (12.7) | 1:6 | 12 |
| | | | | | | | | | - | | | |
| 13 | Guyuron 2015 | A Prospective Randomized Outcomes Comparison of Two Temple Migraine Trigger Site Deactivation Techniques | Plastic and Reconstructive Surgery | USA | RCT | Avulsion of the zygomaticotemporal branch of the trigeminal nerve (one side) | Nerve (avulsion) | 19 | 19 | 38.2 (19-62) | 1:18 | 12 |
| | | | | | | Decompression via fasciotomy and removal of the zygomaticotemporal artery (other side) | | | 19 | | | |
| 14 | Lin 2015 | Experience of Surgical Treatment for Occipital Migraine in Taiwan | Annals of Plastic Surgery | Taiwan | Case series | Greater occipital nerve decompression with/without lesser occipital nerve excision | Nerve (decompression) and nerve (excision) | 9 | - | 51.3 (10.6) | 1:8 | - |
| | | | | | | | | | - | | | |
| 15 | Edoardo 2015 | Frontal Endoscopic Myotomies for Chronic Headache | Journal of Craniofacial Surgery | Italy | Case series | Glabellar myectomy | Muscle (resection) | 43 | - | 18-72***** | 1:8 | 6 |
| | | | | | | | | | - | | | |
| 16 | Omranifard 2016 | A comparison of outcome of medical and surgical treatment of migraine headache: In 1 year follow-up | Advanced Biomedical Research | Iran | RCT | Multiple trigger site deactivation using any combination of the following: glabellar myectomy, zygomaticotemporal nerve excision, occipital nerve decompression (with/without occipital artery resection) and/or septoplasty (with/without turbinectomy) | Muscle (resection), nerve (excision) and nose surgery | 50 | 25 | 42.2 (6.9) | 1:9 | 12 |
| | | | | | | Medical therapy | | | 25 | | | |
| 17 | Ascha 2017 | In-Depth Review of Symptoms, Triggers, and Treatment of Occipital Migraine Headaches (Site IV) | Plastic and Reconstructive Surgery | USA | Case series | Greater occipital nerve decompression (with/without occipital artery resection) | Nerve (decompression) and artery (resection) | 195 | - | 47.0 (16-76) | 1:9 | 44 |

*Ordered chronologically

**Surgical approach (open vs. endoscopic) not included

***Mean age with standard deviation or range, if provided

****Patient numbers at one-year follow-up

*****Range only, no average available

**Legend – SD, standard deviation; RCT, randomised controlled trial**

**Table 2**
Diagnostic criteria.

| Primary author & year | Diagnostic criteria* | Length of migraine history (months, SD/range) | Pre-operative migraine trigger point identification | | | Clinician** | No. of trigger sites*** |
|---|---|---|---|---|---|---|---|
| | | | Clinical | Imaging | Interventional | | |
| Knight 1962 | – | 152 (108) | Clinical | – | – | – | 1–2 (U/L) |
| Rapidis 1976 | – | 48 (31) | Clinical | – | LA | – | 1 (U/L) |
| Behin 2004 | ICDH1 | 132 (3–480) | Clinical | CT | LA | ENT | 3–6 (U/L) |
| Dirnberger 2004 | IHS | – | – | – | – | – | 1 (B/L) |
| Poggi 2008 | IHS | – | Clinical | – | Botox | Neurologist | 1–4 (U/L) |
| Ducic 2009 | IHS | 204 (111) | Clinical | – | Botox/LA | Neurologist | 1–2 (B/L) |
| Guyuron 2005<br>Guyuron 2011 | IHS | – | Clinical | – | Botox | Neurologist | 1–4 (B/L) |
| Janis 2011 | IHS | – | Clinical | – | Botox | – | 1–4 (B/L) |
| Chepla 2012 | – | – | Clinical | – | – | – | 1–4 (B/L) |
| Chmielewski 2013 | – | – | Clinical | – | – | – | 1–4 (B/L) |
| Lee 2013 | – | – | Clinical | – | – | – | 1–4 (B/L) |
| Gferer 2014 | – | – | Clinical | – | Botox | Neurologist | 1–3 (B/L) |
| Guyuron 2015 | ICDH2 | – | Clinical | – | Botox | Neurologist | 1 (B/L) |
| Lin 2015 | – | >120 | Clinical | – | – | – | 1 (B/L) |
| Edoardo 2015 | ICDH2 | – | Clinical | – | – | Neurologist | 1 (B/L) |
| Omranifard 2016 | IHS | – | Clinical | CT | Botox | Neurologist | 1–4 (B/L) |
| Ascha 2017 | – | – | Clinical | – | Botox | Neurologist | 1–4 (B/L) |

SD - standard deviation.
ICHD - International Classification of Headache Disorders.
IHS - International Headache Society guidelines (exact criteria not specified).
U/L - unilateral.
B/L - bilateral.
ENT - ear, nose and throat surgeon.
LA - local anaesthetic.
CT - computed tomography scan.
Blank cells (-) indicate not specified by authors.
* Diagnostic criteria provided in as much detail as specified in paper – e.g., specific ICHD criteria vs IHS guidelines vs unspecified.
** Clinician diagnosing chronic migraine.
*** Number of discrete surgical sites listed per side; e.g., 1–4 (B/L) indicates one-to-four sites per hemicranium (i.e., between two and eight total operative sites); U/L indicates surgery on one side only.

case series and three were prospective RCTs, one of which published two reports of the same trial, one containing data at one-year follow-up and one at five-year follow-up.[21,23] The follow-up periods were not reported in five included studies. In the other studies, the follow-up periods ranged from 6 months to 5 years but were most commonly 12 months or longer.

Across all studies, the median age was 44 years (range 35–51 years) with a female preponderance in all but one study.[24] Nine of the included studies reported using an established diagnostic classification system for migraine: six used IHS guidelines and three used a specific ICHD classification (Table 2).

The remaining eight studies did not report on whether the diagnosis of migraine was made with reference to any diagnostic criteria. The clinician making a diagnosis of migraine was specified in 10 studies: in nine of these, this was a board-certified neurologist, and in the remaining one study, this was an ear, nose and throat surgeon. One study did not report on how the diagnosis of migraine was made.[46] Only five studies reported on the pre-intervention length of migraine history, which ranged from 48 to 204 months. Only six studies reported on pre-intervention medication usage.

Trigger point identification methods varied between studies. Five studies used clinical assessment in isolation to guide operative site selection. History and examination findings were further investigated by a trial of local anaesthetic or botulinum toxin injections in 11 studies and adjunct computed tomography imaging in two.

*Interventions*

A number of trigger sites were identified and operated on across the included studies. Four studies evaluated unilateral trigger site deactivation only; the remaining 13 studies surgically deactivated identified trigger sites bilaterally. This appears to be a more recent trend, as no studies since 2009 have used a unilateral approach (Table 2). Five studies evaluated a single trigger site, whereas 12 performed between 1 and 6 trigger site deactivations synchronously.

Surgical interventions were extremely heterogeneous both within studies and between studies (Table 1). Only six of the studies evaluated a single surgical intervention; the other studies involved more complex surgical interventions, with some including up to six different procedures in the treatment group. In these studies, each patient received a different overall intervention consisting of multiple synchronous procedures. Four studies focussed solely on extracranial peripheral nerves, with interventions directed at the superior cervical sympathetic chain, the zygomaticotemporal nerve, the auriculotemporal nerve and the greater and lesser occipital nerves. Two studies looked solely at resection of the glabellar muscle group in isolation. One study evaluated the effect of excision of the superficial temporal artery in isolation. The remaining studies involved, in various combinations, surgical interventions directed at nerves, arteries, muscle groups and nasal structures. Surgery on nasal structures typically involved a combination of selective turbinectomy and/or septoplasty. One study included additional sinus surgery (in this case, ethmoidectomy and maxillary antrostomy). The three RCT study populations each had different intervention and control groups; therefore, the data could not be synthesised in a meta-analysis.

*GRADE assessment*

All included studies were evaluated against the validated Grading of Recommendations, Assessment, Development and Evaluations (GRADE) standards.[34] A summary of the quality of evidence for each study, with reasons, is detailed in Table 3.

The overwhelming majority of the literature on migraine surgery is based upon ‘low’- or ‘very low’-quality observational data. Owing to a paucity of high quality evidence, no studies were excluded from the data set following GRADE assessment.

Most observational studies were based on small cohorts of patients undergoing surgical intervention for migraine in a single centre. Although these studies typically report similar improvements in the outcome measures assessed, their conclusions are limited by small sample sizes without evidence of preparatory power calculation, unclear enrolment methods, variability in the surgical intervention offered and poor follow-up (Table 3). In a number of studies, the diagnostic criteria for migraine are not specified.[24,29,42,44,45,49,50,53] Without a clearly defined patient population, these studies have limited generalisability and do not explicitly identify patients who may benefit from migraine surgery. This is confounded by significant between-study variation in the pre-intervention workup: for example, a proportion of studies used a positive response to botulinum toxin as part of the eligibility criteria, whereas others did not.[24,29,43–46,48,50,53] Similarly, surgical intervention for migraine is assumed to be appropriate only for treatment-refractory cases (i.e. in those patients who fail to respond to multimodal best medical therapy or non-invasive options). However, most studies do not report on previous medication use or length of migraine history.[19,25,27,28,44–46,48–52] A number of studies failed to report on adverse outcomes, raising the possibility of selective outcome reporting.[24,28,29,43–46,50,51,53] In general, recent studies have typically used nerve decompression approaches – it is unclear as to what extent this is comparable with older studies using alternative surgical interventions (e.g. superficial temporal artery excision or cervical sympathectomy).[24,53]

The three randomised controlled trials (RCTs) were assessed according to GRADE standards with additional consideration given to CONSORT Statement guidelines.[34,54] One of these trials failed to report complete baseline data.[25,27] Another study using a side-specific randomisation protocol failed to account for correlation in their data set and appeared to apply contradictory statistical tests.[28] Two RCTs did not adequately describe their patient enrolment criteria or randomisation methodology.[28,51] In the two studies, where a surgical treatment arm was compared with a no-intervention control arm,

**Table 3**
GRADE criteria.

| Primary author & year | Study design | Methodological limitations | Grade score |
|---|---|---|---|
| Knight 1962 | Observational - Retrospective | Very small study size no statistical data migraine diagnosis unclear no description of surgical methods variable surgical intervention variable length of follow-up subjective outcome assessment no adverse outcome reporting | Very low |
| Rapidis 1976 | Observational - Retrospective | Very small study size no statistical data migraine diagnosis unclear subjective outcome assessment no adverse outcome reporting | Very low |
| Behin 2004 | Observational - Retrospective | Migraine diagnosis unclear unclear patient enrolment non-validated outcome measures loss to follow-up no adverse outcome reporting | Very low |
| Dirnberger 2004 | Observational - Retrospective | Leading outcome measure questions post-hoc sub-group analysis selective outcome reporting non-validated outcome measures incomplete reporting of absolute data inadequate length of follow-up no adverse outcome reporting | Very low |
| Poggi 2008 | Observational - Retrospective | Small study size non-validated outcome measures inadequate methodological detail variable surgical intervention risk of participant recall bias | Very low |
| Ducic 2009 | Observational - Retrospective | Migraine diagnosis unclear variable surgical intervention | Low |
| Guyuron 2005<br>Guyuron 2011 | RCT | Randomisation not described no power calculation unspecified control group medical therapy loss to follow-up selective participant exclusion from statistical analysis significant improvements in control group (regression to the mean) | Low |
| Janis 2011 | Observational - Retrospective | Small study size selective patient enrolment loss to follow-up non-validated outcome measures | Very low |
| Chepla 2012 | Observational - Retrospective | Variable anatomy between control and treatment groups unspecified method for control group inclusion no adverse outcome reporting | Low |
| Chmielewski 2013 | Observational - Retrospective | Unbalanced baseline migraine symptoms unspecified method for control group inclusion heterogeneous results multiple retrospective analyses no adverse outcome reporting | Very low |
| Lee 2013 | Observational - Retrospective | Selective outcome reporting no adverse outcome reporting | Low |
| Gferer 2014 | Observational - Retrospective | Small study size selective outcome reporting inclusion of re-interventions in statistical analysis conflicting results compared with external study control | Low |
| Guyuron 2015 | RCT | Selective patient enrolment outcomes analysed per site rather than per patient unclear application of statistical tests | Low |
| Lin 2015 | Observational - Retrospective | Small study size unclear patient enrolment sparse data inadequate length of follow-up inadequate description of diagnostic work-up no adverse outcome reporting | Very low |
| Edoardo 2015 | Observational - Retrospective | Small study size sparse data unclear migraine diagnosis - variable headache syndromes loss to follow-up selective outcome reporting statistical comparison to unrelated study | Very low |
| Omranifard 2016 | RCT | Small study size no power calculation unclear patient enrolment randomisation not described unblinded results significant improvements in control group (regression to the mean) | Low |
| Ascha 2017 | Observational - Retrospective | Unclear patient enrolment loss to follow-up variable pre-operative work up lack of site-specific data | Low |

**Table 4**
Migraine intensity.

| Primary author & year | Baseline migraine intensity | | Post-intervention migraine intensity | |
|---|---|---|---|---|
| | VAS score | SD | VAS score | SD |
| Knight 1962 | – | – | 50% experienced less intense MH symptoms** | – |
| Rapidis 1976 | – | – | 87.5% experienced complete resolution of MH symptoms** | – |
| Behin 2004 | 7.8 | 1.5 | 3.6 | 3.7 |
| Dirnberger 2004 | – | – | 63% experienced reduction or resolution of MH symptoms** | – |
| Poggi 2008 | 8.0 | 7.9 | 6.0 | 4.8 |
| Ducic 2009 | 7.9 | 1.4 | 1.9 | 1.8 |
| Guyuron 2005* Guyuron 2011* | 8.5 | 1.2 | 4.5 | 3.2 |
| Janis 2011 | 7.3 | 2.1 | 3.3 | 2.5 |
| Chepla 2012 | 8.3 | 0.2 | 5.0 | 0.3 |
| Chmielewski 2013 | 8.0 | 2.9 | 4.7 | 3.1 |
| | 8.2 | 1.9 | 4.1 | 3.7 |
| Lee 2013 | 8.0 | – | 4.6 | – |
| | 8.3 | – | 4.5 | – |
| Gferer 2014 | 9.2 | 1.0 | 3.3 | 3.3 |
| Guyuron 2015 | 6.8 | 0.3 | 2.6 | 0.8 |
| | 7.0 | 0.3 | 2.9 | 0.8 |
| Lin 2015 | 8.2 | 1.8 | 2.7 | 2.5 |
| Edoardo 2015 | – | – | – | – |
| Omranifard 2016 | 8.3 | 0.3 | 4.1 | 0.2 |
| Ascha 2017 | – | – | – | – |

MH - migraine headache.
SD - standard deviation.
VAS - visual analogue scale, scored 0–10, where higher numbers indicate more severe symptoms.
Blank cells (-) indicate data not collected by authors.
All scores given to 1 dp (where appropriate).
* Migraine parameters provided at baseline and five-year follow-up.
** Detail as specified in paper.

statistically significant improvements were also noted in the control group, raising the possibility of regression to the mean.[25,51]

*Migraine headache outcomes*

Outcome reporting was variable, although pre- and post-operative migraine intensity, frequency, duration and MHI scores were relatively consistently reported. In general, surgical intervention improved scores across these outcomes. Migraine intensity, as measured on a visual analogue scale (range 0–10), was reported in 13 studies and improved from a pooled average of 8.0 to 3.9 following surgical intervention (Table 4).

Migraine frequency was measured in 11 studies and reduced from an average of 15.6 migraine headaches per month to 5.1 (Table 5).

Migraine duration (days) was reported in eight studies, with an average pre-operative duration of 0.9 and an average post-operative duration of 0.4 (Table 6).

Eight studies calculated a composite migraine headache index (MHI) by multiplying frequency, intensity and duration scores; this improved from a pooled average of 115.2 preoperatively to 14.5 postoperatively (Table 7).

*Adverse outcomes and recurrence rates*

Only 10 of the 18 included studies commented on adverse events (Table 8).

Of these, seven described variable rates of post-operative complications and three studies reported no adverse events. The overall rate of adverse events was 11.6%, ranging from 0 to 38%. In the 14

**Table 5**
Migraine frequency.

| Primary author & year | Baseline migraine frequency | | Post-intervention migraine frequency | |
|---|---|---|---|---|
| | MH/month | SD | MH/month | SD |
| Knight 1962 | >5 | – | – | – |
| Rapidis 1976 | – | – | – | – |
| Behin 2004 | 17.7 | 11.2 | 7.7 | 7.6 |
| Dirnberger 2004 | 45% >15, 40% 5–14, 15% 1–4** | – | 58.4% experienced >50% headache per day reduction** | – |
| Poggi 2008 | 11.9 | 9.3 | 1.3 | 2.9 |
| Ducic 2009 | – | – | – | – |
| Guyuron 2005* | 10.9 | 7.5 | 4 | 5.3 |
| Guyuron 2011* | | | | |
| Janis 2011 | 16.5 | 11.1 | 3.8 | 6.5 |
| Chepla 2012 | 13.9 | 0.9 | 5.9 | 0.8 |
| Chmielewski 2013 | 19.3 | 8.4 | 9.9 | 9.8 |
| | 14.6 | 9.4 | 5.1 | 7.6 |
| Lee 2013 | 18.1 | – | 7.2 | – |
| | 16.1 | – | 7.1 | – |
| Gferer 2014 | 18.5 | 10.4 | 3.7 | 6 |
| Guyuron 2015 | 14.2 | 1.8 | 1.9 | 0.7 |
| | 14.6 | 1.8 | 2.2 | 0.8 |
| Lin 2015 | – | – | – | – |
| Edoardo 2015 | >15 | – | – | – |
| Omranifard 2016 | 15.9 | 3.3 | 6.4 | 2.3 |
| Ascha 2017 | – | – | – | – |

MH - migraine headache.
SD - standard deviation.
Blank cells (-) indicate data not collected by authors.
All scores given to 1 dp (where appropriate).
* Migraine parameters provided at baseline and five-year follow-up.
** Detail as specified in paper.

studies, where complete elimination of migraine headache was reported, the average percentage of patients with recurrence of migraine following surgery was 57% (range 13–92%). No studies reported complete migraine elimination in all patients following surgery. A greater than 50% reduction in the MHI score was a commonly reported indicator of surgery success; in the 10 studies where this was reported, an average of 83.3% of participants achieved this threshold (range 71–95%).

*Quality of life outcome measures*

Assessment of additional generic and/or disease-specific patient-reported outcome measures was beyond the scope of this review. However, only 5 included studies reported on patient outcomes not directly related to the surgical intervention.[19,25,27,46,47,52] One study reported statistically significant improvements using a previously validated migraine-specific disability assessment tool.[25,27] The remaining four studies described qualitative benefits using non-validated questionnaires.[19,46,47,52] No included study used a generic quality of life or depression tool. Where reported, migraine surgery appears to be associated with quality of life improvements, although these findings must be interpreted in the context of the quality of evidence provided.

## Discussion

This paper describes the first PRISMA-compliant systematic review of surgical intervention for chronic migraine. It provides a descriptive, critical synthesis of the literature with particular attention to migraine-specific outcome measures and adverse event rates. Overall, our review suggests

**Table 6**
Migraine duration.

| Primary author & year | Baseline migraine duration | | Post-intervention migraine duration | |
|---|---|---|---|---|
| | Days | SD | Days | SD |
| Knight 1962 | – | – | – | – |
| Rapidis 1976 | – | – | – | – |
| Behin 2004 | – | – | – | – |
| Dirnberger 2004 | – | – | – | – |
| Poggi 2008 | 50% <24 h, 44% 2 h–1 wk, 6% >1 wk** | – | – | – |
| Ducic 2009 | – | – | – | – |
| Guyuron 2005* | 1.4 | 1.4 | 0.3 | 0.9 |
| Guyuron 2011* | | | | |
| Janis 2011 | 1 | 0.9 | 0.5 | 0.4 |
| Chepla 2012 | 1.1 | 0.1 | 0.4 | 0.5 |
| Chmielewski 2013 | 0.7 | 0.7 | 0.4 | 0.7 |
| | 1.2 | 1.4 | 0.4 | 0.9 |
| Lee 2013 | 0.9 | – | 0.5 | – |
| | 1.1 | – | 0.5 | – |
| Gferer 2014 | 0.7 | 0.5 | 0.2 | 0.4 |
| Guyuron 2015 | 0.4 | 0.1 | 0.2 | 0.04 |
| | 0.4 | 0.1 | 0.1 | 0.04 |
| Lin 2015 | – | – | – | – |
| Edoardo 2015 | – | – | – | – |
| Omranifard 2016 | 1.1 | 0.5 | 0.5 | 0.3 |
| Ascha 2017 | – | – | – | – |

MH - migraine headache
SD - standard deviation
hr - hour
wk - week
Blank cells (-) indicate data not collected by authors
All scores given to 1 dp (where appropriate)
* Migraine parameters provided at baseline and five-year follow-up.
** Detail as specified in paper.

that surgical trigger site deactivation leads to symptomatic benefits in appropriately selected patients with chronic migraine, in that across all included studies, a positive intervention effect was observed. Nonetheless, flawed research methodology throughout the literature prevents this review from definitively supporting or refuting the hypothesis that surgical intervention is effective for chronic migraine.

All included studies reported an improvement in post-operative migraine intensity, with an average reduction of nearly 50% – a figure consistent with that given in the three included RCTs. Similar improvements were seen across other disease-specific endpoints including migraine duration, frequency and composite headache scores, although this should be interpreted in the context of the benefits of placebo as seen in the PREEMPT trials.[13–16]

Fourteen of the included studies were based on observational data. Significant methodological flaws in nine of these studies meant that their evidence quality assessment was downgraded to 'very low' according to GRADE criteria. Despite using a randomised trial design, the three prospective clinical trials did not provide enough reliable data to allow us to conclusively achieve our second and third review objectives, largely owing to flaws in trial methodology and intervention heterogeneity. For example, Guyuron et al. randomised patients to a complex intervention (including facial muscle resection, cranial nerve excision and/or nasal surgery – where each patient received a different combination based on trigger sites) versus no intervention.[25,27] Each participant in the treatment group therefore received an essentially different intervention, furthering the intra-group heterogeneity. A number of other methodological flaws in the trial design are detailed in Table 2. The second RCT, also conducted by Guyuron et al. was a quasi-randomised trial where the same patient received one treatment on one hemi-cranium and the alternative intervention on the opposite side.[28] There are issues with this trial design, including difficulties when interpreting results and the importance of the unit

**Table 7**
Migraine headache index scores.

| Primary author & year | Baseline MHI | | Post-intervetion MHI | |
|---|---|---|---|---|
| | Score | SD | Score | SD |
| Knight 1962 | – | – | – | – |
| Rapidis 1976 | – | – | – | – |
| Behin 2004 | – | – | – | – |
| Dirnberger 2004 | – | – | – | – |
| Poggi 2008 | – | – | – | – |
| Ducic 2009 | 287.0 | 14.9 | 24.0 | 11.8 |
| Guyuron 2005* | 90.3 | 80.1 | 11.4 | 29.9 |
| Guyuron 2011* | | | | |
| Janis 2011 | 106.6 | 89.7 | 10.3 | 28.2 |
| Chepla 2012 | 114.0 | 13.3 | 18.8 | 3.6 |
| Chmielewski 2013 | – | – | – | – |
| | – | – | – | – |
| Lee 2013 | 130.3 | – | 25.6 | – |
| | 107.7 | – | 27.4 | – |
| Gferer 2014 | 99.4 | 95.7 | 10.1 | 18.0 |
| Guyuron 2015 | 41.0 | 9.6 | 2.5 | 0.9 |
| | 42.0 | 9.5 | 2.9 | 0.9 |
| Lin 2015 | – | – | – | – |
| Edoardo 2015 | – | – | – | – |
| Omranifard 2016 | 134.0 | 41.7 | 11.8 | 9.0 |
| Ascha 2017 | 111.8 | – | 45.4 | – |

MHI - migraine headache index (calculated by frequency x intensity x duration).
SD - standard deviation.
All scores provided to 1 dp.
* MHI scores provided at baseline and five-year follow-up.

of analysis.[55] Similar issues were encountered in the third RCT: here, Omranifard et al. evaluated a complex intervention versus non-standardised medical therapy, again reducing the reliability of the observed effects due to intra- and inter-group heterogeneity.[51] These issues meant that the quality of evidence provided by these RCTs was downgraded to low, using the GRADE approach.

Adverse event reporting was inconsistent and ranged from 0% to 38% in 10 studies. Inconsistent adverse event reporting complicates interpreting this variability; indeed, the other seven studies did not report on adverse events at all. Such inconsistency is concerning, particularly when considering the proposed benefits of migraine surgery versus botulinum toxin regimens, which has consistently low rates of adverse events. This must be considered a standard outcome in future research on migraine surgery.

Extracranial migraine trigger site deactivation is based on the theoretical mechanism that surgical intervention is able to make permanent the temporary effects of botulinum toxin. This is the rationale for our evaluation of the 'permanence' of the surgical intervention, in terms of both migraine recurrence and complete elimination. Interestingly, there was a pooled average of 60% of study participants who had recurrence of migraine after surgical intervention – i.e., only 40% of patients who underwent surgical intervention achieved permanent symptomatic relief. In one paper, 92% of patients had recurrence of symptoms following multiple trigger site deactivation.[19] This was also seen in a similar study involving multiple trigger site deactivation, where an 83% recurrence rate was observed.[52] Only in four studies was the rate of recurrence less than 50% during the follow-up period.[28,49,51,53] However, some consider migraine to be a largely genetically determined disorder of brain biology that cannot be cured, and therefore, modulatory interventions are required. Considering this concept, the recurrence of symptoms may be unavoidable.

In contrast to the high rates of migraine recurrence, all studies reported symptomatic improvement, with a pooled average of 83% of study participants achieving a greater than 50% reduction in MHI scores. The migraine headache index (MHI) is a widely used tool that combines migraine

**Table 8**
Recurrence of migraine and adverse outcomes.

| Primary author & year | Incomplete MH elimination* (% of patients) | >50% Reduction in MHI (% of patients) | Adverse outcomes (% of patients) | Adverse outcomes (type) |
|---|---|---|---|---|
| Knight 1962 | – | – | – | – |
| Rapidis 1976 | 13 | – | – | – |
| Behin 2004 | – | – | – | – |
| Dirnberger 2004 | 72 | – | – | – |
| Poggi 2008 | 83 | – | 28 | Itching, numbness, alopecia, asymmetric brow elevation, corrugator muscle contraction, ptosis, frontalis contracture |
| Ducic 2009 | 57 | 81 | 1 | Incisional cellulitis |
| Guyuron 2005** | 75 | 88 | 13 | Nerve injury, neck stiffness/weakness, numbness, altered sensation, haematoma |
| Guyuron 2011** | | | | |
| Janis 2011 | 92 | 71 | 38 | Haematoma, paraesthesia, alopecia, altered sensation |
| Chepla 2012 | – | – | – | – |
| Chmielewski 2013 | 62 | 80 | – | – |
| | 36 | 91 | – | – |
| Lee 2013 | 74 | 80 | – | – |
| | 71 | 81 | – | – |
| Gferer 2014 | 49 | 91 | 11 | Numbness, itching |
| Guyuron 2015 | 42 | 95 | 0 | – |
| | 47 | 84 | 0 | – |
| Lin 2015 | – | – | – | – |
| Edoardo 2015 | 61 | – | 0 | – |
| Omranifard 2016 | 36 | 76 | 0 | – |
| Ascha 2017 | 48 | 82 | 25 | Neck discomfort, itching, altered sensation, hypertrophic scar, dehiscence |

MHI - migraine headache index.
MH - migraine headache.
Blank cells (-) indicate not reported by authors.
All figures rounded to the nearest integer.
* Incomplete MH elimination defined as persistent migraine symptoms (i.e., <100% relief).
** Data at five-year follow-up.

duration, migraine intensity and migraine frequency to generate a composite outcome. The MHI was initially developed to ensure compatibility of outcome measures between studies, including key migraine-specific variables of interest. However, MHI scores from separate studies are very difficult to compare statistically because of differences in the collection of baseline data and the inherent variability of each component of the MHI. In addition, extrinsic factors affecting one or more of these subjectively assessed components are not accounted for. For example, if a patient used an abortive medication, reducing the duration of the migraine attack, but not affecting its frequency or severity, there will be an unrepresentative change in the overall MHI. This may act as a confounding factor when measuring the effect of surgical intervention. The authors feel that the individual components of the MHI, along with more objective measures of intervention effect, are best employed in the migraine population.

Despite the methodological issues already described, the consistent improvement in migraine-related outcomes demonstrates that, while surgery may not achieve permanence of the 'Botox effect', it may be associated with symptomatic improvement for a period of time. The actual difference in effectiveness at improving symptoms between botulinum toxin alone versus surgery remains to be proven in an adequately powered clinical trial.[56] Of note, of the 15 studies using an extracranial nerve deactivation strategy, only nine employed preoperative response to botulinum toxin or local anaesthetic as part of their trigger site identification algorithm.

This systematic review draws two key conclusions: 1. There is insubstantial evidence supporting the effectiveness of surgical intervention for chronic migraine primarily due to flaws; 2. An analysis of the current primary clinical research data suggests that surgical intervention may benefit appropriately selected chronic migraine patients. Considering these findings, the authors believe that an adequately powered, randomised clinical trial of a well-defined surgical intervention for migraine compared to botulinum toxin and/or placebo is needed. It should include a variety of outcome measures including objective measures of effect, validated generic and migraine-specific patient-reported outcome measures and comprehensive reporting of adverse event and recurrence rates. Follow-up will need to be of sufficient length to compare the longevity of surgical intervention versus botulinum toxin. This proposed trial could provide definitive evidence for clinicians and patients alike, ensuring best practice and fully informed consent.

### *Strengths and limitations*

This systematic review is the first PRISMA-compliant, prospectively registered, critical assessment of the evidence base for migraine surgery. Throughout, we have focused on sound systematic review methodology to present an unbiased and scientific assessment of the body of knowledge for migraine surgery. Our search strategy included a broad range of study types to capture all relevant reports of primary clinical research, enabling a global evaluation of the topic. Although we were unable to perform statistical meta-analysis, our descriptive analysis allows an overview of the likely effect of a variety of surgical interventions, with a snapshot of the rates of recurrence and adverse events. This review also identifies specific flaws that have affected the reliability of migraine surgery research to date, with a view to providing direction towards definitive, clinically meaningful research.

This review was limited by a paucity of methodological quality in included studies, heterogeneous interventions and inconsistent outcome reporting. Variability in baseline data, intervention data and outcome data precluded formal meta-analysis. The authors of 7 studies eligible for inclusion were contacted with requests for additional data to enable data extraction. The data requested from these 7 studies included baseline demographics, preoperative migraine data and post-operative outcome data. Unfortunately, none of the authors of these papers were able to provide data, which significantly reduced our final cohort of included studies. These limitations prevent the authors from providing definitive clinical recommendations either for or against migraine surgery, based on the current evidence.

## Conclusion

The current literature supporting surgical intervention for chronic migraine is insufficient to provide reliable guidance for clinicians. All 18 of the studies included in our review suggest a beneficial effect of surgical intervention for migraine in selected patients; however, methodological flaws throughout the literature reduce the reliability of these findings. According to the GRADE approach, we cannot definitively state that surgery for migraine is effective for relief of symptoms. Migraine surgery is an evolving field and future research should build on deficiencies in the current literature. A definitive, multicentre trial of migraine surgery will provide substantive evidence to guide patients and clinicians.

## Funding

JCRW is an NIHR Academic Clinical Fellow. This research is supported by the National Institute for Health Research (NIHR) infrastructure at NDORMS. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care. No funding was directly received for the development of this manuscript.

## Conflict of interest

Thomas Muehlberger is founder of the Migraine Surgery Centre, London, UK.

## Contributor's statement

All authors named above actively contributed to the production and completion of this manuscript in the following roles, as pre-defined in the protocol stage:

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jpra.2019.01.002.

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